EU RMP	
Drug Substance	dapagliflozin + metformin fixed dose combination
Version Number	V 12
Succession Number	3
Data lock point	5 December 2019
Report date	08 May 2020

EUROPEAN UNION RISK MANAGEMENT PLAN (EU RMP) for XIGDUO™ and EBYMECT™ (dapagliflozin + metformin fixed dose combination)

The content of this RMP has been reviewed and endorsed by QPPV

Administrative Information

Rationale for submitting an updated RMP:

This RMP is submitted together with the study report on the meta-analysis data describing events of amputation and risk factors of amputation.

This RMP includes minor template changes compared with the previous EU RMP version. These changes are in document format only and are not included in the summary of changes.

Summary of significant changes in this RMP

Part II SVII

Information on the meta-analysis added to lower limb amputation risk definition.

Part III

Removal of the meta-analysis across studies D1690C00018, D1690C00019, and D1693C00001 (Category 3) from the list of additional pharmacovigilance activities.

Inclusion of studies D169AC00001, D169CC00001, D169EC00001, D169EC00002 to the list of PV activities.

Part V

Inclusion of studies D169AC00001, D169CC00001, D169EC00001, D169EC00002 to the list of PV activities.

Part VI

Inclusion of studies D169AC00001, D169CC00001, D169EC00001, D169EC00002 to the list of PV activities.

Other RMP versions under evaluation	Not applicable
Details of currently approved RMP	**Version Number**: 11 **Approved with procedure**: XIGDUO EMEA/H/C/002672/WS1539/0046 EBYMECT EMEA/H/C/004162/WS1539/0035 **Date of approval:** Xigduo: 25 Jul 2019; Ebymect 1 Aug 2019

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation/ Special term	Definition/Explanation
ACEi	Angiotensin-converting enzyme inhibitor
AE	Adverse event
ADR	Adverse drug reaction
AKI	Acute kidney injury
ALI	Acute liver injury
ARB	Angiotensin receptor blocker
AUC	Area under the curve
CHF	Congestive heart failure
C_{max}	Maximum plasma drug concentrations
CPRD	Clinical Practice Research Database
CV	Cardiovascular
DKA	Diabetic ketoacidosis
EEA	European economic area
EMA	European medicines agency
EU	European union
HIRDSM	Health Core Integrated Research Database
MedDRA	Medical Dictionary for Regulatory Activities
N	Number
NYHA	New York Heart Association
PAD	Peripheral artery disease
PL	Package Leaflet
PV	Pharmacovigilance
QPPV	Qualified Person for Pharmacovigilance
RMP	Risk management plan
SGLT2	Sodium glucose co-transporter 2
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Query
SU	Sulphonylurea
T2DM	Type 2 diabetes mellitus
UTI	Urinary tract infection
XR	Extended release

I. PART I: PRODUCT OVERVIEW

Table I-1 Product Overview

Active substance(s) (INN or common name)	dapagliflozin + metformin hydrochloride
Pharmacotherapeutic group(s) (ATC Code)	A10BD15
Marketing Authorisation Holder	AstraZeneca AB
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Xigduo, Ebymect
Marketing authorisation procedure	centralised
Brief description of the product	**Chemical class:** Human renal sodium-glucose co-transporter 2 (SGLT2) inhibitor. Biguanide
	Summary of mode of action: Dapagliflozin propanediol monohydrate is a highly potent, selective and orally active SGLT2 inhibitor, the major transporter responsible for renal glucose reabsorption. Dapagliflozin improves glycaemic control in patients with type 2 diabetes mellitus (T2DM) by reducing renal glucose reabsorption leading to urinary glucose excretion. Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Metformin is a biguanide and is not chemically or pharmacologically related to any other class of oral antihyperglycemic agents. Metformin decreases hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis, decreases intestinal absorption of glucose, and increase insulin sensitivity by improving peripheral glucose uptake and utilization.
	Important information about its composition: None
Hyperlink to the Product Information	Xigduo, Ebymect, Summary of Product Characteristics

Table I-1 Product Overview

Indication(s) in the EEA	Current: Xigduo is indicated in adults aged 18 years and older with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control: • in patients inadequately controlled on their maximally tolerated dose of metformin alone • in combination with other glucose-lowering medicinal products, including insulin, in patients inadequately controlled with metformin and these medicinal products • in patients already being treated with the combination of dapagliflozin and metformin as separate tablets. **Proposed indication** Xigduo is indicated in adults for the treatment of type 2 diabetes mellitus as an adjunct to diet and exercise: – in patients insufficiently controlled on their maximally tolerated dose of metformin alone – in combination with other medicinal products for the treatment of diabetes in patients insufficiently controlled with metformin and these medicinal products – in patients already being treated with the combination of dapagliflozin and metformin as separate tablets. For study results with respect to combination of therapies, effects on glycaemic control and cardiovascular (CV) events, and the populations studied, see sections 4.4, 4.5 and 5.1.
	Proposed: Not applicable
Dosage in the EEA	Current: Xigduo 5 mg/850 mg film-coated tablets Xigduo 5 mg/1,000 mg film-coated tablets
	Proposed: Not applicable

Table I-1 Product Overview

Pharmaceutical form(s) and strengths	Current: Xigduo 5 mg/850 mg film-coated tablets Brown, biconvex, 9.5 x 20 mm oval, film-coated tablets engraved with "5/850" on one side and "1067" engraved on the other side. Xigduo 5 mg/1,000 mg film-coated tablets Yellow, biconvex, 10.5 x 21.5 mm oval, film-coated tablets engraved with "5/1000" on one side and "1069" engraved 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

Dapagliflozin + metformin FDC is a fixed combination medicinal product which do not contain a new active substance. No epidemiological information is available in addition to what is known for the included components.

II.2 MODULE SII: NON-CLINICAL PART OF THE SAFETY SPECIFICATION

II.2.1 Summary of key findings from non-clinical data

Dapagliflozin + metformin FDC is a fixed combination medicinal product which do not contain a new active substance. No non-clinical information is available in addition to what is known for the included components.

II.3 MODULE SIII: CLINICAL TRIAL EXPOSURE

A total of 11 clinical trials in healthy subjects have been conducted with the dapagliflozin + metformin FDC tablets (Bioequivalence-trials) until 15 January 2018. Bioequivalence was established with dapagliflozin and metformin administered separately in the same dosages as dapagliflozin + metformin FDC constituents.

Table II-1 Estimated cumulative[a] subject exposure to dapagliflozin + metformin FDC tablets from clinical trials

Treatment	Healthy subjects	Total
Xigduo XR FDC	425	425
Comparator in XR trials	350	350
Xigduo IR FDC	175	175
Comparator in IR trials	157	157
Total	**612**	**612**

[a] Cumulative numbers from initiation of the first clinical trial up to 15 January 2018. Note: Most subjects received both FDC and comparators due to the cross-over designs of all trials. The table includes data from trials: MB102-065, MB102-071, MB102-092, MB102-100, MB102-112, MB102-125, D1691C00008, D1691C00012, D1691C00002 IR, D1691C00005 IR and D1691C00007 IR. No subjects have received randomised treatment at the time of the data lock point in study D1691C00016.

Table II-2 Estimated cumulative subject exposure to dapagliflozin + metformin FDC tablets from completed clinical trials by age and sex

	Number of healthy subjects		
Age range	**Male**	**Female**	**Total**
< 18 years	0	0	0
18 – 64 years	354	246	600
≥ 65 years	0	0	0
Total	**354**	**246**	**600**

[a] Data from completed clinical trials as of 15 January 2018. The table includes data from trials: MB102-065, MB102-071, MB102-092, MB102-100, MB102-112, MB102-125, D1691C00008, D1691C00012, D1691C00002 IR, D1691C00005 IR and D1691C00007 IR.

Table II-3 Estimated cumulative subject exposure to dapagliflozin + metformin FDC tablets from completed clinical trials by racial group

Racial group	Number of healthy subjects
Caucasian	348
Black or African American	99
Asian	11
Other	10
Unknown	132
Total	**600**

[a] Data from completed clinical trials of 15 January 2018. The table includes data from trials: MB102-065, MB102-071, MB102-092, MB102-100, MB102-112, MB102-125, D1691C00008, D1691C00012, D1691C00002 IR, D1691C00005 IR and D1691C00007 IR.

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

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

The foundation for the dapagliflozin+metformin FDC is the dapagliflozin clinical 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 (PK) 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. Eighteen subjects received dapagliflozin. 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 maximum plasma drug concentrations (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. Clinical trials with metformin included additional exclusion criteria, based on metformin restrictions.

Is it considered to be included as missing information: No

Rationale: The anticipated use in diabetic patients with severe renal impairment is expected to be low as use is contraindicated in the label (SmPC Section 4.3) due to that moderate to severe

renal insufficiency increases the risk of lactic acidosis (metformin component); this population is therefore not relevant for consideration as missing information.

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.

Is it considered to be included as missing information: No

Rationale: The anticipated use in diabetic patients with a history of unstable or rapidly progressing renal disease is expected to be low as use in patients with severe renal impairment is contraindicated in the label (SmPC Section 4.3) based on metformin restrictions; this population is therefore not relevant for consideration as missing information.

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: 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: The use of dapagliflozin in this population is expected to be limited. Patients with Congestive heart failure (CHF) may potentially have an increased sensitivity to volume depletion, but this is managed with the guidance on volume depletion in the SmPC.

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

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

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

No clinical trials have been performed with the dapagliflozin + metformin FDC that include populations typically under-represented in clinical trial development programmes.

II.5 MODULE SV: POST-AUTHORISATION EXPERIENCE

II.5.1 Method used to calculate exposure

The post-marketing patient exposure data presented is estimated based on dapagliflozin + metformin FDC's monthly actual ex-factory sales volume from each local marketing company. These data represent all dapagliflozin + metformin FDC formulation delivered to various distribution channels (for example wholesalers, pharmacies etc) worldwide.

The sales volume is provided as the number of tablets distributed. The estimated postmarketing patient exposure data for the reporting period is an approximation based on the assumption of each patient's daily dose by formulation:

- 2 tablets of 5 mg/850 mg or 5 mg/1000 mg per day of the IR formulation or
- 1 tablet of 5 mg/500 mg, 5 mg/1000 mg, 10 mg/500 mg or 10 mg/1000 mg per day of the XR formulation.

Therefore, a patient-year of exposure is the number of tablets using the above defined daily doses divided with 365 days.

The current methodology does not distinguish between sales that are related to initial prescriptions versus those related to repeat prescriptions. Therefore, it is not possible to estimate the number of patients exposed to dapagliflozin + metformin FDC. 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-4.

Table II-4 Dapagliflozin + metformin FDC sales quantity by region

Region	**Estimated exposure (patient-years)[a]**
Europe	171781
North America	100724
Japan	0
Rest of the world	196595
Total	**469100**

[a] Cumulative exposure as of 31 December 2017.

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

Potential for misuse for illegal purposes

The potential for drug abuse for dapagliflozin + metformin FDC has not been studied. Based on its pharmacological properties, dapagliflozin + metformin FDC 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 concern

No new safety concerns were identified following the results from the meta-analysis of amputation data from studies D1690C00018, D169C00019 and DECLARE CV outcomes study.

II.7.2.2 Reclassification of safety concerns

Not applicable.

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

Safety data available for co-administration of dapagliflozin and metformin are consistent with observations on dapagliflozin and metformin as individual treatments; thus, it is appropriate to base the safety profile of dapagliflozin + metformin FDC on both the experience with the combined use of dapagliflozin and metformin and on the safety profiles of the component products.

There are no unique important identified risks or important potential risks for dapagliflozin + metformin FDC.

II.7.3.2 Presentation of missing information

No missing information.

II.8 MODULE SVIII: SUMMARY OF THE SAFETY CONCERNS

II.8.1 Summary of the safety concerns

Table II-5 Summary of safety concerns

Important identified risks	Urinary tract infection (dapagliflozin) Lactic acidosis (metformin) Renal impairment (dapagliflozin) Diabetic Ketoacidosis including events with atypical presentation (dapagliflozin)

Table II-5 Summary of safety concerns

Important potential risks	Liver injury (dapagliflozin) Bladder cancer (dapagliflozin) Breast cancer (dapagliflozin) Prostate cancer (dapagliflozin) Lower limb amputation (dapagliflozin)
Missing information	None

III. PART III: PHARMACOVIGILANCE PLAN

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

Specific adverse reaction follow-up questionnaires for safety concern

See Annex 4 for copies of AE follow-up questionnaires for serious spontaneous reports of urinary tract infection, lactic-/ketoacidosis, renal impairment, liver injury, hypersensitivity reactions, bladder cancer, breast cancer, prostate cancer, and lower limb amputations.

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

There are no additional pharmacovigilance activities to address specific safety concerns or to measure effectiveness of risk minimisation measures for dapagliflozin + metformin FDC.

For information, there are ongoing/planned additional pharmacovigilance activities to address specific concerns or to measure effectiveness of risk minimisation measures for dapagliflozin. These activities are summarized below:

MB102103 (D1690R00008): Complications of UTI in Patients on Dapagliflozin (Category 3)

Comparison of the Risk of Severe Complications of UTI Between Patients with T2DM Exposed to Dapagliflozin and Those Exposed to Other Antidiabetic Treatments.

This is a cohort study conducted in data from the Clinical Practice Research Datalink (CPRD), HealthCore Integrated Research Database (HIRDSM), and US Medicare comparing hospitalisation or emergency department visit for severe complications of UTI and outpatient visits for pyelonephritis among new users of dapagliflozin and among those who are new users of anti-diabetic drugs (AD) in classes other than SGLT2 inhibitors, insulin monotherapy, metformin monotherapy, or Sulphonylurea (SU) monotherapy.

MB102104 (D1690R00005): Acute Liver Injury in Patients on Dapagliflozin (Category 3)

Comparison of the Risk of Acute Liver Injury (ALI) Between Patients With Type 2 Diabetes Exposed to Dapagliflozin and Those Exposed to Other Antidiabetic Treatments.

This is a cohort study in data from the CPRD, HIRDSM, and US Medicare comparing hospitalisation for ALI among new users of dapagliflozin with that among new users of ADs in classes other than SGLT2 inhibitors, insulin monotherapy, metformin monotherapy, or SU monotherapy.

MB102110 (D1690R00004): Acute Kidney Injury in Patients on Dapagliflozin and Other Antidiabetic Medications (Category 3)

Comparison of the Risk of Acute Kidney Injury (AKI) Between Patients with Type 2 Diabetes Exposed to Dapagliflozin and Those Exposed to Other Antidiabetic Treatment.

This is a cohort study conducted in data from the CPRD comparing hospitalisation for AKI among new users of dapagliflozin with hospitalisation among new users of ADs in classes other than SGLT2 inhibitors, insulin monotherapy, metformin monotherapy, or SU monotherapy.

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

Comparison of the Risk of Cancer Between Patients with Type 2 Diabetes Exposed to Dapagliflozin and Those Exposed to Other Antidiabetic Treatment.

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.

Externally sponsored research (independent investigator initiated): nonclinical mechanistic model studies (Category 3)

Studies aimed to elucidate the metabolic adaptations in term of glucose flux, lipolysis, and ketogenesis following insulin withdrawal in subjects with diabetes mellitus and absolute or relative endogenous insulin deficiency, when treated with dapagliflozin.

D169AC00001 dapaCKD (Category 3)

International, multicentre, event-driven, randomised, double-blind, parallel group, placebo-controlled study, evaluating the effect of dapagliflozin 10 mg versus placebo, given once daily in addition to standard of care, to prevent the progression of chronic kidney disease (CKD) or cardiovascular (CV)/renal death. Study includes additional eCRF for categorisation of amputation events and risk factors for amputation.

D169EC00001 Determine HFpEF (Category 3)

International, multi-centre, parallel-group, randomised, double-blind, placebo-controlled, phase III study in heart failure patients with preserved left ventricular ejection fraction, evaluating the effect of dapagliflozin 10 mg versus placebo, given once daily in addition to background local standard of care therapy, including treatments to control co-morbidities, on

change in heart failure symptoms as measured by the KCCQ-TSS, physical limitation as measured by the KCCQ-PLS, and exercise capacity as measured by 6MWD. Study includes additional eCRF for categorisation of amputation events and risk factors for amputation.

D169EC00002 Determine HFrEF (Category 3)

International, multi-centre, parallel-group, randomised, double-blind, placebo-controlled, phase III study in heart failure patients with left ventricular reduced ejection fraction, evaluating the effect of dapagliflozin 10 mg versus placebo, given once daily in addition to background local standard of care therapy, including treatments to control co-morbidities, on change in heart failure symptoms as measured by the KCCQ-TSS, physical limitation as measured by the KCCQ-PLS, and exercise capacity as measured by 6MWD. Study includes additional eCRF for categorisation of amputation events and risk factors for amputation.

D169CC00001 Deliver (Category 3)

International, multicentre, parallel-group, event-driven, randomised, double-blind study in patients with HFpEF, evaluating the effect of dapagliflozin 10 mg versus placebo, given once daily in addition to background regional standard of care therapy, including treatments to control co-morbidities, in reducing the composite of CV death and heart failure events (hospitalisations for HF or urgent HF visits). Study includes additional eCRF for categorisation of amputation events and risk factors for amputation.

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

There are no ongoing or planned additional pharmacovigilance studies or activities for dapagliflozin + metformin FDC.

The pharmacovigilance activities listed in Table III-1 are planned or ongoing for dapagliflozin, and are included in this RMP as the results will potentially provide information relevant to the safety profile of the dapagliflozin + metformin FDC. This information is provided for information only and these studies will be maintained though the dapagliflozin RMP.

Table III-1 Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				

Table III-1 Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
MB102103 (D1690R00008)- Observational study: Complications of UTI in Patients on Dapagliflozin Ongoing	Assess the incidence of hospitalization or emergency department visit for severe complications of UTI among new users of dapagliflozin compared to those who are new users of certain other antidiabetic drugs	Severe complications of UTI	Submission of interim data Submission of final data	2016, 2019 2020
MB102104 (D1690R00005) - Observational study: Acute Liver Injury in Patients on Dapagliflozin Ongoing	To assess the incidence of hospitalization for ALI among new users of dapagliflozin compared to those who are new users of certain other antidiabetic drugs	Risk of acute hepatic failure	Submission of Interim data Submission of final data	2016, 2019 2020
MB102110 (D1690R00004) - Observational study: Acute Kidney Injury in Patients on Dapagliflozin and Other Antidiabetic Medications Ongoing	To assess the incidence of hospitalization for AKI among new users of dapagliflozin compared to those who are new users of certain other antidiabetic drugs	Risk of AKI	Submission of Interim data Submission of final data	2016, 2019 2020
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	Risk of cancer	Interim data Final data	2016, 2019, 2021, 2023 2025
Nonclinical mechanistic model studies relating to diabetic ketoacidosis Ongoing	Research aiming to elucidate impact on cellular processes where presence of dapagliflozin may impact acid balance.	Ketoacidosis	Submission of final data	When available

Table III-1 Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
D169AC00001 dapaCKD A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients with Chronic Kidney Disease Ongoing	To determine if dapagliflozin is superior to placebo in reducing the incidence of the primary composite endpoint of ≥50% sustained decline in estimated glomerular filtration rate (eGFR), reaching end stage renal disease (ESRD), CV or renal death when added to current background therapy in patients with eGFR ≥25 and ≤75 mL/min/1.73m2 and albuminuria (urine albumin creatinine ratio [UACR] ≥200 and ≤5000 mg/g).	Lower limb amputation	Submission of final data	Q4 2020
D169EC00001 Determine HFpEF DETERMINE-preserved – Dapagliflozin EffecT on ExeRcise capacity using a 6-MINutE walk test in patients with heart failure with preserved ejection fraction	To determine whether dapagliflozin is superior to placebo in patients with chronic HF NYHA Functional Class II-IV and preserved ejection fraction (LVEF>40%) [HFpEF] in: • reducing patient-reported HF symptoms • reducing patient-reported physical limitation • improving exercise capacity	Lower limb amputation	Submission of final data	Q1 2021
D169EC00002 Determine HFrEF DETERMINE-reduced – Dapagliflozin EffecT on ExeRcise capacity using a 6-MINutE walk test in patients with heart failure with reduced ejection fraction	To determine whether dapagliflozin is superior to placebo in patients with chronic HF NYHA Functional Class II-IV and reduced ejection fraction (LVEF≤40%) [HFrEF] in: • reducing patient-reported HF symptoms • reducing patient-reported physical limitation • improving exercise capacity	Lower limb amputation	Submission of final data	Q1 2021

Table III-1 Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
D169CC00001 Deliver An International, Double-blind, Randomised, Placebo-Controlled Phase III Study to Evaluate the Effect of Dapagliflozin on Reducing CV Death or Worsening Heart Failure in Patients with Heart Failure with Preserved Ejection Fraction (HFpEF)	To determine whether dapagliflozin is superior to placebo, when added to standard of care, in reducing the composite of CV death and HF events (hospitalisation for HF or urgent HF visit) in patients with HF and preserved systolic function	Lower limb amputation	Submission of final data	Q3 2022

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
Urinary tract infection	Routine risk communication: SmPC section 4.8. PL section 4.
Lactic acidosis	Routine risk communication: SmPC sections 4.8. PL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: Symptoms of lactic acidosis included, and direction to assess patients immediately if these symptoms occur. Avoidance of excessive alcohol intake. Information included that Xigduo should be interrupted in relation to dehydration or conditions that could lead to hypoxia. In case of suspected symptoms, the patient should stop taking Xigduo and seek immediate medical attention. Discontinuation prior to intravascular administration of iodinated contrast agents due to risk of lactic acidosis. Laboratory abnormalities or clinical illness should be evaluated promptly and if evidence of acidosis, treatment must be stopped immediately. In the case of uncontrolled diabetes, Xigduo should not be taken (SmPC section 4.4, PL section 2). Xigduo is contraindicated in any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis) (SmPC section 4.3). Information on how to detect symptoms of lactic acidosis and instructions to seek medical attention (PL section 2, 4).
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 on how to detect symptoms of DKA and instructions to seek medical attention (PL section 2, 4).
Renal impairment	Routine risk communication: SmPC section 4.3

Table V-1 Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
	Routine risk minimisation activities recommending specific clinical measures to address the risk: Guidance is provided on monitoring renal function, and dosage adjustment (SmPC section 4.2, 4.4 and PL section 2). Contraindication in patients with severe renal failure or acute conditions with the potential to alter renal function (GFR < 30 mL/min) (SmPC section 4.3 and PL section 2).
Liver injury	None
Bladder cancer	None
Breast cancer	None
Prostate cancer	None
Lower limb amputation	Routine risk minimisation activities recommending specific clinical measures to address the risk: Guidance provided on potential class effect (SmPC section 4.4) and counsel on routine preventative foot care (SmPC section 4.4 and PL section 2).

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		
Urinary tract infection	Routine risk minimisation measures: SmPC section 4.8. PL section 4.	Routine PV: AE follow-up forms for serious spontaneous reports Additional PV: Study MB102103: Complications of UTI in Patients on Dapagliflozin
Lactic acidosis	Routine risk minimisation measures: SmPC sections 4.8. PL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk:	Routine PV: AE follow-up forms for spontaneous reports

Table V-2 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Symptoms of lactic acidosis included, and direction to assess patients immediately if these symptoms occur. Avoidance of excessive alcohol intake. Information included that Xigduo should be interrupted in relation to dehydration or conditions that could lead to hypoxia. In case of suspected symptoms, the patient should stop taking Xigduo and seek immediate medical attention. Discontinuation prior to intravascular administration of iodinated contrast agents due to risk of lactic acidosis. Laboratory abnormalities or clinical illness should be evaluated promptly and if evidence of acidosis, treatment must be stopped immediately. In the case of uncontrolled diabetes, Xigduo should not be taken (SmPC section 4.4, PL section 2). Xigduo is contraindicated in any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis) (SmPC section 4.3). Information on how to detect symptoms of lactic acidosis and instructions to seek medical attention (PL section 2, 4).	
Diabetic Ketoacidosis including events with atypical presentation	Routine risk minimisations measures: SmPC sections 4.4, 4.8. PL sections 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 on how to detect symptoms of DKA and instructions to seek medical attention (PL section 2, 4).	Routine PV: AE follow-up forms for spontaneous reports Additional PV: Nonclinical mechanistic model studies

Table V-2 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Renal impairment	Routine risk minimisations measures: SmPC section 4.3 Routine risk minimisation activities recommending specific clinical measures to address the risk: Guidance is provided on monitoring renal function, and dosage adjustment (SmPC section 4.2, 4.4 and PL section 2). Contraindication in patients with severe renal failure or acute conditions with the potential to alter renal function (GFR < 30 mL/min) (SmPC section 4.3 and PL section 2).	Routine PV AE follow-up forms for spontaneous reports Additional PV: MB102110: Acute Kidney Injury in Patients on Dapagliflozin and Other Antidiabetic Medications
Important potential risks		
Liver injury	No risk minimisation measures.	Routine PV: AE follow-up forms for spontaneous reports Additional PV: MB102104: Acute Liver Injury in Patients on Dapagliflozin
Bladder cancer	None	Routine PV: AE follow-up forms for spontaneous reports Additional PV: MB102118 [a]: Cancer in Patients on Dapagliflozin and Other Antidiabetic Treatment
Breast cancer	None	Routine PV: AE follow-up forms for spontaneous reports Additional PV: MB102118 [a]: 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	None	Routine PV: AE follow-up forms for spontaneous reports Additional PV: MB102118 [a]: Cancer in Patients on Dapagliflozin and Other Antidiabetic Treatment
Lower limb amputation	No risk minimisation measures.	Routine PV: AE follow-up forms for spontaneous reports Additional PV: Dedicated eCRF for Lower Limb Amputation will be evaluated in studies D169AC00001, D169CC00001, D169EC00001, D169EC00002

VI. PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN FOR XIGDUO/EBYMECT (DAPAGLIFLOZIN+METFORMIN FDC)

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

Xigduo/Ebymect's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Xigduo/Ebymect should be used.

This summary of the RMP for Xigduo/Ebymect 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 Xigduo/Ebymect's RMP.

VI.1 THE MEDICINE AND WHAT IT IS USED FOR

Xigduo/Ebymect is authorised for treatment of type 2 diabetes in adult patients as an adjunct to diet and exercise (see SmPC for the full indication). It contains dapagliflozin and metformin as the active substances and it is given orally.

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

Xigduo:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002672/human_med_001721.jsp&mid=WC0b01ac058001d124

Ebymect:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/004162/human_med_001926.jsp&mid=WC0b01ac058001d124

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

Important risks of Xigduo/Ebymect, together with measures to minimise such risks and the proposed studies for learning more about Xigduo/Ebymect'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 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 routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR 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 Xigduo/Ebymect 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 Xigduo/Ebymect. 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 longterm use of the medicine).

Table VI-1 List of important risks and missing information

Type of safety concern	Safety concern
Important identified risks	Urinary tract infection (dapagliflozin) Lactic acidosis (metformin) Diabetic Ketoacidosis including events with atypical presentation (dapagliflozin) Renal impairment (dapagliflozin)

Table VI-1 List of important risks and missing information

Type of safety concern	Safety concern
Important potential risks	Liver injury (dapagliflozin) Bladder cancer (dapagliflozin) Breast cancer (dapagliflozin) Prostate cancer (dapagliflozin) Lower limb amputation (dapagliflozin)
Missing information	None

VI.2.2 Summary of important risks

Table VI-2 Important identified risk – Urinary tract infection

Evidence for linking the risk to the medicine	Clinical trial data with use of dapagliflozin.
Risk factors and risk groups	Premenopausal women: coitus, spermicide exposure. In postmenopausal women: incontinence, urinary retention, cystocele, relative lack of estrogen accompanying menopause. In elderly males: prostatic hyperplasia, prostatitis.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.8 PL Section: 4
Additional pharmacovigilance activities	Study MB102103: Complications of UTI in Patients on Dapagliflozin See section VI.2.3 of this summary for an overview of the post-authorisation development plan.

Table VI-3 Important identified risk – Lactic acidosis

Evidence for linking the risk to the medicine	Postmarketing experience with use of metformin.
Risk factors and risk groups	Diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypoperfusion,,often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis. Poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency, dehydration, major surgery, and any conditions associated with hypoxia. Situations where renal function may become impaired, for example in the elderly, when initiating antihypertensive therapy, diuretic therapy or therapy with a nonsteroidal anti-inflammatory drug. Intravascular contrast with iodinated materials can lead to acute renal function deterioration.

Table VI-3 Important identified risk – Lactic acidosis

Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4, 4.8. PL section 2, 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: Symptoms of lactic acidosis included, and direction to assess patients immediately if these symptoms occur. Avoidance of excessive alcohol intake. Information included that Xigduo should be interrupted in relation to dehydration or conditions that could lead to hypoxia. In case of suspected symptoms, the patient should stop taking Xigduo and seek immediate medical attention. Discontinuation prior to intravascular administration of iodinated contrast agents due to risk of lactic acidosis. Laboratory abnormalities or clinical illness should be evaluated promptly and if evidence of acidosis, treatment must be stopped immediately. In the case of uncontrolled diabetes, Xigduo should not be taken (SmPC section 4.4, PL section 2). Xigduo is contraindicated in any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis) (SmPC section 4.3). Information on how to detect symptoms of lactic acidosis and instructions to seek medical attention (PL section 2, 4).

Table VI-4 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.
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 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).
Additional pharmacovigilance activities	Nonclinical mechanistic model studies relating to diabetic ketoacidosis See section VI.2.3 of this summary for an overview of the post-authorisation development plan.

Table VI-5 Important identified risk – Renal impairment

Evidence for linking the risk to the medicine	Clinical trial data with use of dapagliflozin.
Risk factors and risk groups	Patients who are elderly or volume depleted. Patients taking medications known to decrease blood pressure. Patients with CHF, arrhythmias, or adrenal insufficiency.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.3 Routine risk minimisation activities recommending specific clinical measures to address the risk: Guidance is provided on monitoring renal function, and dosage adjustment (SmPC section 4.2, 4.4 and PL section 2). Contraindication in patients with severe renal failure or acute conditions with the potential to alter renal function (GFR < 30 mL/min) (SmPC section 4.3 and PL section 2).
Additional pharmacovigilance activities	MB102110 (dapagliflozin) – Comparison of risk of acute kidney injury between patients with T2DM exposed to dapagliflozin and those exposed to other anti-diabetic treatments. See section VI.2.3 of this summary for an overview of the post-authorisation development plan.

Table VI-6 Important potential risk – Liver injury

Evidence for linking the risk to the medicine	Clinical trial data with use of dapagliflozin.
Risk factors and risk groups	Hepatotoxic drugs (such as non-steroidal anti-inflammatories, carbamazepine, isoniazid, statins), chronic liver disease (including cirrhosis), viral hepatitis infections (mainly B or C), alcohol consumption, diabetes.
Risk minimisation measures	None.
Additional pharmacovigilance activities	MB102104: Acute Liver Injury in Patients on Dapagliflozin See section VI.2.3 of this summary for an overview of the post-authorisation development plan.

Table VI-7 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, chemical exposure to known carcinogens (cyclophosphamide and aniline dyes, etc), and haematuria.
Risk minimisation measures	None

Table VI-7 Important potential risk - Bladder cancer

Additional pharmacovigilance activities	MB102118: Cancer in Patients on Dapagliflozin and Other Antidiabetic Treatment See section VI.2.3 of this summary for an overview of the post-authorisation development plan.

Table VI-8 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 estrogen (ie, 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.2.3 of this summary for an overview of the post-authorisation development plan.

Table VI-9 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.2.3 of this summary for an overview of the post-authorisation development plan.

Table VI-10 Important potential risk – Lower limb amputation

Evidence for linking the risk to the medicine	**Clinical trial data with another SGLT2 inhibitor.**
Risk factors and risk groups	Subjects with diabetes are at high risk for amputation due to a high prevalence of CV disease, including PAD, dyslipidaemia, peripheral neuropathy, and chronic kidney disease. Minor trauma can be an increased risk due to existing neuropathy and may led to ulcers that get infected and do not heal. The non-healing, infected ulcers may lead to gangrene and amputation.
Risk minimisation measures	None

Table VI-10 Important potential risk – Lower limb amputation

Additional pharmacovigilance activities	Dedicated eCRF for Lower Limb Amputation will be evaluated in studies D169AC00001, D169CC00001, D169EC00001, D169EC00002 See section VI.2.3 of this summary for an overview of the post-authorisation development plan.

VI.2.3 Post-authorisation development plan

VI.2.3.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Xigduo/Ebymect.

VI.2.3.2 Other studies in post-authorisation development plan

There are no ongoing or planned additional pharmacovigilance studies or activities for Xigduo. The information below is provided for information only and these studies will be maintained though the dapagliflozin RMP.

Study short name: MB102103 (D1690R00008) – Complications of UTI in Patients on Dapagliflozin [Observational study].

Purpose of the study: To compare, by insulin use at the index date, the sex-specific incidence of hospitalisation or emergency department visit for severe complications of UTI, defined as pyelonephritis and urosepsis, among patients with T2DM who are new users of dapagliflozin with those who are new users of antidiabetic drugs in classes other than SGLT2 inhibitors, insulin monotherapy, metformin monotherapy, or SU monotherapy.

Study short name: MB102104 (D1690R00005) – Acute Liver Injury in Patients on Dapagliflozin [Observational study].

Purpose of the study: To compare, by insulin use at the index date, the incidence of hospitalisation for acute liver injury among patients with T2DM who are new users of dapagliflozin with those who are new users of antidiabetic drugs in classes other than SGLT2 inhibitors, insulin monotherapy, metformin monotherapy, or SU monotherapy.

Study short name: MB102110 (D1690R00004) – Acute Kidney Injury in Patients on Dapagliflozin [Observational study].

Purpose of the study: To compare, by insulin use at the index date, the incidence of hospitalisation for acute kidney injury (AKI) among patients with T2DM who are new users of dapagliflozin with those who are new users of antidiabetic drugs in classes other than SGLT2 inhibitors, insulin monotherapy, metformin monotherapy, or SU monotherapy.

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: D169AC00001 dapaCKD

Purpose of the study: Evaluate the effect of dapagliflozin on renal outcomes and cardiovascular mortality in patients with chronic kidney disease.

Study short name: D169EC00001 Determine A HFpEF

Purpose of the study: Evaluating the effect of dapagliflozin on exercise capacity in heart failure patients with preserved ejection fraction (HFpEF)..

Study short name: D169EC00002 Determine B HFrEF

Purpose of the study: Evaluating the effect of dapagliflozin on exercise capacity in heart failure patients with reduced ejection fraction (HFrEF).

Study short name: D169CC00001 Deliver

Purpose of the study: Evaluate the effect of dapagliflozin on reducing cardiovascular death or worsening heart failure in patients with heart failure with preserved ejection fraction (HFpEF).

LIST OF REFERENCES

No references.

EU RMP Part VII Annex 4

Drug Substance	dapagliflozin + metformin fixed dose combination
Version Number of EU RMP when last updated	v 11

EUROPEAN UNION RISK MANAGEMENT PLAN (EU RMP) FOR DAPAGLIFLOZIN AND METFORMIN FIXED DOSE COMBINATION

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

Active substance(s) (INN or common name)	dapagliflozin + metformin FDC
Product(s) concerned (brand names(s))	Xigduo, Ebymect
Name of Marketing Authorisation Holder or Applicant	AstraZeneca AB

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1. SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

The following adverse drug reaction follow-up forms are in use for dapagliflozin + metformin FDC:

- Questionnaire (dapagliflozin + metformin FDC) - urinary tract infection
- Questionnaire (dapagliflozin + metformin FDC) - lactic-/ketoacidosis
- Questionnaire (dapagliflozin + metformin FDC) - renal impairment
- Questionnaire (dapagliflozin + metformin FDC) - liver injury
- Questionnaire (dapagliflozin + metformin FDC) - hypersensitivity reactions, including severe cutaneous reactions
- Questionnaire (dapagliflozin + metformin FDC) - bladder cancer
- Questionnaire (dapagliflozin + metformin FDC) - breast cancer
- Questionnaire (dapagliflozin + metformin FDC) - prostate cancer
- Questionnaire (dapagliflozin + metformin FDC) - lower limb amputations

Urinary Tract Infection 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 (for renal failure be specific about chronicity: acute, chronic or acute on chronic)			
Adverse Event(s)	**Start Date** *(DD/MM/YY)*	**End Date** *(DD/MM/YY)*	**Outcome**
			☐ Event ongoing ☐ Recovered ☐ Recovered with /sequele ☐ Patient Died
			☐ Event ongoing ☐ Recovered ☐ Recovered with sequele ☐ Patient Died
			☐ Event ongoing ☐ Recovered ☐ Recovered with sequele ☐ Patient Died

Diagnostic criteria and clinical diagnosis of the event(s) (brief description), please specify how the diagnosis was performed:

Please also specify signs and symptoms associated with the event(s), i.e pain or burning or uncomfortable pressure in the lower abdomen/pelvic area while passing urine, blood in the urine, and symptoms of urinary urgency (a strong and uncontrolled urge to pass urine). Other suggestive signs or symptoms such as dysuria, urgency or frequency of urination, suprapubic or perineal discomfort, flank, back or abdominal pain, costovertebral angle tenderness, nausea, vomiting, chills or sepsis:

Fever? If yes, please add degree
☐ Yes ☐ No ☐ Unknown

Was the patient hospitalized for the event(s)?
☐ Yes ☐ No ☐ Unknown

Was treatment provided? if yes, please describe
☐ Yes ☐ No ☐ Unknown

Urinary Tract Infection Questionnaire
Request for Additional Information

Case ID #:_____

Manufacturer Date of Receipt: _____

First event of urinary infection while on treatment with DAPA? if no, please specify episode and date
☐ Yes ☐ No ☐ Unknown

Were there any complications caused by the event(s)? if yes, please describe
☐ Yes ☐ No ☐ Unknown

Did the patient receive antimicrobial medication? if yes, please describe
☐ Yes ☐ No ☐ Unknown

Dapagliflozin+metformin therapy			
Indication:	**Daily dosage:**	**Start date** *(DD/MM/YY)*:	**Stop date** *(DD/MM/YY)*:
Was dapagliflozin+metformin stopped due to the event(s)? ☐ Yes, permanently ☐ Yes, temporarily ☐ No ☐ N/A			
If yes, did the event(s) improve after stopping/altering dapagliflozin+metformin? ☐ Yes, date stopped or dose changed: _____ ☐ No ☐ N/A			
Was dapagliflozin+metformin re-introduced? ☐ Yes, date re-introduced: _____ ☐ No ☐ N/A			
If yes, did the event(s) recur after reintroduction? ☐ Yes, date recurred: _____ ☐ No ☐ N/A			
Does the reporter consider there to be a causal relationship between dapagliflozin+metformin and the adverse event(s)? ☐ Yes ☐ No Please explain:			

Concomitant medications
Exclude drugs used 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

Urinary Tract Infection Questionnaire
Request for Additional Information

Case ID #:_____

Manufacturer Date of Receipt: _____

Relevant medical history/concurrent diseases Please provide details: approximate dates of diagnosis and resolution if applicable	
- Catheter or urinary tractinstrumentation/surgery: ☐Yes ☐No ☐UNK - Bladder pathology: ☐Yes ☐No ☐UNK - Chronic prostatitis: ☐Yes ☐No ☐UNK - Chronic pyelonephritis: ☐Yes ☐No ☐UNK - Estrogen deficiency: ☐Yes ☐No ☐UNK - Urine incontinence: ☐Yes ☐No ☐UNK - Vesicoureteral reflux: ☐Yes ☐No ☐UNK - Urethral obstruction: ☐Yes ☐No ☐UNK - Recurrent UTI: ☐Yes ☐No ☐UNK	- Smoking: ☐Yes ☐No ☐UNK - Alcoholism: ☐Yes ☐No ☐UNK - Glucocorticoid treatment: ☐Yes ☐No ☐UNK - Recent or ongoing treatment with antibiotics: ☐Yes ☐No ☐UNK - Birth control pills: ☐Yes ☐No ☐UNK Other, please specify:_____

Was any diagnostic test performed? (e.g. CRP, leucocyte count)
☐ Yes ☐ No ☐ Uknown; if yes, please describe below

Name of test	Test date	Results (describe abnormality)
		☐ Normal ☐ Abnormal, Describe:
		☐ Normal ☐ Abnormal, Describe:
		☐ Normal ☐ Abnormal, Describe:

Urinary culture performed? ☐ Yes ☐ No ☐ Unknown; if yes, tick below question
Results indicative of UTI? ☐ Yes ☐ No ☐ Unknown; if yes, please describe below

Organism	Test date	Quantification

Did this event require more than one course of antimicrobial treatment?
☐ Yes ☐ No ☐ Unknown, if yes, please describe below

Urinary Tract Infection Questionnaire
Request for Additional Information

Case ID #:_____

Manufacturer Date of Receipt: _____

Date and Signature

Date: _____

Signature (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 Acidosis

V2.0

Case ID: Manufacturer Date of Receipt:

Reporter Information		
Reporter Name:		
Reporter Address:		
Telephone:	Fax:	Email:

Patient Detail	
Initials:	Sex: ☐Female ☐Male
Weight: ☐kg☐lb	Height: ☐cm☐in
Date of Birth (YY/MM/DD):	or Age:
Ethnic Origin: ☐hispanic ☐non-hispanic	Race: ☐Asian ☐Black ☐White ☐Other

Type of diabetes				
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	Start Date (YY/MM/DD)	Stop Date (YY/MM/DD)	Outcome
			☐ Ongoing ☐ Recovered ☐ Recovered w. sequelae ☐ Patient died
			☐ Ongoing ☐ Recovered ☐ Recovered w. sequelae ☐ Patient died
			☐ Ongoing ☐ Recovered ☐ Recovered w. sequelae ☐ Patient died
			☐ Ongoing ☐ Recovered ☐ Recovered w. sequelae ☐ Patient died
			☐ Ongoing ☐ Recovered ☐ Recovered w. sequelae ☐ Patient died
Diagnostic criteria and clinical diagnosis of event(s) – brief description include symptoms and findings from physical examinations:			

Was the patient hospitalized for the event?	☐ Yes	☐ No
Was treatment provided? If yes, please describe	☐ Yes	☐ No

Request for Additional Information in response to event or symptoms of Acidosis

V2.0

Was there any complications caused by the event(s)? If yes, please describe	☐ Yes	☐ No

Dapagliflozin + metformin therapy					
Indication:	Daily dosage:	Start date:	Stop date:		
Was dapagliflozin + metformin stopped or the dose altered due to the event(s)?	☐ Yes, permanently	☐ Yes, temporarily	☐ No	☐ N/A	
If yes, did the event(s) improve after stopping/altering the dose? Date treatment stopped / changed:	☐ Yes	☐ No	☐ N/A		
Was dapagliflozin + metformin reintroduced? Date treatment was reintroduced:	☐ Yes	☐ No	☐ N/A		
If yes, did the events reoccur after restart of treatment? Date of reoccurence:	☐ Yes	☐ No	☐ N/A		
Does the reporter consider there to be a casual relationship between dapagliflozin + metformin and the adverse event(s)?		☐ Yes	☐ No		
Please explain:					
Metformin in addition to dapagliflozin + metformin? If yes, specify below:		☐ Yes	☐ No		
Indication:	Daily dose:	Start date:	Stop date:		

Antidiabetic medications (include treatments up to 3 months in advance of the reported event)					
Drug Name	Indication	Daily Dosage	Route	Start date YY/MM/DD	Stop date YY/MM/DD
Was this a suspect medication?				☐ Yes	☐ No
Was this a suspect medication?				☐ Yes	☐ No
Was this a suspect medication?				☐ Yes	☐ No
Was this a suspect medication?				☐ 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	Stop date
Was this a suspect medication?				☐ Yes	☐ No
Was this a suspect medication?				☐ Yes	☐ No
Was this a suspect medication?				☐ Yes	☐ No
Was this a suspect medication?				☐ Yes	☐ No
Please commen on any known, missed or changed doses in addition to what is listed above:					

Request for Additional Information in response to event or symptoms of Acidosis

V2.0

Relevant medical history, concurrent diseases or other contributing factors		**Start date**	**Stop date**	**Please provide details**
Previous episodes of acidosis	☐ Yes ☐ No			
Carbohydrate reduced diet	☐ 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			
Renal disease	☐ Yes ☐ No			
Exposure to contrast media	☐ Yes ☐ No			
Dehydration	☐ Yes ☐ No			
Diarrhea	☐ Yes ☐ No			
Vomiting	☐ Yes ☐ No			
Acute heart failure	☐ Yes ☐ No			
Acute myocardial infarction	☐ Yes ☐ No			
Other conditions with hypoxia, specify:	☐ Yes ☐ No			
Other, specify:				

Request for Additional Information in response to event or symptoms of Acidosis

V2.0

Laboratory tests				
Laboratory test	**Sample**	**Unit**	**Sample date**	**Reference Values (… to …)**
Blood/Plasma Glucose	Pre treatment			
	Peak value			
	Follow-up value			
Blood pH	Pre treatment			
	Peak value			
	Follow-up value			
PCO_2	Pre treatment			
	Peak value			
	Follow-up value			
Serum Bicarbonate	Pre treatment			
	Peak value			
	Follow-up value			
Serum Potassium (K)	Pre treatment			
	Peak value			
	Follow-up value			
Serum Sodium (Na)	Pre treatment			
	Peak value			
	Follow-up value			
Blood/Serum Ketones	Pre treatment			
	Peak value			
	Follow-up value			
Urine Ketones	Pre treatment			
	Peak value			
	Follow-up value			
c-Peptide	Pre treatment			
	Peak value			
	Follow-up value			
Lactate	Pre treatment			
	Peak value			
	Follow-up value			
Serum creatinine	Pre treatment			
	Peak value			
	Follow-up value			
GFR	Pre treatment			
	Peak value			
	Follow-up value			
Anion gap	Pre treatment			
	Peak value			
	Follow-up value			
β-hydroxybutyrate	Pre treatment			
	Peak value			
	Follow-up value			

Request for Additional Information in response to event or symptoms of Acidosis

V2.0

Laboratory tests				
Laboratory test	**Sample**	**Unit**	**Sample date**	**Reference Values (… to …)**
Metformin plasma levels	Pre treatment			
	Peak value			
	Follow-up value			
Metformin concentration in erythrocytes	Pre treatment			
	Peak value			
	Follow-up value			
Other, please specify:	Pre treatment			
	Peak value			
	Follow-up value			
Other, please specify:	Pre treatment			
	Peak value			
	Follow-up value			
Other, please specify:	Pre treatment			
	Peak value			
	Follow-up value			

Date and Signature

Date:

Signature (Reporting Physician): _____

Contact Information

Please return completed form to:

Fax:

E-mail:

Mail:

Thank you for completing this form!

Potential Renal Impairment/Failure 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 (for renal failure be specific about chronicity: acute, chronic or acute on chronic)			
Adverse Event(s)	**Start Date** *(DD/MM/YY)*	**End Date** *(DD/MM/YY)*	**Outcome**
			☐ Event ongoing ☐ Recovered ☐ Recovered with sequele ☐ Patient Died
			☐ Event ongoing ☐ Recovered ☐ Recovered wth sequele ☐ Patient Died
			☐ Event ongoing ☐ Recovered ☐ Recovered with sequele ☐ Patient Died

Diagnostic criteria and clinical diagnosis of the event(s) (brief description, including (a) symptoms, abdominal pain, mental status changes etc, (b) Findings from physical examination and (c) clinical diagnosis of the renal adverse event).
If a nephrologist consult was obtained please specify the findings or provide the consultation report:

Type of renal failure

☐ pre-renal ☐ renal (intrinsic) ☐ post-renal ☐ Other(e.g. acute glomerulonephritis, interstitial nephritis, tubular necrosis)

Was the patient hospitalized for the event(s)?

☐ Yes ☐ No ☐ Unknown

Was treatment provided? if yes, please describe

☐ Yes ☐ No ☐ Unknown

Were there any complications caused by the event(s)? if yes, please describe

☐ Yes ☐ No ☐ Unknown

Dapagliflozin+metformin therapy			
Indication:	**Daily dosage:**	**Start date** *(DD/MM/YY)*:	**Stop date** *(DD/MM/YY)*:

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

If yes, did the event(s) improve after stopping/altering dapagliflozin+metformin?

☐ Yes, date stopped or dose changed: _____ ☐ No ☐ N/A

Potential Renal Impairment/Failure Questionnaire
Request for Additional Information

Case ID #:_____

Manufacturer Date of Receipt: _____

Was dapagliflozin+metformin re-introduced? ☐ Yes, date re-introduced: _____ ☐ No ☐ N/A
If yes, did the event(s) recur after reintroduction? ☐ Yes, date recurred: _____ ☐ No ☐ N/A
Does the reporter consider there to be a causal relationship between dapagliflozin+metformin 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

Relevant medical history/concurrent diseases
Please provide details: approximate dates of diagnosis and resolution if applicable

Hypertension: ☐Yes ☐No ☐UNK

Diabetes mellitus: ☐Yes ☐No ☐UNK

Heart failure: ☐Yes ☐No ☐UNK

Drug abuse: ☐Yes ☐No ☐UNK

Exposure to contrast media: ☐Yes ☐No ☐UNK

Obstruction of urinary tract: ☐Yes ☐No ☐UNK

HIV/AIDS: ☐Yes ☐No ☐UNK

Organ transplantation: ☐Yes ☐No ☐UNK

Hematological disorder, if yes, specify: ☐Yes ☐No ☐ UNK

SLE: ☐Yes ☐No ☐UNK

Rhabdomyolysis: ☐Yes ☐No ☐UNK

Sepsis/shock: ☐Yes ☐No ☐UNK

Thrombosis: ☐Yes ☐No ☐UNK

Tumor lysis syndrome: ☐Yes ☐No ☐UNK

Malignant disease, if yes, specify: ☐Yes ☐No ☐UNK

Trauma: ☐Yes ☐No ☐UNK

Liver disease, if yes, specify: ☐Yes ☐No ☐UNK

Other, specify:_____

Potential Renal Impairment/Failure Questionnaire
Request for Additional Information

Case ID #:_____

Manufacturer Date of Receipt: _____

Laboratory Results- Before/During/After Treatment: or provide a copy of the results with special importance to renal function tests (serum and urine creatinine, BUN, urea, GFR, cystatin C, glucose/creatinine ratio, urianalysis, urine volume, proteinuria, etc) or any other testing done at. a) baseline, b) at time of the event, c) after interrupting/discontinuing suspect medication, d) after restarting suspect medication, e) if the suspect medication was continued, uninterrupted, subsequent test results

Test	**Reference Values** (please provide units) (…….to …….)	**Baseline Value** (pre-treatment) Date *(DD/MM/YY)/* Result	**Event Onset Value** Date *(DD/MM/YY)/* Result	**Peak Value** Date *(DD/MM/YY)/* Result	**Post-withdrawal Test Value** Date *(DD/MM/YY)/* Result	**Return to Normal** Date *(DD/MM/YY)/* Result
Serum creatinine						
BUN/Urea						
GFR						
Proteinuria						
Other, please specify :						

Relevant imaging studies (e.g., abdominal ultrasound, CT scan, MRI) and other investigations (e.g., drug screening, biopsy, autopsy):

Name of Test	**Test Date**	**Results (describe abnormality)**
		☐ Normal ☐ Abnormal, Describe:
		☐ Normal ☐ Abnormal, Describe:
		☐ Normal ☐ Abnormal, Describe:

Date and Signature

Date: _____

Signature (Reporting Physician): _____

Contact information

Please return comlpeted form to:

Fax:

E-mail:

Mail:

Thank you for completing this form.

Potential Liver Injury 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
			☐ Event ongoing ☐ Recovered ☐ Recovered with sequele ☐ Patient Died
			☐ Event ongoing ☐ Recovered ☐ Recovered with sequele ☐ Patient Died

Diagnostic criteria and clinical diagnosis of the event(s) (brief description, including (a) symptoms, abdominal pain, jaundice, mental status changes etc, (b) Findings from physical examination and (c) clinical diagnosis of the liver adverse event). If a GI consult was obtained please specify the findings or provide the consultation report:

Was the patient hospitalized for the event(s)?
☐ Yes ☐ No ☐ UNK

Was treatment provided? if yes, please describe ☐ Yes ☐ No ☐ Unknown

Were there any complications caused by the event(s)?
if yes, please describe ☐ Yes ☐ No ☐ Unknown

Potential Liver Injury Questionnaire Request for Additional Information

Case ID #:_____

Manufacturer Date of Receipt: _____

Dapagliflozin+metformin therapy			
Indication:	**Daily dosage:**	**Start date** *(DD/MM/YY)*:	**Stop date** *(DD/MM/YY)*:
Was dapagliflozin+metformin stopped or the dosage altered due to the event(s)? ☐ Yes, permanently ☐ Yes, temporarily ☐ No ☐ N/A			
If yes, did the event(s) improve after stopping/altering dapagliflozin+metformin? ☐ Yes, date stopped or dose changed: _____ ☐ No ☐ N/A			
Was dapagliflozin+metformin re-introduced? ☐ Yes, date re-introduced: _____ ☐ No ☐ N/A			
If yes, did the event(s) recur after reintroduction? ☐ Yes, date recurred: _____ ☐ No ☐ N/A			
Does the reporter consider there to be a causal relationship between dapagliflozin+metformin 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 a suspect medication?**
						☐ Yes ☐ No
						☐ Yes ☐ No
						☐ Yes ☐ No

Relevant medical history/concurrent diseases
Please provide details: approximate dates of diagnosis and resolution if applicable

- Hepato-biliary disease (if yes, specify): ☐Yes ☐No ☐UNK
- Hyperlipidemia: ☐Yes ☐No ☐UNK
- Bleeding disorders (if yes, specify): ☐ Yes ☐No ☐UNK
- Ischemic hepatitis (eg: hypotension or CHF): ☐Yes ☐No ☐UNK
- Viral hepatitis A, B, C or E (specify): ☐Yes ☐No ☐UNK
- Cardiovascular disease (if yes, specify): ☐Yes ☐No ☐UNK
- Autoimmune disease/ immune-compromised status (if yes, specify): ☐Yes ☐No ☐ UNK
- Obesity: ☐Yes ☐No ☐UNK
- Alcohol and/or drug abuse (if yes, specify): ☐Yes ☐No ☐UNK
- Recent vaccinations or travels (if yes, specify): ☐Yes ☐No ☐UNK
- Occupational toxic agent/environmental exposure (if yes, specify): ☐Yes ☐No ☐UNK
- Relevant family history (if yes, specify): ☐Yes ☐No ☐UNK
- Neoplasm (if yes, specify): ☐Yes ☐No ☐UNK

Other (specify):_____

Potential Liver Injury Questionnaire Request for Additional Information

Case ID #:_____

Manufacturer Date of Receipt: _____

Laboratory Results- Before/During/After Treatment: or provide a copy of the results with special importance to liver function tests (AST, ALT, Total Bilirubin Alk-phosphatase), albumin, PT, INR, bicarbonate, eosinophils, imaging studies, serology for viral hepatitis (antigen/antibody/DNA), histopathology/biopsy, immune-histochemistry (antinuclear antibody, antismooth muscle antibody etc) or any other testing done at. a) baseline, b) at time of the event, c) after interrupting/discontinuing suspect medication, d) after restarting suspect medication, e) if the suspect medication was continued, uninterrupted, subsequent test results

Test	**Reference Values** (please provide units) (……..to …….)	**Baseline Value** (pre-treatment) Date *(DD/MM/YY)/* Result	**Event Onset Value** Date *(DD/MM/YY)/* Result	**Peak Value** Date *(DD/MM/YY)/* Result	**Post-withdrawal Test Value** Date *(DD/MM/YY)/* Result	**Return to Normal** Date *(DD/MM/YY)* Result
ALT						
AST						
Bilirubin						
ALP						
Other, please specify :						

Relevant imaging studies (e.g., abdominal ultrasound, CT scan, MRI) and other investigations (e.g., drug screening, biopsy, autopsy):

Name of Test	**Test Date**	**Results (describe abnormality)**
		☐ Normal ☐ Abnormal Describe:
		☐ Normal ☐ Abnormal Describe:

Date and Signature

Date: _____

Signature (Reporting Physician): _____

Contact information

Please return completed form to:

Fax:

E-mail:

Mail:

Thank you for completing this form.

Hypersensitivity Reaction, including Severe Cutaneous Adverse Reaction, 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)*	**Stop Date** *(DD/MM/YY)*	**Outcome**	
			☐ Recovered ☐ Event ongoing	☐ Recovered with sequlae ☐ Patient died
			☐ Recovered ☐ Event ongoing	☐ Recovered with sequlae ☐ Patient died
			☐ Recovered ☐ Event ongoing	☐ Recovered with sequlae ☐ Patient died
Diagnostic criteria and clinical diagnosis of the event(s):				
Was the patient hospitalized for the ev ent(s)? ☐ Yes ☐ No **Was treatment provided?** ☐ 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):*	

Did the patient experience any of the following:		**Start Date** *(DD/MM/YY)*	**Stop Date** *(DD/MM/YY)*	**Comments**
Anaphylactoid reaction, anaphylactic reaction/shock	☐ Yes ☐ No			
Angioedema	☐ Yes ☐ No			
Respiratory reaction, including dyspnea, wheezing, bronchospasm, tongue swelling and/or throat swelling/obstruction	☐ Yes ☐ No			
Rash,urticaria with/without pruritis	☐ Yes ☐ No			
Rash with eosinophilia and systemic symptoms	☐ Yes ☐ No			
Serious skin reaction, such as erythema multiforme, SJS, TEN, or exfoliative dermatitis (please specify)	☐ Yes ☐ No			
Other, please specify:	☐ Yes ☐ No			

Dapagliflozin+metformin therapy					
Indication:	**Daily dosage:**	**Start Date** *(DD/MM/YY):*		**Stop Date** *(DD/MM/YY):*	
Was dapagliflozin+metformin stopped due to the event(s)?		☐ Yes, permanently	☐ Yes, temporarily	☐ No	☐ N/A
If yes, did the event(s) improve after stopping dapagliflozin+metformin?		☐ Yes, permanently	☐ Yes, temporarily	☐ No	☐ N/A
Was dapagliflozin+metformin 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+metformin and the adverse event(s)?		☐ Yes	☐ No Please explain:		

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

Does the patient possess any of the following disorders or risk factors?		**Start Date** *(DD/MM/YY)*	**Stop Date** *(DD/MM/YY)*	**If yes, please provide details**
History of allergies	☐ Yes ☐ No			
Family history of allergies	☐ Yes ☐ No			
Previous drug reactions	☐ Yes ☐ No			
Asthma or COPD	☐ Yes ☐ No			
Significant cardiac disorders	☐ Yes ☐ No			
Autoimmune disease	☐ Yes ☐ No			
Immunocompromised status	☐ Yes ☐ No			
Recent vaccination	☐ Yes ☐ No			
Infection	☐ Yes ☐ No			
Other, please specify:	☐ Yes ☐ No			
	☐ Yes ☐ No			

Diagnostic Investigations (drug screening, biopsy, lab tests, autopsy):			
Name of Test	**Was the test performed?**	**Test Date** *(DD/MM/YY)*	**Results (specify abnormality)**
Skin test or biopsy	☐ No ☐ Yes		☐ Normal ☐ Abnormal
Drug provocation test	☐ No ☐ Yes		☐ Normal ☐ Abnormal
Immunoglobulin tests (please specify):	☐ No ☐ Yes		☐ Normal ☐ Abnormal
Other, please specify:	☐ No ☐ Yes		☐ Normal ☐ Abnormal

Specialist consultation

Has a specialist been consulted? ☐ No ☐ Yes (If yes, please summarize or send a copy of the consultation report)

Please provide any further relevant information about the Adverse Event

Include any other treatments received that have not been previously stated.

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: _____

Bladder Cancer Questionnaire
Request for Additional Information

Case ID #:_____

Manufacturer Date of Receipt: _____

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

Bladder Cancer Questionnaire
Request for Additional Information

Case ID #:_____

Manufacturer Date of Receipt: _____

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

☐ 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)

Bladder Cancer Questionnaire
Request for Additional Information

Case ID #:_____

Manufacturer Date of Receipt: _____

Date and Signature

Date: _____

Signature (Reporting Physician): _____

Contact information

Please return completed form to:

Fax:

E-mail:

Mail:

Thank you for completing this form.

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

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

dapagliflozin questionnaire
Request for Additional Information Amputation and Adverse Events that may precede Amputation

Case ID #:_____

Manufacturer Date of Receipt: _____

In diabetic patients, events such as gangrene, irreversibile infection, ulceration and peripheral vascular disease may lead to amputation. This is a request for information if the patient have had an amputation performed after initiation of dapagliflozin or dapagliflozin-metformin.

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:**

Amputation			
Did the patient have an amputation?		☐ Yes ☐ No ☐ Unknown	
If yes, type of event:			
Trauma by accident ☐	Surgical amputation ☐	Spontaneous/Non-Surgical ☐	
Location of amputation:			
Left	☐	Right	☐
Below knee	☐	Below elbow	☐
Above knee	☐	Above elbow	☐
Foot	☐	Hand	☐
Big toe	☐	Thumb	☐
Index toe	☐	Index finger	☐
Middle toe	☐	Middle finger	☐
Fourth toe	☐	Ring finger	☐
Little toe	☐	Little finger	☐

dapagliflozin questionnaire
Request for Additional Information Amputation and Adverse Events that may precede Amputation

Case ID #:_____

Manufacturer Date of Receipt: _____

Amputation	
Trans metatarsal	☐
Other	☐
specify:_____	

Adverse event contributing to/leading up to the amputation			
Adverse Event(s)	**Start Date** *(DD/MM/YY)*	**End Date** *(DD/MM/YY)*	**Outcome**
			Event ongoing ☐ Recovered ☐ Recovered with sequele ☐ Specify_____ ☐ Patient Died
			Event ongoing ☐ Recovered ☐ Recovered with sequele ☐ Specify_____ ☐ Patient Died
			Event ongoing ☐ Recovered ☐ Recovered with sequele ☐ Specify_____ ☐ Patient Died

Diagnostic criteria and clinical diagnosis of the event(s) (brief description, including (a) symptoms, (b) Findings from physical examination and (c) clinical diagnosis of the event(s) leading up to the amputation

Was the patient hospitalized for the event(s)?
☐ Yes ☐ No ☐ Unknown

Was treatment provided?
☐ Yes ☐ No ☐ Unknown

If yes, please describe: _____

Were there any complications caused by the event(s)?
☐ Yes ☐ No ☐ Unknown

If yes, please describe: _____

Dapagliflozin therapy			
Indication:	**Daily dosage:**	**Start date** *(DD/MM/YY)*:	**Stop date** *(DD/MM/YY)*:
Was dapagliflozin stopped or the dosage altered due to the event(s)? ☐ Yes, permanently ☐ Yes, temporarily ☐ No ☐ N/A			
If yes, did the event(s) improve after stopping/altering dapagliflozin? ☐ Yes, date stopped or dose changed: _____ ☐ No ☐ N/A			
Was dapagliflozin re-introduced? ☐ Yes, date re-introduced: _____ ☐ No ☐ N/A			

dapagliflozin questionnaire
Request for Additional Information Amputation and Adverse Events that may precede Amputation

Case ID #:_____

Manufacturer Date of Receipt: _____

Dapagliflozin therapy	
If yes, did the event(s) recur after reintroduction?	☐ Yes, date recurred: _____ ☐ 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, including antidiabetic and diuretic 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 a suspect medication?**
						☐ Yes ☐ No
						☐ Yes ☐ No
						☐ Yes ☐ No

Relevant medical history/ risk factors/concurrent diseases Please provide details: approximate dates of diagnosis and resolution if applicable	
Diabetes:	☐Yes ☐No ☐UNK
Diabetes Type:	☐Type I ☐Type II
Date of Diabetes diagnosis:	Day:_____ Month:_____Year_____
Ankle-brachial pressure index measured	☐Yes ☐No ☐UNK
If yes, Date of measurement	Day:_____ Month:_____Year_____
Results:_____	
est. Glomerular Filtration Rate (eGFR) prior to treatment	☐Yes ☐No ☐UNK
If yes, Date of measurement:	Day:_____ Month:_____Year_____
Result:_____	
Diabetic neuropathy	☐Yes ☐No ☐UNK
Renal disease	☐Yes ☐No ☐UNK

dapagliflozin questionnaire
Request for Additional Information Amputation and Adverse Events that may precede Amputation

Case ID #:_____

Manufacturer Date of Receipt: _____

Relevant medical history/ risk factors/concurrent diseases Please provide details: approximate dates of diagnosis and resolution if applicable	
Dehydration	☐Yes ☐No ☐UNK
Infection (of limb):	
Wet gangrene	☐Yes ☐No ☐UNK
Non-healing infectious ulcer	☐Yes ☐No ☐UNK
Osteomyelitis	☐Yes ☐No ☐UNK
Other Infection	☐Yes ☐No ☐UNK
If yes, please specify:	

Tobacco use		
Never smoked ☐	Current smoker ☐	Former smoker ☐
Tobacco stop date:	Day:_____ Month:_____Year_____	
If current or former smoker		
Amount of smokes/day:_____		
Number of years smoking:_____		
Tobacco type:_____		

Date and Signature

Date: _____

Signature (Reporting Physician): _____

Contact information

Please return completed form to:
Mail:

Fax: E-mail:

Thank you for completing this form.