EU RMP	
Drug Substance	dapagliflozin
Version Number	30
Succession Number	1
Data lock point	31 March 2023
Date of final sign off	See e-signature page

EUROPEAN UNION RISK MANAGEMENT PLAN (EU RMP) for FORXIGA™, EDISTRIDE™ (dapagliflozin)

The content of this RMP has been reviewed and approved by the QPPV.

Administrative Information

Rationale for submitting an updated RMP:

This RMP is updated to remove the important potential risk of Lower Limb amputation .

This RMP is submitted with a meta-analysis of the dapagliflozin studies D1693C00001 (DECLARE), D1699C00001 (DAPA-HF), D169AC00001 (DAPA-CKD), D169CC00001 (DELIVER), D1690C00018, and D1690C00019, describing events of amputation and risk factors of amputation. The analysis supports the removal of the risk of Lower Limb Amputation.

Summary of significant changes in this RMP:

Part II Module V

Post-authorisation exposure data are updated.

Part II Module SVII

Following completion of the meta-analysis of amputation data, lower limb amputation is removed as an important potential risk.

Part II Module SVIII

Important potential risk of Lower Limb Amputation (LLA) is removed.

Part III

Removal of follow-up questionnaire following the removal of Lower limb amputation as an important potential risk.

Part V

Removal of the important potential risk of Lower limb amputation.

Part VI

Removal of the important potential risk of Lower limb amputation.

Other RMP versions under evaluation	Not applicable
Details of currently approved RMP	**Version Number:** v 29 **Assessment report date:** 14 April 2023 **Procedure number:** EMEA/H/C/2322/WS2421 (FORXIGA) EMEA/H/C/4161/WS2421 (EDISTRIDE)

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation/ Special term	Definition/Explanation
30-MSU	30 Month safety update
AA	Aldosterone agonists
ACC	American College of Cardiology
ACEi	Angiotensin-converting enzyme inhibitor
AD	Anti-diabetic drug
ADR	Adverse drug reaction
AE	Adverse event
AHA	American Heart Association
AKI	Acute kidney injury
ALI	Acute liver injury
ALT	Alanine aminotransferase
ANCA	Anti-neutrophil cytoplasmic antibody
ARB	Angiotensin receptor blocker
AST	Aspartate aminotransferase
aTRH	apparent treatment-resistant hypertension
AUC	Area under the curve
BBN	N-butyl-N-(4-hydroxybutyl)-nitrosamine
BMI	Body Mass Index
CHF	Congestive heart failure
CI	Confidence interval
CKD	Chronic kidney disease
C_{max}	Maximum plasma drug concentrations
COPD	Chronic obstructive pulmonary disease
CPN	Chronic progressive nephropathy
CPRD	Clinical Practice Research Database
CSII	Continuous subcutaneous insulin infusion
CV	Cardiovascular
DAE	AEs leading to discontinuation of study drug
DALY	Disability adjusted life years
DKA	Diabetic ketoacidosis
DKD	Diabetic kidney disease
eGFR	Estimated glomerular filtration rate (unit: mL/min/1.73 m^2)
EMA	European medicines agency

Abbreviation/ Special term	Definition/Explanation
EPAR	European Public Assessment Report
ESC	European Society of Cardiology
ESRD	End-stage renal disease
EU	European union
GFR	Glomerular filtration rate
HF	Heart failure
HfrEF	Heart Failure with reduced Ejection Fraction
HFSA	Heart Failure Society of America
HIRDSM	Health Core Integrated Research Database
ICD	Implantable cardioverter defibrillator
IP	Investigational Product
LT	Long-term
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MRA	Mineral corticoid Receptor Antagonist
MRHD	Maximum recommended human dose
N	Number
NHANES	National Health and Nutrition Examination Survey
NYHA	New York Heart Association
PACD	Primary analysis censoring date
PAD	Peripheral artery disease
PASS	Post Authorisation Safety Study
PND	Postnatal day
PT	Preferred Term
PV	Pharmacovigilance
PY	Person-years
QPPV	Qualified Person for Pharmacovigilance
RAS	Renin-angiotensin system
RMM	Risk minimisation measure
RMP	Risk Management Plan
SAE	Serious adverse event
SAS	Safety analysis set
SGLT2	Sodium glucose co-transporter 2
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Query

Abbreviation/ Special term	Definition/Explanation
SoC	Standard of Care
ST	Short-term
SU	Sulphonylurea
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TBL	Total bilirubin
TCC	Transitional cell carcinoma
UACR	Urine Albumin-to-Creatinine Ratio
ULN	Upper limit of normal
US	United States
UTI	Urinary tract infection

I. PART I: PRODUCT OVERVIEW

Table I-1 Product Overview

Active substance(s) (INN or common name)	Dapagliflozin
Pharmacotherapeutic group(s) (ATC Code)	A10BK01
Marketing Authorisation Holder	AstraZeneca AB
Medicinal products to which this RMP refers	1
Invented names in the European Economic Area(EEA)	FORXIGA, EDISTRIDE
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class:** Human renal sodium-glucose co-transporter 2 (SGLT2) inhibitor
	Summary of mode of action: Dapagliflozin is a highly potent, selective, and reversible SGLT2 inhibitor. Inhibition of SGLT2 by dapagliflozin reduces reabsorption of glucose from the glomerular filtrate in the proximal renal tubule with a concomitant reduction in sodium reabsorption leading to urinary excretion of glucose and osmotic diuresis. Dapagliflozin therefore increases the delivery of sodium to the distal tubule which increases tubuloglomerular feedback and reduces intraglomerular pressure. This combined with osmotic diuresis leads to a reduction in volume overload, reduced blood pressure, and lower preload and afterload, which may have beneficial effects on cardiac remodelling and diastolic function, and preserve renal function. The cardiac and renal benefits of dapagliflozin are not solely dependent on the blood glucose-lowering effect and not limited to patients with diabetes as demonstrated in the DAPA-HF, DELIVER and DAPA-CKD studies. Other effects include an increase in haematocrit and reduction in body weight. Dapagliflozin improves both fasting and post-prandial plasma glucose levels by reducing renal glucose reabsorption leading to urinary glucose excretion. This glucose excretion (glucuretic effect) is observed after the first dose, is continuous over the 24-hour dosing interval and is sustained for the duration of treatment. The amount of glucose removed by the kidney through this mechanism is dependent upon the blood glucose concentration and GFR. Thus, in subjects with normal blood glucose dapagliflozin has a low propensity to

Table I-1 Product Overview

	cause hypoglycaemia. Dapagliflozin does not impair normal endogenous glucose production in response to hypoglycaemia. Dapagliflozin acts independently of insulin secretion and insulin action. Improvement in homeostasis model assessment for beta cell function (HOMA beta-cell) has been observed in clinical studies with dapagliflozin. The SGLT2 is selectively expressed in the kidney. Dapagliflozin does not inhibit other glucose transporters important for glucose transport into peripheral tissues and is > 1,400 times more selective for SGLT2 versus SGLT1, the major transporter in the gut responsible for glucose absorption.
	Important information about its composition: Not applicable
Hyperlink to the Product Information	FORXIGA/EDISTRIDE Summary of Product Characteristics
Indications in the EEA	**Current:** <u>Type 2 diabetes mellitus</u> FORXIGA/EDISTRIDE is indicated in adults and children aged 10 years and above for the treatment of insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise: – as monotherapy when metformin is considered inappropriate due to intolerance. – in addition to other medicinal products for the treatment of type 2 diabetes. For study results with respect to combination of therapies, effects on glycaemic control, cardiovascular and renal events, and the populations studied see sections 4.4, 4.5 and 5.1 in SmPC. <u>Heart failure</u> FORXIGA/EDISTRIDE is indicated in adults for the treatment of symptomatic chronic heart failure. <u>Chronic kidney disease</u> FORXIGA/EDISTRIDE is indicated in adults for the treatment of chronic kidney disease.

Table I-1 Product Overview

	Proposed: Not applicable
Dosage in the EEA	**Current:** Tablets 5 mg and 10 mg
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	**Current:** Dapagliflozin propanediol 5 mg tablets are yellow, biconvex, round, film-coated tablets with "5" debossed on one side and "1427" debossed on the other side. Dapagliflozin propanediol 10 mg tablets are yellow, biconvex, diamond-shaped, film-coated tablets with "10" debossed on one side and "1428" debossed on the other side.
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

II. PART II: SAFETY SPECIFICATION

II.1 MODULE SI: EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION

II.1.1 Type 2 diabetes mellitus

Incidence

Estimating incidence in type 2 diabetes mellitus (T2DM) is limited because a large portion of individuals with diabetes remain undiagnosed. The time at which the disease process commenced is unknown for most, perhaps all, cases of this disease. It is estimated that globally as many as 193 million people, or close to half (46.5%) of all people with diabetes, are unaware of their disease (IDF 2015). Therefore, prevalence is a better indicator of the burden of T2DM.

Prevalence:

For the year 2015 it was estimated that diabetes would affect approximately 415 million people worldwide in the age range 20 to 79 years, or a global prevalence of 8.8% (95% confidence interval [CI]: 7.2% to 11.4%). This estimate is expected to increase to 642 million, a prevalence of 10.4% (8.5% to 13.5%) of the adult population, by the year 2040. For the European region (including Russia and Central Asia) 59.8 million individuals in the age range 20 to 79 years, or a prevalence of 9.1% (6.85 to 13.0%), are estimated to have diabetes in the year 2015. The projection for 2040 is a prevalence of 10.7% (8.2% to 14.9%) or 71.1 million persons (IDF 2015).

Demographics of the population in the indication –and risk factors for the disease:

Currently, about 77% of persons with diabetes are of working age (20 to 65 years old). with some 320.5 million estimated in 2015; about 75% reside in low- and middle-income countries. There were an estimated 15.6 million more men than women with diabetes in 2015 (215.2 million men vs. 199.5 million women). This difference is expected to decrease to 15.1 million by the year 2040 (328.4 million men vs. 313.3 million women). Currently, more individuals with diabetes live in urban than rural areas; this discrepancy is expected to widen (IDF 2015).

The exact causes of T2DM are not completely understood, but it is known that the disease has a strong hereditary component. Individuals who have a parent or sibling with T2DM have a 10% to 15% chance of developing the disease (the risk is much higher if the sibling is an identical twin). Environmental factors like an excess body weight, inactive lifestyle, or poor nutrition may act as a trigger for someone with a genetic tendency towards T2DM. Other potential causes of T2DM include a family history of diabetes, history of gestational diabetes, and advancing age (IDF 2015).

The main existing treatment options:

There are many medications approved for the treatment of T2DM but achieving and maintaining treatment goals can be challenging. The glucose-lowering effect of most available antidiabetic agents is limited by a loss of efficacy over time, in part due to progressive worsening of insulin resistance and beta cell function (UKPDS 1998, Viberti et al 2002). Most patients eventually require a combination of agents to achieve glycaemic targets (Nathan et al 2009).

Antidiabetic medications treat T2DM by lowering glucose levels in the blood. With the exceptions of insulin, exenatide, liraglutide, and pramlintide, all are administered orally and are thus also called oral hypoglycaemic agents or oral antihyperglycaemic agents. There are different classes of antidiabetic drugs (ADs), which include but are not limited to insulin, biguanides (metformin), thiazolidinediones, sulphonylureas (SUs), alpha-glucosidase inhibitors, dipeptidyl peptidase-4 inhibitors, sodium glucose co-transporter 2 (SGLT2) inhibitors, and glucagon-like peptide-1 receptor agonists.

Natural history of the indicated condition in the population, including mortality and morbidity:

T2DM is progressive without adequate treatment and contributes to serious comorbid conditions. Chronic comorbid conditions associated with diabetes can lead to restricted mobility of hands, feet, and large joints; microvascular complications causing blindness or diabetic foot ulcers; increased risk of hearing and visual impairments, infectious complications, vitamin D deficiencies, and cognitive decline (Almdal et al 2004). Macrovascular complications include stroke, ischaemic cardiovascular disease, congestive

heart failure (CHF), and peripheral artery disease (PAD) (Wilke et al 2015). Worldwide, diabetes is the fourteenth largest cause of disability adjusted life years (DALY), accounting for about 2.6% of global DALY in 2015. The global disability burden (number of years lived with disability) attributable to diabetes increased by 67.2% from 1990 to 2010 (WHO 2000-2015).

Diabetes increases the risk of mortality nearly 2-fold and is associated with mean reduction in life expectancy of approximately 8 years in both men and women. Global mortality attributable to diabetes in the adult population aged 20 to 79 years in the year 2015 was estimated at 5.0 million deaths with nearly half (44.6%) of these occurring in people less than 60 years old. More than 627000 people are expected to die due to diabetes-related causes in the European region in the year 2015; about 26.3% of these deaths are in people less than 60 years old (IDF 2015).

Important co-morbidities:

The aetiology and natural history of T2DM is complex and it shares risk factors with cardiovascular and kidney diseases, so it can be difficult to distinguish whether associated conditions are risk factors, complications, or comorbidities. Multiple chronic conditions are highly prevalent among patients with T2DM. A majority of patients with T2DM have at least one comorbid condition while nearly 40% have 3 or more comorbid conditions (Lin et al 2015). Hypertension, hyperlipidaemia, and obesity are very prevalent in adults with T2DM, often being reported in a majority of incident T2DM in clinical and observational studies (Lin et al 2015, Reach et al 2013).

Macrovascular and microvascular complications arising from diabetes include cardiovascular disease, diabetic nephropathy, peripheral neuropathy, retinopathy (blindness), and amputation. Heart failure is more common in the T2DM population than in those without, perhaps due in part to the high prevalence in T2DM patients of hypertension and kidney disease, which can also lead to heart failure. Non-alcoholic fatty liver disease can arise due to metabolic disruptions associated with T2DM. As T2DM prevalence increases with age, other diseases associated with increased age, such as COPD, arthritis, and cancers, are common comorbidities (Lin et al 2015, Chen and Tseng 2013).

II.1.2 Heart Failure

Incidence

The incidence of heart failure (HF) varies widely ranging between 1 and 9 per 1000 person-years (PY) (Savarese et al 2022), with incidences of 3 to 5 per 1000 PY in Europe and 2.2 per 1000 in the US (McDonagh et al 2021). The age-adjusted incidence of HF in high income countries is stable or declining, reflecting better management, however, the overall incidence is increasing due to the ageing population (Groenewegen et al 2020, McDonagh et al 2021).

Over the last 2 decades, the incidence of HF with LVEF < 40% has slightly decreased, while HF with LVEF > 40% was shown to increase (Tsao et al 2018). Nearly half of the incident HF-related hospitalisation in the US are attributed to HF with LVEF > 40 % (Benjamin et al 2019).

Prevalence

Over 64 million people, approximately 1% to 2% of the general adult population, are affected by HF worldwide (Groenewegen et al 2020, McDonagh et al 2021). The prevalence is increasing due to the aging population, global population growth, and better survival following diagnosis (Groenewegen et al 2020). Of all hospitalisations worldwide, 1% to 2% are due to HF (Groenewegen et al 2020) and readmissions are common (Cheng et al 2014, Cui et al 2020).

Demographics of the population in the authorised indication and risk factors for the disease

Both incidence and prevalence of HF increase with advancing age (Odegaard et al 2020, McDonagh et al 2021). Elderly women are overrepresented among patients with HF and LVEF > 40% (Romiti et al 2022), whereas HF with LVEF < 40% is more common in younger men (Lam et al 2019). US studies have reported a higher incidence of HF in African-American patients, followed by Spanish-American, Caucasians, and Chinese-American patients (Tsao et al 2022).

The main existing treatment options

The current European and US guidelines recommend different treatment paradigms for HF across the LVEF spectrum (Heidenreich et al 2022, McDonagh et al 2021). Recommended treatment of HF with LVEF < 40% with effects on mortality and HF events includes 4 classes: renin-angiotensin system inhibitors, beta blockers, mineralocorticoid receptor antagonists, and SGLT2i (Heidenreich et al 2022, McDonagh et al 2021), where SGLT2i is recommended to reduce hospitalisation and cardiovascular mortality in symptomatic patients with chronic LVEF < 40% , regardless of the presence of T2DM.

The US guideline includes a new moderate (class IIa) recommendation for SGLT2i in patients with HF and LVEF >40% (Heidenreich et al 2022), but the European guideline does not yet include SGLT2i for this HF subpopulation (McDonagh et al 2021). Unlike the US guideline, the European guideline recommends SGLT2i in patients with diabetes at high risk of CV disease or with CV disease in order to prevent HF hospitalisations (McDonagh et al 2021).

Management of HF with LVEF > 40% is directed towards comorbidities and risk factors for development of HF, underlying cardiovascular disease, and symptomatic treatment of volume overload (Heidenreich et al 2022, McDonagh et al 2021).

Natural history of the indicated condition in the untreated population, including mortality and morbidity

HF is a common, chronic, progressive disease, and despite substantial improvements in HF diagnosis over the last few decades, the overall prognosis remains poor with reduced quality of life, high healthcare consumption, and high mortality, with an estimated 5-year mortality rate after diagnosis of 50% (McDonagh et al 2021).

Studies among hospitalised patients with HF indicate a decline in rehospitalisation and mortality rates over the last 4 decades (Kimmoun et al 2021). However, the absolute number of hospital admissions for HF is expected to increase by approximately 50% in the next 25 years due to population growth, ageing, better survival, and the increasing prevalence of co-morbidities (Savarese and Lund 2017).

Important co-morbidities

Multimorbidity is a common feature in patients with HF, with over 85% of the patients having 2 or more co-morbid chronic conditions (Heidenreich et al 2022). In a recent systematic review, the most commonly recorded major comorbid disorders were hypertension, ischaemic heart disease, hyperlipidaemia, diabetes, chronic kidney disease and atrial fibrillation (Khan et al 2020). Co-morbidities are major contributors to high hospitalisation rates (Streng et al 2018, Savarese et al 2022), with an 1.5 times higher risk in patients with diabetes, atrial fibrillation, obesity, and chronic kidney disease (CKD) (Mosterd and Hoes 2007). Women have a higher prevalence of co-morbidities leading to higher hospitalisation rates (Lawson et al 2019).

Patients with HF and LVEF < 40% are more likely to have ischemic cardiovascular co-morbidities, whereas patients with LVEF > 40% have a higher prevalence of atrial fibrillation, hypertension, and non-CV comorbidities (eg diabetes, obesity, and CKD) (Savarese and Lund 2017, McDonagh et al 2021).

II.1.3 Chronic Kidney Disease (CKD)

Incidence

The global incidence of CKD in 2016 was > 21 million (Xie et al 2018). The global incidence rate of stage 3 to 5 CKD was estimated at 288.53/100000 people (95% UI: 258.38, 319.24) in 2016 (310.13/100000 people when age-standardised) (Xie et al 2018). Despite increasing interest in the burden of CKD worldwide, there is evidence that a substantial number of CKD cases remain undiagnosed leading to underestimation of the true burden of disease (Bakris 2019; Hirst et al 2020; Wong et al 2018).

Prevalence

The global prevalence of stage 1–5 CKD has been reported as between 9.1 to 13.4% (GBD Chronic Kidney Disease Collaboration 2020; Hill et al 2016), and age-standardised prevalence

for Central, Eastern and Western Europe was reported as 7.6%, 12.4%, and 5.4% respectively (GBD Chronic Kidney Disease Collaboration 2020). The prevalence of stage 3–5 CKD was estimated as 10.6% in 2016, translating into > 275 million cases globally (Hill et al 2016, Xie et al 2018).

Prevalence estimates for each stage of CKD vary, but the majority of patients with diagnosed CKD have early-stage disease, with a much lower proportion of patients progressing to kidney failure. For example, the global prevalence of stage 3 CKD (eGFR 30–59ml/min/1.73 m^2) is estimated to be between 3.6% to 7.6%, whereas estimates of the global prevalence of stage 5 CKD (eGFR < 15 ml/min/1.73 m^2) range from 0.1% to0.7% (GBD Chronic Kidney Disease Collaboration 2020, Hill et al 2016)

A 2020 systematic review identified ten studies across the USA, China, France, Italy and Spain that classified patients according to both GFR and albuminuria status (Murton et al 2021). Of patients with CKD stage 2–5, the prevalence of individuals with albuminuria stage A1 (UACR < 30 mg/g) was 27.4% to 56.4%, A2 (UACR 30 to 300 mg/g) was 2.9% to 10.0%, and A3 (UACR > 300 mg/g) was 0.4% to 3.2% (Murton et al 2021).

Demographics of the population in the authorised indication and risk factors for the disease

The prevalence of CKD increases with advancing age with a reported prevalence of 13.7% in those aged 30 to 39 years up to 34.3% for those aged 70 to 79 years (Hill et al 2016). The proportion of CKD prevalence is highest between the sixth and seventh decade of life (Xie et al 2018).

Whilst the prevalence of CKD tends to be higher in women, men experience more severe disease. For instance, a recent global burden of disease study reported a 1.3-fold higher age-standardised CKD prevalence among females than males, however, age-standardised incidence of dialysis and transplantation was 47% higher in males than females and age-standardised CKD mortality was 39% higher in males than females (GBD Chronic Kidney Disease Collaboration 2020).

Finally, CKD is more common in blacks than in whites, non-Hispanic Asians and Hispanics (Centers for Disease Control and Prevention 2020). Another study reported that Black Americans experienced a disproportionate burden of ESRD in United States with the risk of ESRD up to 5 times those of age-adjusted white counterparts, despite comparable rate of for early stage of CKD (Hsu et al 2003).

The main existing treatment options

Blockade of the angiotensin system with ACEi or ARB represents the mainstay of standard of care treatment for CKD in patients with T2DM and without diabetes. Cardiovascular risk and

glycaemic control are pharmaceutically managed as necessary within this patient group (Inker et al 2014).

Recently, a member of the SGLT2 inhibitor class, canagliflozin, demonstrated a 30% cardiorenal risk reduction and a 34% risk reduction for renal adverse events in patients with diabetic nephropathy (Perkovic et al 2019). Following positive EMA (June 2020) assessment of phase III CREDENCE study, the canagliflozin product labelling has been extended to include evidence of canagliflozin's treatment benefits in treatment of DKD with T2DM patients.

Interventional studies assessing the use of ACEi or ARB for the treatment of diabetic kidney disease (DKD) (Lewis et al 2001, Brenner et al 2001) or SGLT2 inhibition on top of SoC in patients with DKD (Perkovic et al 2019) indicate that patients treated with ACEi or ARB remain at risk of morbidity, mortality, and progression to ESRD. Additionally, a significant proportion of patients with CKD treated with SoC (23% of patients with diabetes; 15% of patients without diabetes) display accelerated disease progression (decline in eGFR of > 4 mL/min/1.73 m^2 per year) (Go et al 2018).

Natural history of the indicated condition in the untreated population, including mortality and morbidity

The progression of CKD can be quantified using measures of changing eGFR and albuminuria over time, which describe the transition of patients with CKD between CKD stages. Patients with CKD are at increased risk of CV events, particularly as CKD progresses to later stages, and this is associated with a significant increase in mortality compared to the general population. For example, two 2016 meta-analyses reported that patients with CKD (eGFR < 60ml/min/1.73m^2) are at increased risk of both new-onset atrial fibrillation (HR 1.47 [95% CI, 1.21–1.78]) (Shang et al 2016) and myocardial infarction (relative risk 1.52 [95% CI 1.39 to 1.67] p = 0.00001), compared to the general population (Vashistha et al 2016). A 2019 systematic literature review identified 18 studies that quantified the risk of CV morbidity (myocardial infarction, stroke and heart failure) by CKD stage, and demonstrated that the risk of CV morbidity increases with both CKD stage and albuminuria progression; patients with stage 5 CKD and macroalbuminuria were shown to have an 11.4-fold increased risk of CV morbidity compared to patients with stage 1 CKD and normoalbuminuria (AstraZeneca 2019).

Patients with CKD are at a higher risk for CV-related and all-cause mortality compared to the general population. In 2017, CKD was associated with an age-standardised mortality rate of 15.9/100000 population (Hill et al 2016). A meta-analysis compiling data from 39 studies found that the relative risk for mortality in those with reduced kidney function, compared to those without, was significantly increased in 93% of cohorts (71% when adjusted for other established risk factors) (Tonelli et al 2006). Where suitable data were available, mortality risk increased exponentially with decreasing renal function (Tonelli et al 2006). All-cause

mortality has been shown to increase with CKD stage; this is likely because patients at later stages of CKD have a greater number of, or more advanced, comorbidities.

Important comorbidities

CKD patients have high prevalence of hypertension (48-66%), diabetes (17% to 33%), ischemic heart disease (2% to 23%), hyperlipidaemia (11%), cerebrovascular disease (6% to 12%), heart failure (1% to3.5%) (Fraser et al 2015, Lee et al 2018, Tuttle et al 2019), however, data on the prevalence of CKD comorbidities according to the KDIGO 2012 categories are limited. Overall, the prevalence of comorbidities increases with albuminuria severity. In a Spanish hypertensive cohort, the prevalence of diabetes was higher in patients with CKD that had greater albuminuria severity; among patients with eGFR < 60mL/min/1.73 m^2, diabetes was present in 26%, 43%, and 53% of individuals with normoalbuminuria, microalbuminuria and macroalbuminuria, respectively (Ruiz-Hurtado et al 2016). In a French CKD cohort, the proportion of patients with atherosclerotic CV disease was higher in microalbuminuric (30.9%) and macroalbuminuric (34.4%) than normoalbuminuric (28.5%) patients (Villain et al 2020). In an analysis of US hypertensive patients, the prevalence of apparent treatment-resistant hypertension (aTRH) was found to increase with both worsening GFR status and increasing albuminuria severity. In hypertensive patients with eGFR 45 to 59 mL/min/1.73 m^2, the prevalence of aTRH was 17.2%, 26.9%, 32.2% and 50.7% in groups with UACR < 10, 10 to 29, 30 to 299 and ≥ 300 mg/g, respectively. In those with eGFR < 45 mL/min/1.73 m^2, the corresponding figures were 22.5%, 24.5%, 32.8%, and 56.4% (Tanner et al 2013). Finally, a 2020 analysis of the US DISCOVER-CKD study found that patients with an eGFR of 25 to 75 ml/min/1.73 m^2 and an elevated UACR (200 to 5000 mg/g) had a higher prevalence of comorbidities such as T2DM, heart failure and hypertension compared to the overall cohort of patients with stage 3 to 5 CKD or kidney failure (Garcia Sanchez et al 2020).

II.2 MODULE SII: NONCLINICAL PART OF THE SAFETY SPECIFICATION

II.2.1 Summary of key findings from nonclinical data

Toxicity

Reproductive and Developmental toxicity: In rats, both maternal and developmental toxicities were observed at ≥ 2300x the maximum recommended human dose (MRHD). Maternal toxicity included mortality. Developmental toxicity consisted of increased embryo foetal lethality, reduced foetal body weights, and increased incidences of foetal malformations and skeletal variations. Based upon the exposure multiples, these effects are not considered relevant to humans.

Increased incidence or severity of renal pelvic dilatation was observed in adult offspring of treated dams, at a dose associated with maternal dapagliflozin exposures of 1415x MRHD. Additional findings included dose-related reductions in pup body weights at maternal

dapagliflozin exposures of ≥ 249x MRHD. In a follow-up study in lactating pups, renal pelvic dilatation was associated with pup dapagliflozin exposures of 138x MRHD and dose-related reductions in pup body weights were observed at pup exposures ≥ 29x MRHD. These results suggest that lactational exposure to dapagliflozin affected renal maturation in rats.

Lactational exposure of dapagliflozin to weanling rats was also associated with glucosuria and reduced weight gain. In contrast to adult rats, new-born rats presumably lack compensatory fat stores and muscle mass with which to counter this increased excretion of glucose. Therefore, there is a risk that dapagliflozin could reduce weight gain in nursing infants whose mothers take dapagliflozin.

In a juvenile toxicity study, with dapagliflozin dosed to young rats from postnatal day (PND) 21 until PND 90, renal pelvic and tubular dilatations were observed at all dose levels; pup exposures at the lowest dose tested were ≥ 15x the MRHD. These findings were associated with dose-related increases in kidney weight and macroscopic kidney enlargement. The renal pelvic and tubular dilatations observed in juvenile animals did not fully reverse within the 1- month recovery period. Consequently, administration of dapagliflozin to weanling juvenile rats and indirect exposure during late pregnancy are associated with renal pelvic and tubular dilatations in progeny, although the long-term (LT) functional consequences of these effects are unknown. Since human anatomic renal maturation occurs in the second and third trimesters of pregnancy while functional maturation continues for the first 2 years of age, dapagliflozin-associated dilated renal pelvis and tubules noted in juvenile rats is a potential risk for human renal maturation.

Dapagliflozin is secreted in milk in lactating rats, but it is not known whether it is secreted in human milk. The negative effects on body weight gain associated with lactational exposures in the rat suggest that dapagliflozin should be avoided in lactating mothers during the first 2 years of life.

Nephrotoxicity: In the 6-month study in rats, cortical and medullary tubular dilatation, medullary tubular reactive hyperplasia with mineralisation, and urothelial hyperplasia were observed at the high dose (≥ 2100x MRHD). In addition, minimal to slight tubular cysts and exacerbated chronic progressive nephropathy (CPN) were observed in high-dose female rats. After a recovery period, exacerbation of CPN persisted in female rats, but there were no other renal lesions. The renal lesions in rats do not represent a safety concern for humans.

Other toxicity-related information or data as applicable

Genotoxicity: Dapagliflozin was negative in the Ames mutagenicity assay and was positive in an *in vitro* clastogenicity assay but only in the presence of S9 activation and at concentrations ≥ 100 µg/mL. Importantly, dapagliflozin was negative when tested in vivo in rats at exposure multiples >2100x the MRHD. In these studies, the estimated or measured maximum plasma

drug concentrations (C_{max}) approached or exceeded the 100 µg/mL level that produced cytogenetic alterations *in vitro*. Because *in vitro* cytogenetics assays are only intended to assist in hazard identification, while *in vivo* cytogenetics studies are used to confirm risk assessment, the weight of evidence supports that dapagliflozin is not genotoxic.

Carcinogenicity: An integrated review of the nonclinical data from the dapagliflozin programme, with additional perspective from the literature, was conducted to assess the biological plausibility and/or potential linkages between dapagliflozin and malignant tumours, especially bladder cancer.

There is no evidence that SGLT2 inhibition or dapagliflozin is a tumour initiator

- Dapagliflozin is not mutagenic and not clastogenic in vivo.
- Dapagliflozin did not induce tumours in 2-year rodent carcinogenicity studies. There were no urinary bladder tumours observed in these carcinogenicity studies.
- Dapagliflozin is highly selective for SGTL2 and there is no evidence for a linkage between its pharmacologic target or its mechanism of action (MOA) and an increased risk of tumours. SGLT2 is not expressed in either bladder or breast tissue.
- In a 15-month phenotyping study, there was no evidence of any difference in survival, body weights, clinical pathology parameters, or histopathologic findings observed between SGLT2 knockout mice and their wild-type counterparts. Despite a lifetime of glucosuria, there was no evidence of any alterations of renal function or proliferative changes observed in the kidneys or urinary bladders of SGLT2 knockout mice. This data strongly suggests that high levels of urinary glucose does not induce urinary tract tumours or accelerate age-related urinary tract pathology.

There is no evidence that dapagliflozin functions as a tumour promoter

- There were no increases in incidence or shortening of the latency period of background tumours following dapagliflozin administration relative to controls in either the mouse or rat 2-year carcinogenicity studies. This data supports our contention that dapagliflozin is not functioning as a non-specific tumour promoter in rodents.
- Risk factors for tumour promotion particularly for bladder tumours include, but are not limited to, immunosuppression, perturbations of hormonal balance, alterations in urinary pH and/or urinary composition leading to crystalluria and bladder irritation, cytotoxicity, local infection, inflammation, and/or cell proliferation. The common theme is interruption of intercellular communication and/or induction of cell proliferation acting as a stimulus for tumour promotion (Trosko et al 1983). Dapagliflozin was not associated with any of the above, except for a low incidence of inflammatory effects in chronic studies in rats and dogs, which did not translate to neoplastic changes.
- Tumour promotion typically occurs through increases in cell proliferation, but no hyperplastic or proliferative changes attributable to dapagliflozin were observed in the bladder (or any other tissue) in any of the toxicity studies, including 2-year rodent

carcinogenicity studies (> 100× the MRHD) and a 12-month dog toxicity study (> 3000× the MRHD). The dog has been considered to be particularly sensitive to urinary bladder tumours (Clayson and Cooper 1970); thus, the absence of any hyperplastic changes at exposures that significantly exceeded human exposures strongly supports the absence of any bladder tumour risk with dapagliflozin (Maeshima et al 2009, Maeshima et al 2010).

- A 6-month bladder tumour initiation-promotion study in rats with dapagliflozin was initiated as a post-approval commitment by the US Food and Drug Administration. The objectives of the study were to determine the potential effect of dapagliflozin on the incidence and degree of invasiveness of urinary bladder carcinomas induced with N-butyl-N-(4-hydroxybutyl)-nitrosamine (BBN). BBN was administered twice weekly by oral gavage for 6 weeks followed by a daily dose of dapagliflozin from Week 8 to Week 34 for 26 weeks. The dose of dapagliflozin was selected to give an exposure of approximately 7x that of the maximum human therapeutic dose as well as polyuria and increased level of glucose in the urine. Uracil was included as a positive control agent and showed effects as a tumour promoter and early progressor. The results showed that dapagliflozin does not act as a promoter or progressor of bladder cancer.

There is no evidence that SGLT2 inhibition or dapagliflozin administration enhances tumour growth

- Data from the nonclinical toxicology studies with dapagliflozin, in which glucosuria was a common feature, suggest that the presence of glucosuria does not lead to hyperplasia or to bladder tumours. Also, an in vitro experiment with 5 cultured bladder cancer cell lines indicated that concentrations of glucose more than 11 mM were not associated with enhanced cell growth, and concentrations of glucose of 50 mM were cytostatic.
- The in vitro effects of dapagliflozin and its primary human metabolite, 3-O-glucuronide, on human transitional cell carcinomas (TCC) tumour cell growth were examined. Six human bladder TCC cell lines were treated with the parent drug or its 3-O-glucuronide metabolite at concentrations of up to 20 µg/mL (≥ 100x human C_{max} at the MRHD) under sub-optimal growth conditions to allow for detection of enhancements in growth. For all 6 TCC cell lines, in vitro exposure to dapagliflozin or dapagliflozin 3-O-glucuronide did not result in stimulation of bladder tumour cell proliferation.
- In a mouse xenograft study, dapagliflozin was administered daily by oral gavage to male and female nude mice bearing human TCC tumours. Administration of dapagliflozin did not significantly enhance the size of EJ1 or UMUC3 tumours in implanted nude mice at exposures ≤ 75× and ≤ 0.9× clinical exposures at the MRHD.
- for dapagliflozin and its 3-O-glucuronide metabolite, respectively. This experiment provides further support that dapagliflozin administration is not associated with the enhancement of urinary bladder tumour growth.

In conclusion, the data from the nonclinical studies indicate that SGLT2 inhibition and/or dapagliflozin is not a tumour initiator, promotor, or tumour growth enhancer and that there is no biological basis for an increased cancer risk with dapagliflozin.

II.3 MODULE SIII: CLINICAL TRIAL EXPOSURE

II.3.1 Subjects with Heart failure

Four Phase III Heart Failure studies have been completed:

DAPA-HF trial (D1699C00001) was an event-driven randomised study in 4744 patients with HFrEF (with and without T2DM), of whom 2373 were randomised to dapagliflozin and 2371 to placebo, evaluating the effect of dapagliflozin 10 mg versus placebo in reducing the incidence of Cardiovascular death or worsening HF event (hospitalization for HF or equivalent HF event). The median duration of exposure to study drug was balanced between treatment groups: 17.8 months in the dapagliflozin group and 17.6 months in the placebo.

The 2 DETERMINE studies were parallel-group, randomised, double-blind, placebo-controlled studies in patients with LVEF > 40% (DETERMINE-preserved, D169EC00001) and LVEF ≤ 40% (DETERMINE-reduced, D169EC00002), including patients with and without T2DM, evaluating the effect of dapagliflozin 10 mg versus placebo on change in HF symptoms, physical limitation and exercise capacity. Patients were treated for 16 weeks, with no post-treatment follow-up period. D169EC00001 and D169EC00002 included 504 and 313 patients respectively, of whom 253 and 156 were randomised to dapagliflozin.

DELIVER (D169CC00001) was an international, multi-centre, parallel-group, event-driven, randomised, double-blind, placebo-controlled Phase III study in HF patients with LVEF > 40%, evaluating the effect of dapagliflozin 10 mg compared with placebo, given once daily in addition to background therapy, including treatments to control co-morbidities, in reducing the composite of CV death or an HF event (hospitalisation for HF or urgent HF visit). DELIVER included 6263 patients of whom 3131 were randomised to dapagliflozin and 3132 to placebo. The median duration of exposure to IP was similar between treatment groups: 26.9 months in the dapagliflozin group and 27.0 months in the placebo group.

A summary of the exposure in patients with HF is presented in Table II-1and Table II-2.

Table II-1 Extent of Exposure Summary For Heart Failure Studies - Safety Population

	DAPA TOTAL (N = 5902)			PLACEBO (N = 5901)		
Duration of Exposure (Months)	**# of Subjects Entering Interval**	**Patient-years Within Interval[a]**	**Cumulative Patient-years (0-End of Interval)[b]**	**# of Subjects Entering Interval**	**Patient-years Within Interval[a]**	**Cumulative Patient-years (0-End of Interval)[b]**
0 to ≤ 3	5902	1414.2	1414.2	5901	1414.8	1414.8

Table II-1 Extent of Exposure Summary For Heart Failure Studies - Safety Population

	DAPA TOTAL (N = 5902)			PLACEBO (N = 5901)		
Duration of Exposure (Months)	**# of Subjects Entering Interval**	**Patient-years Within Interval[a]**	**Cumulative Patient-years (0-End of Interval)[b]**	**# of Subjects Entering Interval**	**Patient-years Within Interval[a]**	**Cumulative Patient-years (0-End of Interval)[b]**
4 to ≤ 6	5608	1286.0	2700.2	5618	1288.0	2702.8
7 to ≤ 9	5009	1215.6	3915.8	5021	1216.9	3919.7
10 to ≤ 12	4839	1170.5	5086.3	4841	1168.1	5087.8
13 to ≤ 15	4634	1085.6	6171.9	4602	1077.0	6164.8
16 to ≤ 18	4137	937.8	7109.7	4093	928.8	7093.6
19 to ≤ 21	3454	762.6	7872.3	3418	755.9	7849.5
22 to ≤ 24	2706	597.5	8469.8	2670	597.2	8446.7
25 to ≤ 27	2143	448.9	8918.7	2154	450.2	8896.9
28 to ≤ 30	1573	332.6	9251.3	1575	329.0	9225.9
31 to ≤ 36	1150	397.3	9648.6	1137	392.7	9618.6
37 to ≤ 42	428	69.9	9718.5	418	71.2	9689.8
43 to ≤ 48	1	0.0	9718.5			

The counts include all subjects who received at least one dose of study drug. Duration of exposure in months where month is defined as 30 days.

[a] Patient-years Within Interval is the sum over the subjects exposure within the interval to study medication expressed in years where subject exposure within interval is the Last dosing date in interval - First dosing date in interval plus 1 day

[b] Cumulative Patient-years: 0 - End of Interval is the sum over the subjects exposure from day 1 of dosing through the end of the interval to study medication expressed in years, where cumulative subject exposure to end of interval is last dosing date in Interval - First dosing date plus 1 day. N is the number of treated subjects.

Studies included in the table are: D1699C00001, D169EC00001, D169EC00002, and D169CC00001.

Table II-2 Demographics Characteristics for Heart Failure studies - Age, Sex and Race for subjects exposed to IP – Randomized subjects

		Dapa 10mg (N=5913)	**Placebo (N=5911)**	**Total (N=11824)**
Demographic characteristic				
Age (years)	n	5913	5911	11824
	Mean	69.5	69.4	69.4
	SD	10.5	10.4	10.4
	Median	70.0	70.0	70.0
	Min	22	25	22

Table II-2 Demographics Characteristics for Heart Failure studies - Age, Sex and Race for subjects exposed to IP – Randomized subjects

		Dapa 10mg (N=5913)	Placebo (N=5911)	Total (N=11824)
Demographic characteristic				
	Max	99	99	99
Age group (years) n (%)	18 - 64	1726 (29.2)	1715 (29.0)	3441 (29.1)
	≥ 65	4187 (70.8)	4196 (71.0)	8383 (70.9)
	Total	5913	5911	11824
Sex n (%)	Male	3849 (65.1)	3855 (65.2)	7704 (65.2)
	Female	2064 (34.9)	2056 (34.8)	4120 (34.8)
	Total	5913	5911	11824
Male Age group (years) n (%)	18 - 64	1274 (21.5)	1249 (21.1)	2523 (21.3)
	≥ 65	2575 (43.5)	2606 (44.1)	5181 (43.8)
	Total	3849	3855	7704
Female Age group (years) n (%)	18 - 64	452 (7.6)	466 (7.9)	918 (7.8)
	≥ 65	1612 (27.3)	1590 (26.9)	3202 (27.1)
	Total	2064	2056	4120
Race n (%)	White	4168 (70.5)	4172 (70.6)	8340 (70.5)
	Black or African American	245 (4.1)	221 (3.7)	466 (3.9)
	Asian	1237 (20.9)	1285 (21.7)	2522 (21.3)
	Other	263 (4.4)	233 (3.9)	496 (4.2)
	Total	5913	5911	11824

The race subgroup of other includes subjects with reported race of American Indian/Alaska Native, Native Hawaiian/Other Pacific Islander, or Other.

Studies included in the table are: D1699C00001, D169EC00001, D169EC00002, and D169CC00001.

II.3.2 Subjects with T2DM

D1693C0001 DECLARE CV outcomes study exposure

There were 17160 subjects randomised in the DECLARE cardiovascular (CV) outcomes study, of whom 8574 were treated with dapagliflozin. Summary of exposure is presented in Table II-3 and Table II-4.

Table II-3 Extent of Exposure Summary for Study D1693C00001 DECLARE, Safety Population

	DAPA TOTAL (N = 8574)			ALL CONTROL (N = 8569)		
Duration of exposure (months)	**# of subjects entering interval**	**Patient-years within interval [a]**	**Cumulative patient-years (0-end of interval) [b]**	**# of subjects entering Interval**	**Patient-years within interval [a]**	**Cumulative patient-years (0-end of interval) [b]**
0 to ≤3	8574	2091.1	2091.1	8569	2092.8	2092.8
4 to ≤6	8394	2050.5	4141.6	8410	2048.4	4141.2
7 to ≤9	8236	2000.1	6141.7	8214	1989.4	6130.6
10 to ≤12	8042	1966.7	8108.4	7978	1948.6	8079.2
13 to ≤15	7903	1922.3	10030.7	7814	1896.2	9975.4
16 to ≤18	7735	1890.3	11921.0	7620	1860.6	11836.0
19 to ≤21	7611	1856.8	13777.8	7474	1819.0	13655.0
22 to ≤24	7475	1828.8	15606.6	7315	1788.0	15443.0
25 to ≤27	7359	1795.1	17401.7	7178	1742.7	17185.7
28 to ≤30	7225	1770.1	19171.8	7005	1709.2	18894.9
31 to ≤36	7121	3444.2	22616.0	6855	3297.7	22192.6
37 to ≤42	6878	3231.3	25847.3	6556	3071.8	25264.4
43 to ≤48	6300	2794.4	28641.7	5984	2640.6	27905.0
49 to ≤54	4413	1330.5	29972.2	4119	1224.7	29129.7
55 to ≤60	1173	207.0	30179.2	1075	187.7	29317.4
>60	38	1.2	30180.4	37	1.6	29319.0

The counts include all subjects who received at least one dose of study drug. Duration of exposure in months where month is defined as 30 days.

[a] Patient-years Within Interval is the sum over the subjects exposure within the interval to study medication expressed in years where subject exposure within interval is the Last dosing date in interval - First dosing date in interval plus 1 day.

[b] Cumulative Patient-years: 0 - End of Interval is the sum over the subjects exposure from day 1 of dosing through the end of the interval to study medication expressed in years, where cumulative subject exposure to end of interval is last dosing date in Interval - First dosing date plus 1 day. N is the number of treated subjects.

Table II-4 Demographic Characteristics Summary, Cumulative Subject Exposure by Age, Sex, and Race for D1693C00001 DECLARE, Randomised Subjects

	DAPA TOTAL (N=8582)	ALL CONTROL (N=8578)
Age range (years) (%)		
18 – 64 years	4677 (54.5)	4681 (54.6)
≥65 years	3905 (45.5)	3897 (45.4)
Total	**8582**	**8578**
Male (%)		
18-64	3176 (37.0)	3080 (35.9)
≥65 years	2235 (26.0)	2247 (26.2)
Total	**5411**	**5327**
Female (%)		
18-64	1501 (17.5)	1601 (18.7)
≥65 years	1670 (19.5)	1650 (19.2)
Total	**3171**	**3251**
Racial group (%)		
White	6843 (79.7)	6810 (79.4)
Black or African-American	295 (3.4)	308 (3.6)
Asian	1148 (13.4)	1155 (13.5)
Other	296 (3.4)	305 (3.6)
Total	**8582**	**8578**

The race subgroup of other includes subjects with reported race of American Indian/Alaska Native; Native Hawaiian/Other Pacific Islander; or Other.

Overall exposure in the adult T2DM clinical programme

The safety and tolerability of dapagliflozin were thoroughly documented and evaluated in the original submission for approval of dapagliflozin for treatment of T2DM, which has been supplemented over time with updated information on the safety and tolerability of dapagliflozin.

The cumulative duration of exposure for randomised subjects from development international birth date to 04 October 2018 is 37428 patient-years for dapagliflozin-treated subjects

(N=16936) and 33666 patient-years for control subjects (N=13503), as presented in Table II-5.

Cumulative summary tabulation of dapagliflozin exposure by age/sex and by racial group from the completed Phase II/III/IV clinical studies in subjects with T2DM is presented in Table II-6.

Table II-5 Extent of Exposure Summary for Phase I/IIb/III/IV Studies – Short-term Plus Long-term Treatment Period Including Data After Rescue – T2DM Treated Subjects, Safety Population

	DAPA TOTAL (N=16936)			ALL CONTROL (N=13503)		
Duration of exposure (months)	**# of subjects entering interval**	**Patient-years within interval[a]**	**Cumulative patient-years (0-End of interval)[b]**	**# of subjects entering interval**	**Patient-years within interval[a]**	**Cumulative patient-years (0-end of interval) [b]**
0 to ≤3	16936	4040.1	4040.1	13503	3237.0	3237.0
4 to ≤6	14827	3460.4	7500.5	12233	2903.4	6140.4
7 to ≤9	12181	2948.7	10449.2	10703	2583.0	8723.4
10 to ≤12	11814	2824.8	13274.0	10320	2483.9	11207.3
13 to ≤15	10580	2393.7	15667.7	9539	2150.8	13358.1
16 to ≤18	9560	2326.0	17993.7	8587	2084.4	15442.5
19 to ≤21	9336	2269.7	20263.4	8352	2026.4	17468.9
22 to ≤24	9108	2208.4	22471.8	8137	1980.3	19449.2
25 to ≤27	8373	1865.2	24337.0	7774	1798.8	21248.0
28 to ≤30	7425	1818.5	26155.5	7188	1753.9	23001.9
31 to ≤36	7316	3536.1	29691.6	7034	3382.7	26384.6
37 to ≤42	7059	3316.0	33007.6	6722	3148.2	29532.8
43 to ≤48	6465	2874.4	35882.0	6133	2712.3	32245.1
49 to ≤54	4571	1337.7	37219.7	4257	1231.3	33476.4
55 to ≤60	1173	207.0	37426.7	1075	187.7	33664.1
> 60	38	1.2	37427.9	37	1.6	33665.7

The counts include all subjects who received at least one dose of study drug in completed studies. Duration of exposure in months where month is defined as 30 days.

[a] Patient-years within interval is the sum over the subjects exposure within the interval to study medication expressed in years where subject exposure within interval is the Last dosing date in interval - First dosing date in interval plus 1 day.

[b] Cumulative Patient-years: 0 - end of interval is the sum over the subjects exposure from day 1 of dosing through the end of the interval to study medication expressed in years, where cumulative subject exposure to end of interval is last dosing date in Interval - First dosing date plus 1 day.
N is the number of treated subjects.

Table II-6 Estimated Cumulative Subject Exposure to Dapagliflozin From Completed Clinical Trials in Subjects with T2DM by Age and Sex, Randomised Subjects

	DAPA TOTAL (N=16966)	ALL CONTROL (N=13523)
Age range (years)		
<18 years	24 (0.1)	0
18 – 64 years	11128 (65.6)	8262 (61.1)
≥65 years	5814 (34.3)	5261 (38.9)
Total	**16966**	**13523**
Male		
<18 years	9 (<0.1)	0
18-64	6640 (39.1)	5108 (37.8)
≥65 years	3305 (19.5)	3016 (22.3)
Total	**9954**	**8124**
Female		
<18 years	15 (<0.1)	0
18-64	4488 (26.5)	3154 (23.3)
≥65 years	2509 (14.8)	2245 (16.6)
Total	**7012**	**5399**
Racial group		
White	12766 (75.2)	10384 (76.8)
Black or African-American	625 (3.7)	507 (3.7)
Asian	3065 (18.1)	2184 (16.2)
Other	510 (3.0)	448 (3.3)
Total	**16966**	**13523**

The counts include all subjects randomised in completed studies as of 04 October 2018.

The race subgroup of other includes subjects with reported race of American Indian/Alaska Native; Native Hawaiian/Other Pacific Islander; or Other.

II.3.3 Subjects with T2DM aged 10 years and above

D1690C00017 study exposure

Extent of exposure during the 24-week double-blind short-term period

There were 72 paediatric subjects randomised in the D1690C00017 study, of whom 39 were treated with dapagliflozin. Summary of exposure is presented in Table II-7 and Table II-8.

Table II-7 Duration of Exposure During the 24-week Double-blind Short-term Period Regardless Rescue Medication Initiation (Treated Subjects Set)

		Dapagliflozin 10mg (N=39)	Placebo (N=33)
Duration of exposure (days)	Mean (SD)	156.0 (37.7)	141.3 (55.3)
	Median	168.0	168.0
	Min, Max	9, 179	7, 202
	1st quartile, 3rd quartile	167.0, 171.0	141.0, 174.0
	Total treatment days	6084	4664
Duration of exposure (patient-year)	Total patient-years	16.7	12.8
Duration of exposure category (days) n (%)	1-7	0	1 (3.0)
	8-14	2 (5.1)	0
	15-28	0	3 (9.1)
	29-42	0	1 (3.0)
	43-56	0	0
	57-70	0	0
	71-84	0	0
	85-98	0	1 (3.0)
	99-140	4 (10.3)	2 (6.1)
	141-182	33 (84.6)	24 (72.7)
	>182	0	1 (3.0)

Percentage is using number of patients from the treated patients set in the treatment group as denominator.

Duration of exposure expressed in patient-year is calculated as sum of exposure duration (days) for each patient divided by 365.25.

Max maximum; Min minimum; N number of patients in treatment group; n number of patients in category or analysis; SD standard deviation.

Table II-8 Demographic Characteristics (Full Analysis Subject Set)

Demographic characteristic		Dapagliflozin 10mg (N=39)	Placebo (N=33)	Total (N=72)
Age (years)	Mean (SD)	16.1 (3.3)	16.2 (3.6)	16.1 (3.4)

Table II-8 Demographic Characteristics (Full Analysis Subject Set)

Demographic characteristic		Dapagliflozin 10mg (N=39)	Placebo (N=33)	Total (N=72)
	Median	16.0	16.0	16.0
	Min, Max	11, 23	11, 24	11, 24
Age group (years) n (%)	≥10 and ≤15	16 (41.0)	14 (42.4)	30 (41.7)
	>15 and <18	13 (33.3)	10 (30.3)	23 (31.9)
	≥18 and <25	10 (25.6)	9 (27.3)	19 (26.4)
	Total	39 (100)	33 (100)	72 (100)
Sex n (%)	Male	15 (38.5)	14 (42.4)	29 (40.3)
	Female	24 (61.5)	19 (57.6)	43 (59.7)
	Total	39 (100)	33 (100)	72 (100)
Race n (%)	White	28 (71.8)	16 (48.5)	44 (61.1)
	Black or African American	8 (20.5)	10 (30.3)	18 (25.0)
	Asian	0	1 (3.0)	1 (1.4)
	Native Hawaiian or other Pacific Islander	1 (2.6)	0	1 (1.4)
	American Indian or Alaska Native	2 (5.1)	3 (9.1)	5 (6.9)
	Other	0	3 (9.1)	3 (4.2)
	Total	39 (100)	33 (100)	72 (100)
Ethnic group n (%)	Hispanic or Latino	12 (30.8)	12 (36.4)	24 (33.3)
	Not Hispanic or Latino	26 (66.7)	21 (63.6)	47 (65.3)
	Total	38 (97.4)	33 (100)	71 (98.6)
Geographic Region n (%)	North America	16 (41.0)	16 (48.5)	32 (44.4)
	Latin America	7 (17.9)	9 (27.3)	16 (22.2)
	Europe	16 (41.0)	8 (24.2)	24 (33.3)
	Asia/Pacific	0	0	0
	Total	39 (100)	33 (100)	72 (100)
Country n (%)	Hungary	2 (5.1)	0	2 (2.8)
	Israel	8 (20.5)	5 (15.2)	13 (18.1)
	Mexico	7 (17.9)	9 (27.3)	16 (22.2)
	Russia	6 (15.4)	3 (9.1)	9 (12.5)

Table II-8 Demographic Characteristics (Full Analysis Subject Set)

Demographic characteristic		Dapagliflozin 10mg (N=39)	Placebo (N=33)	Total (N=72)
	United States	16 (41.0)	16 (48.5)	32 (44.4)
	Total	39 (100)	33 (100)	72 (100)

Percentage is using the number of patients from the FAS in the treatment group as denominator.

Max maximum; Min minimum; N number of patients in treatment group; n number of patients in category or analysis; SD standard deviation.

Extent of exposure during the 52-week short-term plus long-term period

The mean (SD) duration of exposure in the dapagliflozin/dapagliflozin group was 308.4 (107.8) days, with a total duration of exposure of 32.9 patient-years.

In the placebo/dapagliflozin group, in which patients switched from double-blind placebo to open-label dapagliflozin, the overall mean (SD) duration of exposure was 284.9 (139.0) days, with a total duration of exposure of 25.7 patient-years. This included exposure to dapagliflozin 10 mg during the open-label (LT) period. During LT the mean (SD) duration of exposure to dapagliflozin 10 mg was 188.1 (40.6) days, with a total duration of exposure of 12.9 patient-years.

Overall, the duration of exposure to dapagliflozin 10 mg was 45.8 patient-years, which is considered as adequate for the evaluation of safety during the ST + LT treatment period in this study.

D1690C00016 study exposure (Paediatric PK/PD study)

A total of 24 patients were administered a single oral dose of dapagliflozin: 8 patients each received 2.5, 5, or 10 mg. All subjects completed the study except 1 patient who discontinued from the study on Day 2 due to personal circumstances after receiving dapagliflozin 2.5 mg on Day 1.

The 24 treated patients with T2DM in Study D1690C00016 were predominantly white or black, with a mean age of 14.5 years (range 11 to 17 years). Per protocol requirement, at least 3 males and 3 females were dosed in each dose group and the 10 to 15 (years) age group and the 16 to 17 (years) age group each included at least 3 patients in each dose group.

II.3.4 Patients with Chronic Kidney Disease (CKD)

D169AC00001 DAPA-CKD outcomes study exposure

There were 4304 subjects randomised in the DAPA-CKD outcomes study, of whom 2152 were treated with dapagliflozin. A summary of the exposure is presented in Table II-9 and Table II-10.

Table II-9 Extent of Exposure Summary for Study D169AC00001 DAPA-CKD, Safety Population

	DAPA TOTAL (N = 2149)			PLACEBO (N = 2149)		
Duration of exposure (months)	**# of subjects entering interval**	**Patient-years within interval [a]**	**Cumulative patient-years (0-end of interval) [b]**	**# of subjects entering Interval**	**Patient-years within interval [a]**	**Cumulative patient-years (0-end of interval) [b]**
0 to ≤ 3	2149	518.4	518.4	2149	518.4	518.4
4 to ≤ 6	2059	490.6	1009.0	2055	487.4	1005.8
7 to ≤ 9	1946	475.2	1484.2	1932	470.3	1476.1
10 to ≤ 12	1906	464.0	1948.2	1876	456.5	1932.6
13 to ≤ 15	1863	452.4	2400.6	1827	443.3	2375.9
16 to ≤ 18	1822	443.1	2843.7	1778	435.2	2811.1
19 to ≤ 21	1772	428.4	3272.1	1745	420.1	3231.2
22 to ≤ 24	1692	388.8	3660.9	1654	379.8	3611.0
25 to ≤ 27	1415	314.0	3974.9	1357	299.0	3910.0
28 to ≤ 30	1125	228.3	4203.2	1071	217.8	4127.8
31 to ≤ 36	726	174.7	4377.9	700	164.0	4291.8
37 to ≤ 42	79	6.0	4383.9	64	4.3	4296.1

The counts include all subjects who received at least one dose of study drug. Duration of exposure in months where month is defined as 30 days.

[a] Patient-years Within Interval is the sum over the subject exposure within the interval to study medication expressed in years where subject exposure within interval is the Last dosing date in interval - First dosing date in interval plus 1 day.

[b] Cumulative Patient-years: 0 - End of Interval is the sum over the subject exposure from day 1 of dosing through the end of the interval to study medication expressed in years, where cumulative subject exposure to end of interval is last dosing date in Interval - First dosing date plus 1 day. N is the number of treated subjects.

Table II-10 Demographic Characteristics Summary, Cumulative Subject Exposure by Age, Sex, and Race for D169AC00001 DAPA-CKD, Randomised Subjects

	DAPA 10mg (N=2152)	PLACEBO (N=2152)	Total (N=4304)
Age (years)			
n	2152	2152	4304
Mean	61.8	61.9	61.8
SD	12.1	12.1	12.1

Table II-10 Demographic Characteristics Summary, Cumulative Subject Exposure by Age, Sex, and Race for D169AC00001 DAPA-CKD, Randomised Subjects

	DAPA 10mg (N=2152)	PLACEBO (N=2152)	Total (N=4304)
Median	63.0	64.0	63.0
Min	23	18	18
Max	93	91	93
Age range (years) (%)			
18 – 64 years	1170 (54.4)	1141 (53.0)	2311 (53.7)
≥65 years	982 (45.6)	1011 (47.0)	1993 (46.3)
Total	2152	2152	4304
Sex n (%)			
Male	1443 (67.1)	1436 (66.7)	2879 (66.9)
Female	709 (32.9)	716 (33.3)	1425 (33.1)
Total	2152	2152	4304
Male (%)			
18-64	768 (35.7)	768 (35.7)	1536 (35.7)
≥65 years	675 (31.4)	668 (31.0)	1343 (31.2)
Total	1443	1436	2879
Female (%)			
18-64	402 (18.7)	373 (17.3)	775 (18.0)
≥65 years	307 (14.3)	343 (15.9)	650 (15.1)
Total	709	716	1425
Racial group (%)			
White	1124 (52.2)	1166 (54.2)	2290 (53.2)
Black or African-American	104 (4.8)	87 (4.0)	191 (4.4)
Asian	749 (34.8)	718 (33.4)	1467 (34.1)
Other	175 (8.1)	181 (8.4)	356 (8.3)
Total	2152	2152	4304

The race subgroup of other includes subjects with reported race of American Indian/Alaska Native; Native Hawaiian/Other Pacific Islander; or Other.

II.3.5 Subjects with T1DM

Although FORXIGA/EDISTRIDE is no longer indicated for use in T1DM, the exposure data in this patient population remain relevant for the characterisation of the safety concern 'Diabetic Ketoacidosis including events with atypical presentation'.

Since patients with T1DM are completely dependent on exogenous insulin, there is a higher background risk of DKA in these patients, as DKA is often precipitated by omissions of or inadequate insulin doses.

There were 1797 subjects randomised in the T1DM Phase III studies, of whom 1265 were treated with dapagliflozin. A total of 1155 subjects completed 24 weeks of treatment with dapagliflozin and 562 subjects were treated with dapagliflozin for > 360 days, for a cumulative exposure to dapagliflozin of 906.8 patient-years.

Of the 1265 subjects in T1DM Phase III studies, 1114 were from placebo-controlled studies MB102229 and MB102230 and were included in the T1DM short-term (ST) placebo-controlled Phase III pool. Summary exposure data for the T1DM ST placebo-controlled Phase III pool are presented in Table II-11 to Table II-13.

Table II-11 Duration of Exposure – T1DM ST Placebo-Controlled Phase III Pool

	Number of subjects (%)[a]	
Duration of exposure (days)	**DAPA 5 MG + INS (N=548)**	**DAPA 10 MG + INS (N=566)**
1-7	3 (0.5)	3 (0.5)
8-30	10 (1.8)	6 (1.1)
31-60	9 (1.6)	8 (1.4)
61-90	12 (2.2)	11 (1.9)
91-120	4 (0.7)	8 (1.4)
121-180	491 (89.6)	505 (89.2)
>180	19 (3.5)	25 (4.4)
Cumulative Exposure (Patient-Years)	**241.6**	**252.3**

[a] ST placebo-controlled Phase III pool (safety analysis set).

Table II-12 Age Group and Sex – T1DM

	Number of subjects T1DM[a]
Age	
<18 years	0
Adults (18 – 64 years)	1057
Elderly (≥65 years)	57
Sex	
Male	510
Female	604

[a] ST placebo-controlled Phase III pool (all doses).

Table II-13 Racial Origin – T1DM

Racial group	Number of subjects T1DM[a]
Asian	103
Black or African-American	23
White	975
Other	13
Total	1114

[a] ST placebo-controlled Phase III pool (all doses).

II.4 MODULE SIV: POPULATIONS NOT STUDIED IN CLINICAL TRIALS

II.4.1 Exclusion Criteria in pivotal clinical studies within the development programme

Severe hepatic insufficiency and/or significant abnormal liver function

Reason for exclusion: Patients were excluded in order to avoid factors that may confound a complete understanding of the safety and efficacy data of dapagliflozin and to ensure interpretability of data.

Is it considered to be included as missing information: No

Rationale: There is scientific evidence to indicate that the safety profile of patients with severe hepatic insufficiency and/or significant abnormal liver function will not be different than that of the general target population. In the Phase 1 single-dose study of the pharmacokinetics and safety of dapagliflozin 10 mg (MB102027), adult subjects with hepatic insufficiency conforming to Child-Pugh classification A, B or C were compared with healthy subjects. Twenty-four subjects received dapagliflozin; 6 subjects for each of the hepatic function groups (normal healthy, and Child-Pugh Classes A, B and C). There were no differences in the protein binding of dapagliflozin between hepatic impairment groups or compared to healthy subjects. In patients with mild or moderate hepatic impairment, mean C_{max} and area under the curve (AUC) of dapagliflozin were up to 12% and 36% higher, respectively, compared with healthy matched control subjects. These differences were not considered to be clinically meaningful and no dose adjustment from the proposed usual dose of 10 mg once daily for dapagliflozin is proposed for these populations. In patients with severe hepatic impairment (Child-Pugh class C), mean C_{max} and AUC of dapagliflozin were up to 40% and 67% higher than matched healthy controls, respectively.

Severe renal impairment

Reason for exclusion: The glucosuric efficacy of dapagliflozin is dependent on renal function. Patients were excluded in order to avoid factors that may confound a complete understanding of the safety and efficacy data of dapagliflozin and to ensure interpretability of data. For studies in CKD this exclusion criteria was not applied.

Is it considered to be included as missing information: No

Rationale: The DAPA-CKD outcomes study has provided evidence of beneficial use in this population. Since the glucose lowering effect of Dapagliflozin is dependent on renal function, the label (SmPC section 4.2) includes advice to consider use of additional glucose lowering treatment in patients with diabetes mellitus and eGRF below 45.

History of unstable or rapidly progressing renal disease

Reason for exclusion: Patients were excluded in order to avoid factors that may confound a complete understanding of the safety and efficacy data of dapagliflozin and to ensure interpretability of data. For studies in CKD this exclusion criteria was not applied.

Is it considered to be included as missing information: No

Rationale: DAPA-CKD outcomes study has provided evidence of beneficial use in this population. The label (SmPC Section 4.2) includes advice to consider use of additional glucose lowering treatment in patients with diabetes mellitus and eGRF below 45.

Volume depletion (Patients who, in the judgment of the investigator, might have been at risk for dehydration)

Reason for exclusion: In the original dapagliflozin clinical programme, patients were excluded in order to avoid factors that may confound a complete understanding of the safety and efficacy data of dapagliflozin and to ensure interpretability of data.

Is it considered to be included as missing information: No

Rationale: In the DECLARE CV outcomes study, T2DM patients were evaluated over a mean exposure to study drug of 48 months in 17143 patients. In this large study, where volume depletion was not an exclusion criterion, the numbers of patients with adverse events (AEs) suggestive of volume depletion were balanced between treatment groups and there was no evidence of an increased risk of AEs suggestive of volume depletion, including serious events, with dapagliflozin treatment. There was no imbalance in events of volume depletion in elderly patients, patients on loop diuretic or angiotensin-converting-enzyme inhibitor/angiotensin receptor blocker (ACEi/ARBs). This population is therefore not relevant for consideration as missing information.

Congestive heart failure defined as New York Heart Association (NYHA) class III or IV, and/or left ventricular ejection fraction of ≤ 40%

Reason for exclusion: In the original dapagliflozin clinical programme patients were excluded in order to avoid factors that may confound a complete understanding of the safety and efficacy data of dapagliflozin and to ensure interpretability of data.

Is it considered to be included as missing information: Yes (NYHA class IV only)

DAPA-HF, DETERMINE-preserved, DETERMINE-reduced and DELIVER studies included in total 11824 patients. Of these, 3168 patients were in NYHA class III and 62 patients were in NYHA class IV.

II.4.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programmes are unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged exposure.

II.4.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Exposure of special populations from completed clinical studies in subjects known to be exposed to dapagliflozin in the clinical development programmes is presented in Table II-14.

Table II-14 Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

	T1DM[a]	T2DM[b]
Type of special population	**Exposure**	
Pregnant women	Not included in the clinical development programme	
Breast-feeding women	Not included in the clinical development programme	
Renal impairment (GFR [mL/min/1.73 m^2])		
<30	0	9
30 - <60	35	668
60 - <90	515	3113
Hepatic impairment (Child Pugh's A, B, C)	0	18

[a] ST placebo-controlled Phase III pool (all doses).

[b] All Phase 2b/3 pool, 30-MSU integrated safety database (all doses).

II.5 MODULE SV: POST-AUTHORISATION EXPERIENCE

II.5.1 Method used to calculate exposure

The post-marketing patient exposure data presented here is based on dapagliflozin monthly actual ex-factory sales volume from each local affiliate. These data represent all dapagliflozin formulations delivered to various distribution channels (eg, wholesalers, pharmacies, etc) worldwide.

The sales volume is provided as the number of tablets distributed. The estimated post-marketing patient exposure data is an approximation based on the assumption that each patient took 1 tablet (5 or 10 mg) once daily. The exposure is expressed in patient-years and is calculated by dividing the number of distributed daily doses by 365 days.

More detailed patient-level data (e.g., gender, ethnicity, age category, off-label use, specific populations etc) are not available.

II.5.2 Exposure

The regional cumulative sales figures are presented by patient-years in Table II-15.

Table II-15 Dapagliflozin Sales Quantity by Region

Region	Estimated exposure (patient-years)[a]
Europe	7297759
North America	4411805
Japan	2825063
Rest of the World	20451578

[a] Cumulative exposure as of March 31st 2023, ref: dapagliflozin PBRER April 4th 2023.

The completed Observational Single-cohort Data Base Study of Dapagliflozin Utilisation in Europe (MB102134/D1690R00006) was conducted to describe the characteristics of European patients using dapagliflozin in routine clinical practice in Europe, with the main objective being to identify and enumerate patients who were prescribed dapagliflozin outside of the recommendations in the approved EU label. The study took place in a primary care setting and included patients newly prescribed dapagliflozin between January 2013 and December 2015 (Germany) or June 2016 (United Kingdom and Spain) by age, sex, dapagliflozin dose, country, selected co-morbidities, and selected concomitant medications. The final results on exposure are presented in Table II-16.

Table II-16 Exposure by Age Group and Sex at Inclusion in the Dapagliflozin Utilisation Study in Europe (MB102134/D1690R00006)

	Number of patients (%)[a]		
	United Kingdom n=8409	**Germany n=1715**	**Spain N=1692**
Age group (years)			
<45	837 (10.0%)	69 (4.1%)	103 (6.1%)
45 to 59	3413 (40.6%)	426 (25.3%)	514 (30.5%)
60 to 74	3709 (44.1%)	884 (52.4%)	917 (54.3%)
>75	450 (5.4%)	308 (18.3%)	154 (9.1%)
Missing	0	28	4
Sex			
Male	4875 (58.0%)	979 (57.2%)	968 (57.6%)
Female	3532 (42.0%)	734 (42.8%)	713 (42.4%)
Missing	2	2	11

[a] Percentages are of non-missing values

II.6 MODULE SVI: ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

The potential for drug abuse for dapagliflozin has not been studied. Based on its pharmacological properties, dapagliflozin is not likely to have a potential for drug abuse and no findings during the clinical programme indicate a risk for abuse, dependence, or misuse for illegal purposes.

II.7 MODULE SVII: IDENTIFIED AND POTENTIAL RISKS

II.7.1 Identification of safety concerns in the initial RMP submission

Not applicable.

II.7.2 New safety concerns and reclassification with a submission of an updated RMP

II.7.2.1 New safety concerns

Not applicable.

II.7.2.2 Reclassification of safety concerns

AstraZeneca has revised the list of safety concerns following the results from a meta-analysis of lower limb amputation data. As a result, the following safety concern (important potential risk) for dapagliflozin is removed from the list of safety concerns.

A summary of the rationale for the removal of the risk is presented below.

Important potential risk: Lower limb amputation

The risk of lower limb amputation previously categorised as an important potential risk is removed from the list of safety concerns.

Increased rates of lower limb amputations were observed in patients treated with the SGLT2 inhibitor canagliflozin in the CANVAS Program (Neal et al 2017). However, no increased risk of lower-limb amputations has been observed in the overall dapagliflozin clinical development programme or in the CREDENCE study for canagliflozin **(**Perkovic et al 2019**)** or in the empagliflozin clinical development programme, including the EMPA-REG, EMPEROR-REDUCED, and EMPEROR-PRESERVED studies (Inzucchi et al 2018, Packer et al 2020, Anker et al 2021**).**

Spontaneous cases of lower limb amputation have been reported for dapagliflozin. In a majority of the reports, there were limited and/or insufficient information with regard to

medical history, concurrent diseases or potential risk factors for amputation including diabetic foot, peripheral vascular diseases, peripheral neuropathy diseases, or infection.

Based on the European Commission decision (EMA/118223/2017) on 20 April 2017, the EU RMPs of dapagliflozin-containing products were updated to include Lower limb amputation as an important potential risk. AstraZeneca was requested to conduct a meta-analysis across studies D1690C00018, D1690C00019, and D1693C00001 (DECLARE). The results of this initial meta-analysis was submitted to the PRAC on 17 December 2019 with procedure EMEA/H/C/002322/WS/1742 (EU RMP version 19).

The current meta-analysis extends the initial meta-analysis by including results from 3 additional long-term studies: D1699C00001 (DAPA-HF), D169AC00001 (DAPA-CKD), and D169CC00001 (DELIVER). Studies D169EC00001 (DETERMINE-Preserved) and D169EC00002 (DETERMINE-Reduced) were also part of the amputation PASS commitment but are not included in the current meta-analysis because these were short-term studies (follow-up period of 16 weeks). No amputation events were reported in these short-term studies.

The pooled meta-analysis population included 34317 patients, 17159 in the dapagliflozin 10 mg group and 17158 in the placebo group. DECLARE contributed 17143 patients, Study D1690C00018 contributed 922 patients, Study D1690C00019 contributed 965 patients, DAPA-HF contributed 4736 patients, DAPA-CKD contributed 4298 patients, and DELIVER contributed 6253 patients.

Patients with T2DM are known to be at much higher risk of amputations than those without diabetes (Johannesson et al 2009) and this was also observed in DAPA-HF, DAPA-CKD, and DELIVER, which included patients both with and without T2DM. For this reason, the primary objectives were to evaluate lower limb amputations and relevant preceding AEs[1] both overall and by diabetes status, whereas the secondary and exploratory variables focused on patients with T2DM.

In the overall pooled meta-analysis population of 34317 patients there were 90810 patient-years of exposure, of which 45905 patient-years of exposure were to dapagliflozin. The median duration of exposure to study drug was 30.8 months. Median duration of exposure was balanced between treatment groups.

Patient characteristics were generally balanced between the treatment groups. Mean age was 65.4 years and 16.2% of patients were aged ≥ 75 years. A majority of patients were male

[1] Relevant preceding events were identified based on a predefined list of PTs from EMA Pharmacovigilance Risk Assessment Committee (PRAC) (Article 20 referral EMA/PRAC/637349/2016)

(64.1%), and white (73.9%). Mean eGFR was 72.3 mL/min/1.73 m^2. At randomisation, approximately 33% of patients had eGFR < 60 mL/min/1.73 m^2 and approximately 15% had eGFR < 45 mL/min/1.73 m^2.

A majority of the patients had a history of established CVD. The remainder were at risk for CVD (either patients with T2DM with multiple risk factors for CVD in DECLARE or patients with CKD at risk for CVD in DAPA-CKD since CKD is a risk factor for CVD). A total of 7.1% of patients had a history of PAD while 1.3% had a history of amputation. At baseline, 59.3% and 34.7% of patients were taking diuretics or loop diuretics, respectively.

In the pooled T2DM population of 26870 patients, there were 77304 patient-years of exposure, of which 39171 patient-years of exposure were to dapagliflozin. Median duration of exposure was balanced between treatment groups. Median duration of T2DM was 10 years, with 74.9% of patients having a duration > 5 years. Baseline patient characteristics were generally balanced between the treatment groups.

In the pooled population of 7447 patients without diabetes, there were 13505 patient-years of exposure, of which 6733 patient-years of exposure were to dapagliflozin. Median duration of exposure was balanced between treatment groups. Baseline patient characteristics were generally balanced between the treatment groups.

In the overall population, there were 163 and 157 patients with lower limb amputations in the dapagliflozin and placebo groups, respectively, corresponding to event rates of 3.5 and 3.5 per 1000 patient-years: HR 1.03 (95% CI 0.83, 1.28), p = 0.796. There were 1276 and 1216 patients with relevant preceding AEs in the dapagliflozin and placebo groups, respectively, corresponding to event rates of 28.8 and 28.0 per 1000 patient-years: HR 1.04 (95% CI 0.96, 1.12) p = 0.336.

As expected, most of the amputations occurred in patients with T2DM. Among patients with T2DM, there were 158 and 150 lower limb amputations in the dapagliflozin and placebo groups, respectively, corresponding to event rates of 4.0 and 3.9 per 1000 patient-years: HR 1.04 (95% CI 0.83, 1.30), p = 0.718. There were 1100 and 1062 patients with relevant preceding AEs in the dapagliflozin and placebo groups, respectively, corresponding to event rates of 29.2 and 28.8 per 1000 patient-years: HR 1.02 (95% CI 0.94, 1.11), p = 0.620.

Among patients without diabetes, there were 5 and 7 lower limb amputations in the dapagliflozin and placebo groups, respectively, corresponding to event rates of 0.7 and 1.0 per 1000 patient-years. There were 176 and 154 patients with relevant preceding AEs in the dapagliflozin and placebo groups, respectively, corresponding to event rates of 26.7 and 23.2 per 1000 patient-years: HR 1.15 (95% CI 0.93, 1.43), p = 0.195.

The results of the meta-analysis do not indicate any risk of lower limb amputation or relevant preceding AEs with dapagliflozin, either overall or by diabetes status.

Furthermore, there are no additional pharmacovigilance activities, additional RMMs or specific clinical measures in place for this risk.

Consequently, the risk of lower limb amputation is removed from the list of safety concerns.

II.7.3 Details of important identified risks, important potential risks and missing information

II.7.3.1 Presentation of important identified risks and important potential risks

Important Identified Risk: Diabetic Ketoacidosis including events with atypical presentation

The T1DM indication was approved in EU on 20 March 2019 (EURMP v16) and removed in 2021. The removal of the T1DM indication in EU was not due to any safety or efficacy concerns. In clinical studies, DKA occurred more frequently in T1DM patients than in T2DM patients, and was included as a common ADR in the SmPC for the T1DM indication. DKA was previously included in the EU-RMP as an important identified risk for the T1DM indication (as well as for the T2DM indication) and aRMM were implemented for T1DM. These aRMM are now removed. The potential for off-label use of FORXIGA for the treatment of T1DM patients cannot be excluded since the product was previously approved in this indication. Guidance is provided in the SmPC (section 4.4).

General information on DKA is included in the SmPC (section 4.4), e.g. regarding cases with atypical presentation (with only moderately increased blood glucose values) and guidance regarding treatment when DKA is suspected.

Potential mechanisms: Unknown.

Evidence source(s) and strength of evidence:

There have been postmarketing reports of ketoacidosis, including DKA, in patients with T2DM taking dapagliflozin or other SGLT2 inhibitors.

In the DECLARE CV outcomes study, events adjudicated as DKA were rare overall. There were more patients with events of adjudicated DKA in the dapagliflozin group compared with the placebo group. In the DAPA-HF, DAPA-CKD and DELIVER studies events of DKA were rare in the T2DM population, and there were no events of ketoacidosis reported in the non-diabetic population.

In clinical studies with T1DM, there was a higher number of diabetic ketoacidosis (DKA) in the dapagliflozin-treated patients compared to placebo.

Characterisation of the risk: SGLT2 inhibitors reduce blood glucose independent of insulin and may result in diabetic patients presenting with DKA and near-normal glucose values.

In the T2DM ST placebo-controlled pool, the search for potential events of ketoacidosis identified 4 events (0.07%) in subjects treated with dapagliflozin versus none in the placebo group. Of these events, there was 1 SAE of DKA, 1 non-serious AE of metabolic acidosis, and 2 non-serious AEs of ketonuria. In addition, 1 SAE of metabolic acidosis occurred in a subject after discontinuation of study drug as per protocol (20 days after last dose of study drug). From postmarketing use, there are cases reported with near-normal glucose values.

In the DECLARE CV outcomes study, there were more patients with events of adjudicated DKA in the dapagliflozin group compared with the placebo group: 27 (0.3%) and 12 (0.1%), respectively. The DKA events were evenly distributed over the study period. Precipitating factors for DKA were as expected in a T2DM population. The most common contributing factors were similar between treatment groups (e.g., illness/severe illness, infection, changed or missed insulin dose or underdose of insulin, and poor intake of food and/or drink). The most common signs and symptoms were similar between treatment groups, e.g., abdominal pain, confusion, fatigue, fever sign, frequent urination, thirst, fruity scented breath, loss of consciousness, nausea, malaise, vomiting, shortness of breath, weakness. Most patients in the dapagliflozin group had concomitant insulin treatment at the time of the DKA event (22 of 27 patients), and all patients in the placebo group. Three patients in the dapagliflozin group with DKA had T1DM, and none in the placebo group.

In the T1DM placebo-controlled Phase III pool, subjects were advised to monitor blood ketones in case of suspected symptoms of DKA and seek medical advice/attention if their self-measured blood ketone reading was ≥ 0.6 mmol/L. In the pooled 52-week data, events adjudicated as DKA were reported in 20 (3.5%) subjects in the dapagliflozin 5 mg group and 6 (1.1%) subjects in the placebo group. DKA events occurred evenly distributed over the clinical trial period. Inadequate insulin doses (missed insulin dose or insulin pump failure) were the most common precipitating factors. Seven of the 20 events of DKA in the dapagliflozin 10 mg group occurred in patients with blood glucose in the euglycemic range (< 14 mmol/l or 250 mg/dl). Subjects with DKA events responded to conventional treatment for DKA.

From postmarketing sources, the most frequently reported events by PT were Diabetic ketoacidosis, Ketoacidosis, Ketonuria, Urine ketone body present, Metabolic acidosis and Euglycaemic diabetic ketoacidosis. Isolated cases had a fatal outcome. The majority of these contained limited relevant information and the remaining contained different confounding factors.

AstraZeneca has conducted a retrospective epidemiology study looking at the incidence of DKA among patients with T2DM in the US (D1690R00013). Among patients with T2DM initiating a new medication or medication class, DKA events were rare: 310 events were identified in over 200000 person-years of exposure to ADs. Overall the DKA rate per 1000 PY was 1.4 (95% CI 1.2-1.6). The rates were similar when age-standardised to the European diabetes population and when limited to episodes where there was no prior diagnosis of DKA.

Risk factors and risk groups: Risk factors include post-operative episodes affecting insulin requirement/deficiency; dehydration and restricted oral glucose intake due to dieting (especially low carbohydrate diet); loss of appetite due to, eg, gastrointestinal infection, depression, or malaise; severe infections or other severe medical conditions such as myocardial infarction and stroke; and pancreatic insufficiencies due pancreatitis, cancer, or alcohol abuse.

Preventability: Awareness about the symptoms of ketoacidosis. Rare cases of DKA, including life-threatening and fatal cases, have been reported in patients treated with SGLT2 inhibitors, including dapagliflozin. In a number of cases, the presentation of the condition was atypical with only moderately increased blood glucose values, below 14 mmol/L (250 mg/dL). The risk of DKA must be considered in the event of non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue, or sleepiness. Patients should be assessed for ketoacidosis immediately if these symptoms occur, regardless of blood glucose level.

Guidance is provided in the SmPC (see Section V.1).

Impact on the benefit-risk balance of the product: Diabetic ketoacidosis is an acute, major, and potentially life-threatening event. The condition is a complex metabolic state generally characterised by hyperglycaemia, ketoacidosis, and ketonuria and is believed to be caused by an absolute lack of insulin.

Public health impact: As the impact is only to the treated population, there is no public health impact.

Important Potential Risk: Bladder cancer

Potential mechanisms: Unknown. No carcinogenicity risk was seen in the nonclinical programme. In 24-month rodent studies, dapagliflozin did not induce tumours or hyperplasia at any dose, despite exposure multiples up to 105x in mice and 186x in rats. Dapagliflozin has not been found to be genotoxic. SGLT2 receptors are not expressed in the urinary bladder.

Evidence source(s) and strength of evidence: No overall imbalance in cancer have been observed between dapagliflozin and placebo in randomised clinical trials. When examining tumours in different organ systems, the frequency of bladder cancer was higher in

dapagliflozin-treated patients than placebo-treated patients, but all patients had established risk factors for bladder cancer at baseline and no causality has been established. There are no carcinogenicity or mutagenicity signals for bladder cancer from the nonclinical data.

In the dapagliflozin clinical development programme, All Phase 2b/3 pool + D1693C00005 (n=6045 dapagliflozin-treated subjects, n=3512 placebo-treated subjects), there were 10 subjects reported with events of bladder cancer following treatment with dapagliflozin compared to 1 in the comparator group. All subjects with bladder cancer had established risk factors for bladder cancer at baseline.

Characterisation of the risk: The relative risk associated with dapagliflozin and bladder cancer was greater than 1 in randomised controlled trials but not considered statistically significant. There was a frequency of 0.2% (n=10) in the dapagliflozin-treated patients and 0.03 (n=1) in the comparator group.

With the exception of 1 subject, where histology data was not obtained, all tumours were of transitional cell type. Of the 10 dapagliflozin-treated subjects with bladder cancer, 8 had haematuria at baseline or within 6 months of starting the study, a strong indicator of pre-existing bladder cancer.

Furthermore, 8 of the 10 dapagliflozin-treated subjects were treated with background antidiabetic medications: insulin (3), metformin (2), metformin and SU (2), and pioglitazone (1). No geographic clustering of the events was observed. Time in the study at the time of diagnosis ranged from 43 to 727 days, with a median time to event of 393 days. This time to event for all bladder cancer events in the dapagliflozin programme is shorter than the latency time associated with carcinogen-induced bladder cancer.

From postmarketing sources, no events had a fatal outcome.

Risk factors and risk groups: Age, sex (male), smoking, chemical exposure to known carcinogens (cyclophosphamide and aniline dyes, etc), and haematuria.

Preventability: Unknown.

Impact on the risk-benefit balance of the product: Bladder cancer, if confirmed, would impact the benefit risk of dapagliflozin. Cases reported during dapagliflozin treatment are considered to be very rare (< 0.01%). However, further characterisation of this risk through additional pharmacovigilance will provide a better understanding of this risk and further define the impact on the benefit-risk of dapagliflozin.

Public health impact: As the potential impact is only to the treated population, there is no public health impact.

Important Potential Risk: Breast cancer

Potential mechanisms: Unknown. No carcinogenicity risk was seen in the nonclinical programme. In 24-month rodent studies, dapagliflozin did not induce tumours or hyperplasia at any dose, despite exposure multiples up to 105x in mice and 186x in rats. Dapagliflozin has not been found to be genotoxic. SGLT2 receptors are not expressed in breast tissue.

Evidence source(s) and strength of evidence: No overall imbalance in cancer have been observed between dapagliflozin and placebo in randomised clinical trials. When examining tumours in different organ systems, the frequency of breast cancer was higher in dapagliflozin-treated patients than placebo-treated patients, but no causality has been established. There are no carcinogenicity or mutagenicity signals for breast cancer from the nonclinical data.

Characterisation of the risk: The relative risk associated with dapagliflozin and breast cancer in females was greater than 1 in randomised controlled trials (All Phase 2b/3 pool) but not considered statistically significant. There was a frequency of 0.4% (n=12) in the dapagliflozin-treated subjects and 0.2% (n=3) in the comparator group.

All breast cancers detected during the dapagliflozin clinical programme occurred after <1-year exposure to dapagliflozin; 2 out of 9 cases were diagnosed within 6 weeks of dapagliflozin treatment initiation. The short duration of exposure to dapagliflozin in subjects with breast cancer argues against a causal relationship. Also, SGLT2 is not expressed in human breast tissue and in nonclinical toxicology studies dapagliflozin showed no evidence of carcinogenicity.

Very few cases of breast cancer have been reported from postmarketing sources. No cases have been reported with a fatal outcome. The information provided in the reports have been limited and inconclusive.

Risk factors and risk groups: Age, sex (female), smoking (now or ever), parity, use of exogenous oestrogen (i.e., hormone replacement therapy), BRCA1 or BRCA2 mutations, family history of breast cancer, breast tissue density, overweight/obesity.

Preventability: Unknown.

Impact on the risk-benefit balance of the product: Breast cancer, if confirmed, would impact the benefit risk of dapagliflozin. Cases reported during dapagliflozin treatment are considered to be very rare (<0.01%). However, further characterisation of this risk through additional pharmacovigilance will provide a better understanding of this risk and further define the impact on the benefit-risk of dapagliflozin.

Public health impact: As the impact is only to the treated population, there is no public health impact.

Important Potential Risk: Prostate cancer

Potential mechanisms: Not known

Evidence source(s) and strength of evidence: No overall imbalance in cancer has been observed between dapagliflozin and placebo in randomised clinical trials. When examining tumours in different organ systems, the frequency of prostate cancer was higher in dapagliflozin-treated patients than placebo-treated patients, but no causality has been established. There are no carcinogenicity or mutagenicity signals for prostate cancer from the nonclinical data.

Characterisation of the risk: In the All Phase 2/3b Pool (n=3243 dapagliflozin-treated male subjects, n=1964 placebo-treated male subjects), 11 (0.3%) subjects reported events of prostate cancer following treatment with dapagliflozin compared to 6 (0.3%) in the comparator group.

There were no deaths related to prostate cancer in the clinical trial programme (All Phase 2b/3 Pool).

Very few cases of prostate cancer have been reported from postmarketing sources. No cases have been reported with a fatal outcome. There have been no reports from postmarketing use with evidence of an increased risk of prostate cancer.

Risk factors and risk groups: Age, smoking.

Preventability: Unknown

Impact on the risk-benefit balance of the product: Prostate cancer, if confirmed, would impact the benefit-risk of dapagliflozin. Cases reported during dapagliflozin treatment are considered to be very rare (<0.01%). However, further characterisation of this risk through additional pharmacovigilance will provide a better understanding of this risk and further define the impact on the benefit-risk of dapagliflozin.

Public health impact: As the impact is only to the treated population, there is no public health impact.

II.7.3.2 Presentation of missing information

Use in patients with NYHA class IV

Evidence source: Use in patients with NYHA class IV is missing information as there is insufficient evidence to determine if the safety profile in this population is different to that of the general target population.

The DAPA-HF study included 4744 patients with heart failure, of which 43 patients (20 received dapagliflozin and 23 received placebo) had NYHA class IV. Although the results from subgroup analysis by NYHA class were similar between treatment groups across NYHA classes with regard to serious adverse events, events suggestive of volume depletion, renal events and fractures, and consistent with the overall population, the limited number of patients means there is insufficient evidence to conclude that the safety profile of this population is different to that of the general target population receiving dapagliflozin.

The SmPC Section 4.4 includes a statement that experience in clinical studies with dapagliflozin in NYHA class IV is limited.

Population in need of further characterisation: Routine pharmacovigilance alone is appropriate as further characterisation through additional pharmacovigilance activities are neither feasible or warranted.

Long-term safety in the paediatric population (aged 10 years and above)

Evidence source: The paediatric clinical study D1690C00017 included 72 children and young adults from 10 to 24 years of age with T2DM, of which 39 received dapagliflozin and 33 received placebo for up to 52 weeks. The total exposure to dapagliflozin was 45.8 patient-years with 29 patients being exposed to dapagliflozin for > 350 days. There is no scientific rationale to suggest that the safety of long-term use in children differs from that in adults. The safety profile of dapagliflozin in children is comparable to that of adults, however, there are limited data in long term use.

Population in need of further characterisation: Long term safety in paediatric patients aged 10 years and above.

Long-term safety data will be collected for up to 104 weeks in the paediatric PASS D1680C00019 (CV181375), to further assess safety and measures of growth and maturity in paediatric T2DM patients receiving dapagliflozin.

II.8 MODULE SVIII: SUMMARY OF THE SAFETY CONCERNS

Table II-17 Summary of Safety Concerns

Important identified risks	Diabetic Ketoacidosis including events with atypical presentation
Important potential risks	Bladder cancer Breast cancer Prostate cancer
Missing information	Use in patients with NYHA class IV Long-term safety in the paediatric population (aged 10 years and above)

III. PART III: PHARMACOVIGILANCE PLAN

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

Specific adverse reaction follow-up questionnaires for safety concerns

See Annex 4 for copies of AE follow-up questionnaires for spontaneous reports of bladder cancer, breast cancer, prostate cancer, and diabetic ketoacidosis.

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

MB102118 (D1690R00007): Cancer in Patients on Dapagliflozin and Other Antidiabetic Treatment (Category 3)

Study short name and title: MB102118 (D1690R00007) – Comparison of the Risk of Cancer Between Patients With Type 2 Diabetes Exposed to Dapagliflozin and Those Exposed to Other Antidiabetic Treatment.

Rationale and study objectives: (1) To compare the incidence of breast cancer, by insulin use at cohort entry, among females with T2DM who are new initiators of dapagliflozin and females who are new initiators of ADs in classes other than SGLT2 inhibitors, insulin, metformin monotherapy, or SU monotherapy and (2) To compare the incidence of bladder cancer, by insulin use at cohort entry and pioglitazone use, among male and female patients with T2DM who are new initiators of dapagliflozin and those who are new initiators of ADs in classes other than SGLT2 inhibitors, insulin monotherapy, metformin monotherapy, or SU monotherapy.

Study design: This is a cohort study conducted in data from the CPRD, PHARMO, HealthCore, and US Medicare comparing cancer among new users of dapagliflozin with cancer among new users of ADs in classes other than SGLT2 inhibitors, insulin monotherapy, metformin monotherapy, or SU monotherapy.

Study population: Eligible patients must meet all of the following inclusion criteria: 1) Patient was newly prescribed dapagliflozin (with or without other ADs) or newly prescribed an AD (with or without other ADs) in a class other than SGLT2 inhibitors, insulin monotherapy, metformin monotherapy, or SU monotherapy on the prescription index date; 2) Patient is aged 40 years or older at cohort entry; 3) Patient was enrolled in the database for at least 180 days before the prescription index date. It is currently projected that over 10 years, there will be 9500 person-years of dapagliflozin exposed follow-up available in the CPRD and 5800 person-years of dapagliflozin exposed follow-up available in PHARMO databases. In the US, there will be approximately 835000 person-years of follow-up available among all new users of dapagliflozin (138000 person-years in the HIRDSM and 697000 person-years in Medicare data) over 9 years.

Milestones: Interim data reports: 2016, 2019, 2021, 2023; Final Report submission estimated in 2025.

D1680C00019 (CV181375) (Category 3)

Study short name and title: T2NOW, A 26-Week, Multicenter, Randomised, Placebo-Controlled, Double-Blind, Parallel Group, Phase 3 Trial with a 26-Week Safety Extension Period Evaluating the Safety and Efficacy of Dapagliflozin 5 and 10 mg, and Saxagliptin 2.5 and 5 mg in Paediatric Patients with T2DM Who Are Between 10 and < 18 Years of Age.

Rationale and study objectives: To assess safety and tolerability in paediatric T2DM subjects receiving 26 weeks of short-term (ST) double-blind treatment, followed by 26-weeks of long-term safety extension period, leading up to 52 weeks of total treatment. Furthermore, patients will be followed for additional 52 weeks after study-related treatment has been discontinued. One of the safety objectives is to assess measures of growth and maturity and Tanner staging and markers of bone health for up to 26 weeks, and, separately, for up to 52 weeks of total treatment, and for an additional 52 weeks after the study has been completed (Week 104).

Study design: Multicenter, 26-week, Phase 3b, randomised, placebo-controlled, double-blind, parallel group study with a 26-week safety extension period (up to 52 weeks of total treatment) to evaluate the safety and efficacy of dapagliflozin (5 and 10 mg) and saxagliptin (2.5 and 5 mg). Additional post-study visit at Week 104 for assessment of measures of growth and maturity.

Study population: Children and young adults ≥ 10 years of age, and up to but not including 18 years of age previously diagnosed with T2DM by World Health Organization/ADA criteria who are eligible according to the inclusion/exclusion criteria will be randomised in a 1:1:1 ratio to receive dapagliflozin, saxagliptin, or placebo.

Milestones: Study is planned to report in 2024.

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table III-1 Ongoing and Planned Additional Pharmacovigilance Activities

Study (study short name, and title) Status (planned/ongoing)	Summary of objectives	Safety concerns addressed	Milestones (required by regulators)	Due dates
Category 3 - Required additional pharmacovigilance activities (by the competent authority)				

Table III-1 Ongoing and Planned Additional Pharmacovigilance Activities

Study (study short name, and title) Status (planned/ongoing)	Summary of objectives	Safety concerns addressed	Milestones (required by regulators)	Due dates
MB102118 (D1690R00007) - Observational study: Cancer in Patients on Dapagliflozin and Other Antidiabetic Treatment Ongoing	To assess the incidence of breast and bladder cancer among new users of dapagliflozin compared to those who are new users of certain other antidiabetic drugs.	Breast cancer, Bladder cancer, Prostate cancer	Submission of Interim data Submission of final data	2016, 2019, 2021, 2023 2025
D1680C00019 (CV181375) T2NOW A 26-Week, Multicenter, Randomised, Placebo-Controlled, Double-Blind, Parallel Group, Phase 3 Trial with a 26-Week Safety Extension Period Evaluating the Safety and Efficacy of Dapagliflozin and Saxagliptin in Paediatric Patients with T2DM Who Are Between 10 and < 18 Years of Age	To assess the safety and tolerability of dapagliflozin and saxagliptin in paediatric T2DM subjects aged from 10 to < 18 years, when administered for up to 52 weeks of total treatment. Long term safety data including measures of growth and maturity and Tanner staging and markers of bone health will be collected for up to 104 weeks.	Long-term safety in the paediatric population (aged 10 years and above)	Submission of final data	2024

IV. PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

No post-authorisation efficacy studies are ongoing or planned at this point in time.

V. PART V: RISK MINIMISATION MEASURES

V.1 ROUTINE RISK MINIMISATION MEASURES

Table V-1 Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Important identified risks	
Diabetic Ketoacidosis including events with atypical presentation	Routine risk communication: SmPC sections 4.4, 4.8. PL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: Symptoms of DKA included, and direction to assess patients immediately, regardless of blood glucose level, if these symptoms occur. Information included that dapagliflozin should be interrupted in relation to major surgical procedures or acute serious medical illnesses, or if DKA is suspected. (SmPC section 4.4, PL section 2). Before initiating dapagliflozin, factors in the patient history that may predispose to ketoacidosis should be considered. (SmPC section 4.4). Information that FORXIGA should not be used for patients with T1DM (SmPC section 4.4). Information on how to detect symptoms of DKA and instructions to seek medical attention (PL section 2, 4).
Important potential risks	
Bladder cancer	None
Breast cancer	None
Prostate cancer	None
Missing information	
Use in patients with NYHA class IV	Routine risk communication: SmPC section 4.4
Long-term safety in the paediatric population (aged 10 years and above)	None

PL Package leaflet; SmPC Summary of product characteristics

V.2 ADDITIONAL RISK MINIMISATION MEASURES

Routine risk minimisation activities as described in Part V:1 are sufficient to manage the safety concerns of the medicinal product.

V.3 SUMMARY OF RISK MINIMISATION MEASURES

Table V-2 Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
Diabetic Ketoacidosis including events with atypical presentation	Routine risk minimisations measures: SmPC sections 4.4, 4.8 PL section 4 Information includes that dapagliflozin should be interrupted in relation to major surgical procedures or acute serious medical illnesses, or if DKA is suspected (SmPC section 4.4, PL section 2). Before initiating dapagliflozin, factors in the patient history that may predispose to ketoacidosis should be considered (SmPC section 4.4). Information that FORXIGA should not be used for patients with T1DM (SmPC section 4.4).	Routine PV: AE follow-up forms for spontaneous reports
Important potential risks		
Bladder cancer	No risk minimisation measures.	Routine PV: AE follow-up forms for spontaneous reports Additional PV: MB102118: Cancer in Patients on Dapagliflozin and Other Antidiabetic Treatment
Breast cancer	No risk minimisation measures.	Routine PV: AE follow-up forms for spontaneous reports Additional PV: MB102118: Cancer in Patients on Dapagliflozin and Other Antidiabetic Treatment

Table V-2 Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Prostate cancer	No risk minimisation measures.	Routine PV: AE follow-up forms for spontaneous reports Additional PV: MB102118: Cancer in Patients on Dapagliflozin and Other Antidiabetic Treatment
Missing information		
Use in patients with NYHA class IV	Routine risk minimisation measures: SmPC section 4.4	None
Long-term safety in the paediatric population (aged 10 years and above)	No risk minimisation measures.	Additional PV: Long term safety data including measures of growth and maturity and Tanner staging and markers of bone health will be collected for up to 104 weeks. D1680C00019 (CV181375) T2NOW

VI. PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN FOR FORXIGA/EDISTRIDE (DAPAGLIFLOZIN)

This is a summary of the risk management plan (RMP) for FORXIGA/EDISTRIDE. The RMP details important risks of FORXIGA/EDISTRIDE, how these risks can be minimised, and how more information will be obtained about FORXIGA/EDISTRIDE'S risks and uncertainties (missing information).

FORXIGA/EDISTRIDE'S Summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how FORXIGA/EDISTRIDE should be used.

This summary of the RMP for FORXIGA/EDISTRIDE should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of FORXIGA/EDISTRIDE'S RMP.

VI.1 THE MEDICINE AND WHAT IT IS USED FOR

FORXIGA/EDISTRIDE is authorised for treatment of type 2 diabetes mellitus in adults and children aged 10 years and above as an adjunct to diet and exercise, for treatment of symptomatic chronic heart failure in adults and for treatment of chronic kidney disease in adults (see SmPC for the full indications). It contains dapagliflozin as the active substance and it is given orally.

Further information about the evaluation of FORXIGA/EDISTRIDE'S benefits can be found in FORXIGA/EDISTRIDE's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

FORXIGA
https://www.ema.europa.eu/en/medicines/human/EPAR/forxiga

EDISTRIDE
https://www.ema.europa.eu/en/medicines/human/EPAR/edistride

VI.2 RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of FORXIGA/EDISTRIDE, together with measures to minimise such risks and the proposed studies for learning more about FORXIGA/EDISTRIDE's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so as to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute the routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities.*

VI.2.1 List of important risks and missing information

Important risks of FORXIGA/EDISTRIDE are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of FORXIGA/EDISTRIDE. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long term use of the medicine).

Table VI-1 List of Important Risks and Missing Information

Important identified risks	Diabetic Ketoacidosis including events with atypical presentation
Important potential risks	Bladder cancer Breast cancer Prostate cancer
Missing information	Use in patients with NYHA class IV Long-term safety in the paediatric population (aged 10 years and above)

Table VI-2 Important Identified Risk – Diabetic Ketoacidosis Including Events with Atypical Presentation

Evidence for linking the risk to the medicine	Postmarketing experience with use of SGLT2 inhibitors, including dapagliflozin. In clinical studies with T1DM, there was a higher number of diabetic ketoacidosis (DKA) in the dapagliflozin-treated patients compared to placebo. DKA was also reported in the T2DM DECLARE study with rare frequency.
Risk factors and risk groups	Postoperative episodes affecting insulin requirement/deficiency; dehydration and restricted oral glucose intake due to dieting (especially low carbohydrate diet); loss of appetite due to, eg, gastrointestinal infection, depression, or malaise; severe infections or other severe medical conditions such as myocardial infarction and stroke; and pancreatic insufficiencies due pancreatitis, cancer, or alcohol abuse.
Risk minimisation measures	Routine risk minimisations measures: SmPC sections 4.4, 4.8 PL sections 2, 4 Information includes that dapagliflozin should be interrupted in relation to major surgical procedures or acute serious medical illnesses, or if DKA is suspected (SmPC section 4.4, PL section 2). Before initiating dapagliflozin, factors in the patient history that may predispose to ketoacidosis should be considered. (SmPC section 4.4).

Table VI-3 Important Potential Risk – Bladder Cancer

Evidence for linking the risk to the medicine	Clinical trial data with use of dapagliflozin.
Risk factors and risk groups	Age, sex (male), smoking (now or ever), chemical exposure to known carcinogens (cyclophosphamide and aniline dyes, etc), and haematuria.
Risk minimisation measures	None.
Additional pharmacovigilance activities	MB102118: Cancer in Patients on Dapagliflozin and Other Antidiabetic Treatment See section VI.2.2 of this summary for an overview of the post-authorisation development plan.

Table VI-4 Important Potential Risk – Breast Cancer

Evidence for linking the risk to the medicine	Clinical trial data with use of dapagliflozin.
Risk factors and risk groups	Age, sex (female), smoking (now or ever), parity, use of exogenous oestrogen (i.e., hormone replacement therapy), BRCA1 or BRCA2 mutations, family history of breast cancer, breast tissue density, overweight/obesity.
Risk minimisation measures	None.
Additional pharmacovigilance activities	MB102118: Cancer in Patients on Dapagliflozin and Other Antidiabetic Treatment See section VI.2.2 of this summary for an overview of the post-authorisation development plan.

Table VI-5 Important Potential Risk – Prostate Cancer

Evidence for linking the risk to the medicine	Clinical trial data with use of dapagliflozin.
Risk factors and risk groups	Age, smoking.
Risk minimisation measures	None.
Additional pharmacovigilance activities	MB102118: Cancer in Patients on Dapagliflozin and Other Antidiabetic Treatment See section VI.2.2of this summary for an overview of the post-authorisation development plan.

Table VI-6 Missing Information – Use in Patients with NYHA Class IV

Risk minimisation measures	Routine risk minimisation measures: SmPC Section: 4.4

Table VI-7 Missing Information – Long-term Safety in the Paediatric Population (Aged 10 years and Above)

Risk minimisation measures	None
Additional pharmacovigilance activities	Long term safety data including measures of growth and maturity and Tanner staging and markers of bone health will be collected for up to 104 weeks in study D1680C00019 (CV181375) T2NOW

VI.2.2 Post-authorisation development plan

Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of FORXIGA.

VI.2.2.1 Other studies in post-authorisation development plan

Study short name: MB102118 (D1690R00007) – Cancer in Patients on Dapagliflozin [Observational study].

Purpose of the study: (1) To compare the incidence of breast cancer, by insulin use at cohort entry, among females with T2DM who are new initiators of dapagliflozin and females who are new initiators of antidiabetic drugs in classes other than SGLT2 inhibitors, insulin, metformin monotherapy, or SU monotherapy and (2) To compare the incidence of bladder cancer, by insulin use and pioglitazone use, among male and female patients with T2DM who are new initiators of dapagliflozin and those who are new initiators of antidiabetic drugs in classes other than SGLT2 inhibitors, insulin monotherapy, metformin monotherapy, or SU monotherapy.

Study short name: D1680C00019 (CV181375) T2NOW

Purpose of the study: To assess safety and tolerability of dapagliflozin and saxagliptin in paediatric T2DM subjects aged from 10 to < 18 years, receiving 26 weeks of short-term (ST) double-blind treatment, followed by 26-weeks of long-term safety extension period, leading up to 52 weeks of total treatment. Safety objectives include assessment of measures of growth and maturity and Tanner staging and markers of bone health for up to 26 weeks, and, separately, for up to 52 weeks of total treatment, and for an additional 52 weeks after the study has been completed (Week 104).

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EU RMP Part VII Annex 4

Drug Substance dapagliflozin

EUROPEAN UNION RISK MANAGEMENT PLAN (EU RMP) for FORXIGA™ and EDISTRIDE™ (dapagliflozin)

Part VII ANNEX 4 - SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Active substance(s) (INN or common name)	dapagliflozin
Product(s) concerned (brand names(s))	FORXIGA™, EDISTRIDE™
Name of Marketing Authorisation Holder or Applicant	AstraZeneca AB

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- Questionnaire (dapagliflozin) – Breast cancer
- Questionnaire (dapagliflozin) – Bladder cancer
- Questionnaire (dapagliflozin) – Prostate cancer
- Questionnaire (dapagliflozin) – Diabetic ketoacidosis

Breast Cancer Questionnaire
Request for Additional Information

Case ID #:_____

Manufacturer Date of Receipt: _____

_

Reporter information		
Reporter Name:	**Reporter address:**	**Telephone #:** **Fax #:**

Patient details			
Initials:	**Sex:** ☐ Male ☐ Female	**Weight:** ☐ lb ☐ kg	**Height:** ☐ in ☐ cm
Date of Birth *(DD/MM/YY)* **or Age:**		**Ethnic Origin:**	**Race:**

Adverse event details			
Adverse Event(s)	**Start Date** *(DD/MM/YY)*	**End Date** *(DD/MM/YY)*	**Outcome**
			☐ Event ongoing ☐ Recovered ☐ Recovered with sequele ☐ Patient Died

1.Please describe the malignancy:

- Anatomical location:_____

- Histological type:_____

- TNM classification:_____

- Grade:_____

- Hormone receptor status- Estrogen:_____
  -Progesterone:_____
  -Her2/neu:_____

- Second/Secondary:_____

Breast Cancer Questionnaire
Request for Additional Information

Case ID #:_____

Manufacturer Date of Receipt: _____

2. Was the event a new diagnosis (acute event) or a relapse/disease progression of a preexisting condition?
☐ New diagnosis ☐Relapse/Disease progression.
What was the prior disease?_____
What was the prior onset date?_____

3. Was there a precipitating factor for exacerbation?
☐ No ☐ UNK ☐ Yes, Please specify:_____

4. Please provide prior screening test results with dates if appropriate (e.g. mammogram):

5. Please provide the method of diagnosis and test result(s). Choose all that apply.
☐ CT/MRI/Ultrasound. Result of:_____
☐ Histopathology. Result of:_____
☐ Cytology. Result of:_____
☐ Genetic testing. Result of:_____
☐ CD marker evaluation. Result of:_____
☐ Other, specify:_____

Dapagliflozin therapy

Indication:	**Daily dosage:**	**Start date** *(DD/MM/YY)*:	**Stop date** *(DD/MM/YY)*:

Was dapagliflozin stopped due to the event(s)? ☐ Yes, permanently ☐ Yes, temporarily ☐ No ☐ N/A

Was dapagliflozin re-introduced? ☐ Yes, date re-introduced: _____ ☐ No ☐ N/A

Does the reporter consider there to be a causal relationship between dapagliflozin and the adverse event(s)?
☐ Yes ☐ No Please explain:

Concomitant medications
Exclude drugs to treat the event(s)

Drug Name	**Indication**	**Daily Dosage**	**Route**	**Start Date** *(DD/MM/YY)*	**Stop Date** *(DD/MM/YY)*	**Was this also a suspect medication?**
						☐ Yes ☐ No
						☐ Yes ☐ No
						☐ Yes ☐ No

Breast Cancer Questionnaire
Request for Additional Information

Case ID #:_____

Manufacturer Date of Receipt: _____

Relevant medical history/concurrent diseases and risk factors, Please provide details if available	
- Alcohol>2drinks/day: ☐Yes ☐No ☐UNK - Overweight/Obese: ☐Yes ☐No ☐UNK - Medication-induced (e.g. hormone replacement therapy (HRT), diethylstilbestrol (DES): ☐Yes ☐No ☐UNK - Radiation exposure: ☐Yes ☐No ☐UNK - Early menarche<12 yrs: ☐Yes ☐No ☐UNK - Late menopause >55 yrs: ☐Yes ☐No ☐UNK - Nulliparous/1st child>30 yrs: ☐Yes ☐No ☐UNK - Past personal history of breast cancer/benign breast disease (e.g fibroadenoma) or ovarian cancer: ☐Yes ☐No ☐UNK	- Family history of breast cancer (1st degree relative w/BC): ☐Yes ☐No ☐UNK - BRCA-1 or BRCA-2 mutation: ☐Yes ☐No ☐UNK - Lobular carcinoma in situ: ☐Yes ☐No ☐UNK - Increased breast density (mammogram): ☐Yes ☐No ☐UNK - Lack of physical activity: ☐Yes ☐No ☐UNK - High fat diet: ☐Yes ☐No ☐UNK - Other gene changes (ATM, p53, CHEK2, PTEN, CDH1): ☐Yes ☐No ☐UNK Other; please specify:_____

Please provide corrective treatment with dates of administration of treatment:
☐ No corrective treatment administered
☐ Surgery: Specify type of surgery: _____ Date of surgery _____/_____/_____ (DDMMYY)
☐ Medical treatment: Specify type of medical treatment: _____Date of treatment_____/_____/_____ (DDMMYY)
☐ Radiotherapy: Date of radiotherapy _____/_____/_____ (DDMMYY)

Date and Signature
Date: _____
Signature (Reporting Physician): _____

Contact information
Please return completed form to:
Fax:
E-mail:
Mail:

Thank you for completing this form.

Bladder Cancer Questionnaire
Request for Additional Information

Case ID #:_____

Manufacturer Date of Receipt: _____

Reporter information		
Reporter Name:	**Reporter address:**	**Telephone #:** **Fax #:**

Patient details			
Initials:	**Sex:** ☐ Male ☐ Female	**Weight:** ☐ lb ☐ kg	**Height:** ☐ in ☐ cm
Date of Birth *(DD/MM/YY)* **or Age:**		**Ethnic Origin:**	**Race:**

Adverse event details			
Adverse Event(s)	**Start Date** *(DD/MM/YY)*	**End Date** *(DD/MM/YY)*	**Outcome**
			☐ Event ongoing ☐ Recovered ☐ Recovered with sequele ☐ Patient Died

1.Please describe the malignancy:

- Anatomical location on bladder (e.g. neck, fundus, body):_____

- Growth pattern (e.g. papillary, non-papillary, metastatic, isolated):_____

- Histological type (e.g. transitional, squamous, adeno):_____

- TNM classification (e.g. pT1, pN2, M0):_____

- Grade/Stages (e.g. high-grade, low-grade or other):_____

Bladder Cancer Questionnaire
Request for Additional Information

Case ID #:_____

Manufacturer Date of Receipt: _____

2. Was the event a new diagnosis (acute event) or a relapse/disease progression of a preexisting condition?

☐ New diagnosis ☐ Relapse/Disease progression. What was the prior disease?_____

What was the prior onset date?_____

3. Does the subject have a history of hematuria (micro and/or macro)?

☐ No ☐ UNK ☐ Yes, (If Yes, please complete information below)

Start date: _____/_____/_____ (DDMMYY)

Other occasion dates:_____

Known cause of the hematuria:_____

4. Does the subject have urinary symptoms (or other symptoms)?

☐ No ☐ UNK ☐ Yes, dysuria, start date of _____/_____/_____ (DDMMYY)

☐ Yes, urgency, start date of _____/_____/_____ (DDMMYY)

☐ Yes, polyuria, start date of _____/_____/_____ (DDMMYY)

☐ Yes, increased frequency, start date of _____/_____/_____ (DDMMYY)

☐ Yes, other:

Specify: _____, start date of _____/_____/_____ (DDMMYY)

5. What prompted the investigations that led to diagnosis?

☐ Urinary or other symptoms, please specify: _____

☐ Hematuria, please specify if gross or microscopic hematuria: _____

☐ Other, please specify: _____

6. Please provide the method of diagnosis and test result(s). Choose all that apply. You may provide copies of any test results.

☐ Cystoscopy. Result of: _____

☐ Histopathology. Result of: _____

☐ Cytology. Results of: _____

☐ Imaging (e.g. CT scan, MRI, ultrasound) Result of: _____

☐ Other, specify: _____

Dapagliflozin therapy

Bladder Cancer Questionnaire
Request for Additional Information

Case ID #:_____

Manufacturer Date of Receipt: _____

Indication:	**Daily dosage:**	**Start date** *(DD/MM/YY)*:	**Stop date** *(DD/MM/YY)*:
Was dapagliflozin stopped due to the event(s)? ☐ Yes, permanently ☐ Yes, temporarily ☐ No ☐ N/A			
Was dapagliflozin re-introduced? ☐ Yes, date re-introduced: _____ ☐ No ☐ N/A			
Does the reporter consider there to be a causal relationship between dapagliflozin and the adverse event(s)? ☐ Yes ☐ No Please explain:			

Concomitant medications
Exclude drugs to treat the event(s)

Drug Name	**Indication**	**Daily Dosage**	**Route**	**Start Date** *(DD/MM/YY)*	**Stop Date** *(DD/MM/YY)*	**Was this also a suspect medication?**
						☐ Yes ☐ No
						☐ Yes ☐ No
						☐ Yes ☐ No
						☐ Yes ☐ No
						☐ Yes ☐ No

Relevant medical history/concurrent diseases and risk factors

a. Does the patient smoke?

☐ No ☐ UNK ☐Yes (If Yes, please complete information below)

Number of packs/day: _____

Number of years been smoking: _____

b. Has the patient ever smoked previously?

☐ No ☐ UNK ☐Yes (If Yes, please complete information below)

Number of packs/day: _____

Number of years been smoking: _____ Stopped smoking: _____ (Year)

c. Does the subject have any of the following risk factors? Check all that apply

i. Exposure to arsenic, aromatic amines (e.g. aniline), phenacetin, Chinese herbs (e.g. aristolochic acid) and chemicals used in the manufacture of dyes, rubber, leather, textiles and paint products, cyclophosphamide

☐ No ☐ UNK ☐ Yes (If Yes, please complete information below)

Compound: _____ Exposure (dose and time): _____

ii. Has the subject ever used products or combination products containing pioglitazone?

Bladder Cancer Questionnaire
Request for Additional Information

Case ID #:_____

Manufacturer Date of Receipt: _____

☐ No ☐ UNK ☐ Yes

If Yes, specify dates: _____

iii. Chronic cystitis

☐ No ☐ UNK ☐ Yes

iv. Indwelling urinary catheter

☐ No ☐ UNK ☐ Yes

v. Radiation exposure

☐ No ☐ UNK ☐ Yes

vi. Past personal history of bladder cancer or benign bladder neoplasms

☐ No ☐ UNK ☐ Yes

vii. Family history of bladder cancer

☐ No ☐ UNK ☐ Yes

viii. Family history of hereditary nonpolyposis colorectal cancer (HNPCC) or Lynch syndrome

☐ No ☐ UNK ☐ Yes

ix. ☐ Other, specify:_____

Please provide corrective treatment with dates of administration of treatment:

☐ No corrective treatment administered
☐ Surgery: Specify type of surgery: _____ Date of surgery _____/_____/_____ (DDMMYY)
☐ Medical treatment: Specify type of medical treatment:_____
Date of treatment_____/_____/_____ (DDMMYY)
☐ Radiotherapy: Date of radiotherapy _____/_____/_____ (DDMMYY)

Date and Signature

Bladder Cancer Questionnaire
Request for Additional Information

Case ID #:_____

Manufacturer Date of Receipt: _____

Date: _____

Signature (Reporting Physician): _____

Contact information

Please return completed form to:

Fax:

E-mail:

Mail:

Thank you for completing this form.

Prostate Cancer Questionnaire
Request for Additional Information

Case ID #:_____

Manufacturer Date of Receipt: _____

Reporter information		
Reporter Name:	**Reporter address:**	**Telephone #:** **Fax #:**

Patient details			
Initials:	**Sex:** ☐ Male ☐ Female	**Weight:** ☐ lb ☐ kg	**Height:** ☐ in ☐ cm
Date of Birth *(DD/MM/YY)* **or Age:**		**Ethnic Origin:**	**Race:**

Adverse event details			
Adverse Event(s)	**Start Date** *(DD/MM/YY)*	**End Date** *(DD/MM/YY)*	**Outcome**
			☐ Event ongoing ☐ Recovered ☐ Recovered with sequele ☐ Patient Died

1.Please describe the malignancy:

- Histological type:_____

-TNM classification (e.g. pT1, pN2, M0):_____

- Grade (Gleason score if available, or other system) :_____
(Please indicate type of grading system)

- Stage:_____

2. ☐ **Has the cancer metastasized (specify secondary location(s))?** _____

☐ Still confined to the prostate

3. Is this a:

☐ New diagnosis (acute event) or

☐Relapse/Disease progression. What was the prior disease?_____

What was the prior onset date?

4. Did the subject have prior elevation of PSA? ☐_____

Highest value of PSA on study drug: _____ on: _____/_____/_____ (DDMMYY)

PSA value prior to beginning of study drug: _____ on: _____/_____/_____ (DDMMYY)

Prostate Cancer Questionnaire
Request for Additional Information

Case ID #:_____

Manufacturer Date of Receipt: _____

5. Please provide prior screening results with dates of tests (e.g. Digital Rectal Exam):_____
_____
_____

6. What prompted the investigations that led to diagnosis?

☐ Routine screening

☐ High PSA values

☐ Other, please specify: _____

7. Specify any history of symptoms preceding the diagnosis and dates (if known)

☐ Hematuria (micro and/or macro) : _____ on: _____/_____/_____ (DDMMYY)

☐ Hematospermia: _____ _____ on: _____/_____/_____ (DDMMYY)

☐ Other urinary symptoms (e.g. dysuria, urgency, polyuria, pollakiuria: _____
_____ on: _____/_____/_____ (DDMMYY)

☐ Persistent pain in the back, hips or pelvis:_____ on: _____/_____/_____ (DDMMYY)

☐ Painful ejaculation: _____ _____ on: _____/_____/_____ (DDMMYY)

8. Please provide the method of diagnosis and test result(s). Choose all that apply. You may provide copies of any test results.

☐ Histopathology. Result of: _____

☐ Cytology. Results of: _____

☐ Imaging (e.g. CT scan, MRI, ultrasound) Result of: _____

☐ Other, specify: _____

Dapagliflozin therapy			
Indication:	**Daily dosage:**	**Start date** *(DD/MM/YY)*:	**Stop date** *(DD/MM/YY)*:
Was dapagliflozin stopped due to the event(s)? ☐ Yes, permanently ☐ Yes, temporarily ☐ No ☐ N/A			
Was dapagliflozin re-introduced? ☐ Yes, date re-introduced: _____ ☐ No ☐ N/A			
Does the reporter consider there to be a causal relationship between dapagliflozin and the adverse event(s)? ☐ Yes ☐ No Please explain:			

Prostate Cancer Questionnaire
Request for Additional Information

Case ID #:_____

Manufacturer Date of Receipt: _____

Concomitant medications
Exclude drugs to treat the event(s)

Drug Name	Indication	Daily Dosage	Route	Start Date *(DD/MM/YY)*	Stop Date *(DD/MM/YY)*	Was this also a suspect medication?
						☐ Yes ☐ No
						☐ Yes ☐ No
						☐ Yes ☐ No
						☐ Yes ☐ No
						☐ Yes ☐ No

Relevant medical history/concurrent diseases and risk factors

a. Does the patient smoke?

☐ No ☐ UNK ☐ Yes (If Yes, please complete information below)

Number of packs/day: _____

Number of years been smoking: _____

b. Has the patient ever smoked previously?

☐ No ☐ UNK ☐ Yes (If Yes, please complete information below)

Number of packs/day: _____

Number of years been smoking: _____ Stopped smoking: _____ (Year)

c. Does the subject have any of the following risk factors? Check all that apply

i. Exposure to heavy metals (e.g. cadmium)

☐ No ☐ UNK ☐ Yes (If Yes, please complete information below)

Compound: _____ Exposure (dose and time): _____

ii. Exposure to agent orange or chlorderone?

☐ No ☐ UNK ☐ Yes

If Yes, specify dates: _____

iii. Prior androgen use?

☐ No ☐ UNK ☐ Yes

iv. High dietary fat intake?

☐ No ☐ UNK ☐ Yes

v. Lack of physical activity / inactivity?

☐ No ☐ UNK ☐ Yes

vi. Past personal history of prostate cancer or benign prostate neoplasms?

Prostate Cancer Questionnaire
Request for Additional Information

Case ID #:_____

Manufacturer Date of Receipt: _____

☐ No ☐ UNK ☐ Yes

vii. Past personal history of prostitis or trichomonas?

☐ No ☐ UNK ☐ Yes

viii. Family history of prostate cancer?

☐ No ☐ UNK ☐ Yes (specify father, brother, son etc):_____

ix. Vasectomy?

☐ No ☐ UNK ☐ Yes

x. BRCA 1 and / or 2 mutation?

☐ No ☐ UNK ☐ Yes

xi. Heavy alcohol use (ethanol >50g per day, > ~5 alcoholic drinks per day)?

☐ No ☐ UNK ☐ Yes

xii. ☐ Other, specify:_____

10. Please provide corrective treatment with dates of administration of treatment:

☐ Surgery :_____ _____ on: _____/_____/_____ (DDMMYY)

☐ Medical treatment :_____ _____ on: _____/_____/_____ (DDMMYY)

☐ Radiotherapy :_____ _____ on: _____/_____/_____ (DDMMYY)

☐ Active monitoring :_____ _____ on: _____/_____/_____ (DDMMYY)

11. Please provide outcome/current status of the disease:

☐Complete response to treatment (no cancer present)

☐Stable disease (no change to report)

☐ Progressive disease (cancer has progressed since initial reporting)

☐ Death, specify date of death : _____/_____/_____ (DDMMYY)

Prostate Cancer Questionnaire
Request for Additional Information

Case ID #:_____

Manufacturer Date of Receipt: _____

Please provide corrective treatment with dates of administration of treatment:

☐ No corrective treatment administered
☐ Surgery: Specify type of surgery: _____ Date of surgery _____/_____/_____ (DDMMYY)
☐ Medical treatment: Specify type of medical treatment:
_____ Date of treatment_____/_____/_____ (DDMMYY)
☐ Radiotherapy: Date of radiotherapy _____/_____/_____ (DDMMYY)

Date and Signature

Date: _____

Signature (Investigator or Reporting Physician): _____

Contact information

Please return completed form to:

Fax:

E-mail:

Mail:

Thank you for completing this form.

Request for Additional Information in response to event or symptoms of diabetic ketoacidosis

Case ID #_____
Manufacturer Date of Receipt _____

Reporter Information		
Reporter Name:	**Reporter address:**	**Telephone #:** **Fax#:** **Email:**

Please note that information already provided in the original event report does not need to be repeated in this form!

Patient Details							
Initials:	**Sex:** ☐ Male ☐ Female	**Weight:**	☐ lb	☐ kg	**Height:**	☐ in	☐ cm
Date of Birth *(DD/MM/YY)* **or Age:**		**Ethnic Origin:**			**Race:**		

Type of diabetes					
Not applicable ☐ (non-diabetic)	T1DM ☐	T2DM ☐	LADA ☐	Ketosis prone ☐	Other:

Duration of diabetes				
< 1 Year ☐	1-3 Year ☐	3-5 Year ☐	5-10 Year ☐	>10 Year ☐

Adverse Event Details				
Adverse Event(s)	**Start Date** *(DD/MM/YY)*	**Stop Date** *(DD/MM/YY)*	**Outcome**	
			☐ Recovered ☐ Event ongoing	☐ Recovered with sequelae ☐ Patient died
			☐ Recovered ☐ Event ongoing	☐ Recovered with sequelae ☐ Patient died
Diagnostic criteria and clinical diagnosis of the event(s):				
Was the patient hospitalized for the event(s)? ☐ Yes ☐ No **Was treatment provided?** ☐ Yes ☐ No			*If 'Yes' to any of the questions to the left, please provide a brief statement of clinical course, relevant treatment and any complications from the event(s):*	

Dapagliflozin therapy			
Indication:	**Daily dosage:**	**Start Date** *(DD/MM/YY):*	**Stop Date** *(DD/MM/YY):*
Was dapagliflozin stopped due to the event(s)?		☐ Yes, permanently ☐ Yes, temporarily	☐ No ☐ N/A

If yes, did the event(s) improve after stopping dapagliflozin?	☐ Yes, permanently ☐ Yes, temporarily	☐ No	☐ N/A
Was dapagliflozin re-introduced?	☐ Yes, permanently ☐ Yes, temporarily	☐ No	☐ N/A
If yes, did the event(s) recur after reintroduction?	☐ Yes, permanently ☐ Yes, temporarily	☐ No	☐ N/A
Does the reporter consider there to be a causal relationship between dapagliflozin and the adverse event(s)?		☐ Yes	☐ No
Please explain:			

Antidiabetic medications (include treatments up to 3 months in advance of the reported event)

Drug Name	Indication	Daily Dosage	Route	Start Date *(DD/MM/YY)*	Stop Date *(DD/MM/YY)*	Was this a suspect medication?
						☐ Yes ☐ No
						☐ Yes ☐ No
						☐ Yes ☐ No
						☐ Yes ☐ No
						☐ Yes ☐ No
						☐ Yes ☐ No
						☐ Yes ☐ No

Please comment on any known missed or changed doses in addition to what is listed above:

Other relevant concomitant medications
Exclude drugs used to treat the event

Drug Name	Indication	Daily Dosage	Route	Start Date *(DD/MM/YY)*	Stop Date *(DD/MM/YY)*	Was this a suspect medication?
						☐ Yes ☐ No
						☐ Yes ☐ No
						☐ Yes ☐ No
						☐ Yes ☐ No
						☐ Yes ☐ No
						☐ Yes ☐ No
						☐ Yes ☐ No

Relevant medical history, concurrent diseases or other contributing factors		Start Date *(DD/MM/YY)*	Stop Date *(DD/MM/YY)*	If yes, please provide details
Previous episodes of ketoacidosis	☐ Yes ☐ No			
Carbohydrate reduced diet/Reduced caloric intake	☐ Yes ☐ No			
Surgery	☐ Yes ☐ No			
Infection	☐ Yes ☐ No			
Alcohol intake	☐ Yes ☐ No			
Recent Cardiovascular Episode	☐ Yes ☐ No			
Missed insulin dose	☐ Yes ☐ No			
Insulin pump failure	☐ Yes ☐ No			
Pancreatic disorder	☐ Yes ☐ No			

Relevant medical history, concurrent diseases or other contributing factors		Start Date *(DD/MM/YY)*	Stop Date *(DD/MM/YY)*	If yes, please provide details
Dehydration	☐ Yes ☐ No			
Increased exercise	☐ Yes ☐ No			
Other, please specify:	☐ Yes ☐ No			
	☐ Yes ☐ No			
	☐ Yes ☐ No			

Laboratory Test	Peak Value	Unit	Sample date *(DD/MM/YY)*	Reference Values (…….to ……)	Follow-up value If available	Follow-up Date *(DD/MM/YY)*
Blood/Plasma Glucose						
Blood pH						
PCO_2						
Serum Bicarbonate						
Serum Potassium (K)						
Serum Sodium (Na)						
Blood/Serum Ketones						
Urine Ketones						
c-Peptide						
Lactate						
Betahydroxybutyrate						
eGFR						
Creatinine						
Other, please specify :						

Date and Signature

Date: _____

Signature (Reporting Physician): _____

Contact Information

Please return completed form to:

Fax:

E-mail:

Mail:

Thank you for completing this form.