EU RMP	
Drug Substance	Dapagliflozin/metformin fixed dose combination
Version Number	V16
Succession Number	1
Data lock point	15 October 2025
Date of final sign off	See e-signature page

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

The content of this EU RMP has been reviewed and approved by the Marketing Authorisation Holder's QPPV

Administrative Information

Rationale for submitting an updated RMP*:*

Completion of Cancer Post-Authorisation Safety Study (PASS) - D1690R00007: Comparison of the Risk of Cancer Between Patients with Type 2 Diabetes Exposed to Dapagliflozin and Those Exposed to Other Antidiabetic Treatments (hereafter, the study is referred to as the 'Cancer PASS' in this document) and subsequent removal of important potential risks i.e. breast cancer, bladder cancer and prostate cancer, from the RMP.

Summary of significant changes in this RMP

Part II Module SV

Post-authorisation exposure data updated.

Part II Module SVII

Important potential risks breast cancer, bladder cancer and prostate cancer are removed.

Part II Module SVIII

Important potential risks breast cancer, bladder cancer and prostate cancer are removed.

Part III
AE follow- up questionnaires for spontaneous reports of breast cancer, bladder cancer, and prostate cancer are removed.

Additional pharmacovigilance activities: Cancer PASS removed.

Part V
Important potential risks breast cancer, bladder cancer and prostate cancer are removed.

Part VI
Important potential risks breast cancer, bladder cancer and prostate cancer are removed.
Cancer PASS completed and removed from the Post-authorisation Development plan.

Part VII
Annexes (2, 3, 4 and 8) updated based on the changes made in the body of the RMP

Other RMP versions under evaluation	Not applicable
Details of currently approved RMP	**Version Number**: 15 **Approved with procedure**: XIGDUO EMEA/H/C/002672/WS2664 EBYMECT EMEA/H/C/004162/WS2664 **Date of approval:** 18 July 2024

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation/ Special term	Definition/Explanation
ACEi	Angiotensin-converting enzyme inhibitor
ADR	Adverse drug reaction
AE	Adverse event
AKI	Acute kidney injury
ARB	Angiotensin receptor blocker
AUC	Area under the curve
CHF	Congestive heart failure
C_{max}	Maximum plasma drug concentrations
CPRD	Clinical Practice Research Datalink
CV	Cardiovascular
DKA	Diabetic ketoacidosis
EEA	European economic area
EMA	European medicines agency
EU	European union
HIRD	Healthcare Integrated Research Database
IR	Immediate release
IRR	Incidence rate ratio
NYHA	New York Heart Association
PASS	Post Authorisation Safety Study
PHARMO	PHARMO Data Network of the PHARMO Institute, part of Lumanity (the Netherlands)
PL	Package Leaflet
PPV	Positive predictive value
PV	Pharmacovigilance
QPPV	Qualified Person for Pharmacovigilance
RMP	Risk management plan
SGLT2	Sodium glucose co-transporter 2
SmPC	Summary of Product Characteristics
T2DM	Type 2 diabetes mellitus
UTI	Urinary tract infection
XR	Extended release

1 PART I: PRODUCT OVERVIEW

Table 1-1 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 is a highly potent, selective, and reversible SGLT2 inhibitor. Inhibition of SGLT2 by dapagliflozin reduces reabsorption of glucose from the glomerular filtrate in the proximal renal tubule with a concomitant reduction in sodium reabsorption leading to urinary excretion of glucose and osmotic diuresis. Dapagliflozin therefore increases the delivery of sodium to the distal tubule which increases tubuloglomerular feedback and reduces intraglomerular pressure. This combined with osmotic diuresis leads to a reduction in volume overload, reduced blood pressure, and lower preload and afterload, which may have beneficial effects on cardiac remodelling and diastolic function, and preserve renal function. The cardiac and renal benefits of dapagliflozin are not solely dependent on the blood glucose-lowering effect. Other effects include an increase in haematocrit and reduction in body weight. Dapagliflozin improves both fasting and post-prandial plasma glucose levels by reducing renal glucose reabsorption leading to urinary glucose excretion. This glucose excretion (glucuretic effect) is observed after the first dose, is continuous over the 24-hour dosing interval and is sustained for the duration of treatment. The amount of glucose removed by the kidney through this mechanism is dependent upon the blood glucose concentration and GFR. Thus, in subjects with normal blood glucose, dapagliflozin has a low propensity to cause hypoglycaemia. Dapagliflozin does not impair normal endogenous glucose production in response to hypoglycaemia. Dapagliflozin acts independently of insulin secretion and insulin action. Improvement in homeostasis model assessment for beta cell function (HOMA beta-cell) has been observed in clinical studies with dapagliflozin. The SGLT2 is selectively expressed in the kidney. Dapagliflozin does not inhibit other glucose transporters important for glucose transport into peripheral tissues and is > 1,400 times more selective for SGLT2 versus SGLT1, the major transporter in the gut responsible for glucose absorption. 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

Table 1-1 Product Overview

	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
Indication(s) in the EEA	Current: 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 in the SmPC.
	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
Pharmaceutical form(s) and strengths	Current: <u>XIGDUO 5 mg/850 mg film-coated tablets</u> 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. <u>XIGDUO 5 mg/1,000 mg film-coated tablets</u> 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.

Table 1-1 Product Overview

	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

2 PART II: SAFETY SPECIFICATION

2.1 MODULE SI: EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION

Dapagliflozin/metformin FDC is a fixed combination medicinal product which does not contain a new active substance. No epidemiological information is available in addition to what is known for the included components and presented in each mono products RMP.

2.2 MODULE SII: NON-CLINICAL PART OF THE SAFETY SPECIFICATION

2.2.1 Summary of key findings from non-clinical data

Dapagliflozin/metformin FDC is a fixed combination medicinal product which does not contain a new active substance. No non-clinical information is available in addition to what is known for the included components and presented in each mono products RMP.

2.3 MODULE SIII: CLINICAL TRIAL EXPOSURE

Estimates of overall cumulative subject exposure are provided in Table 2-1, based on actual exposure data from completed clinical trials.

Table 2-1 Estimated cumulative subject exposure from clinical trials

Treatment	Number of subjects
Dapagliflozin/metformin XR FDC	791
Comparator in XR trials	429
Dapagliflozin/metformin IR FDC	175
Comparator in IR trials	157
Total	979[a]

[a] Most subjects received both FDC and comparators due to the cross-over designs of all trials. Total includes 13 patients who did not receive FDC treatment.

Data from completed clinical trials as of 15 January 2025. The table includes data from trials: MB102-065, MB102-071, MB102-092, MB102-100, MB102-112, MB102-125, D1691C00008, D1691C00012, D1691C00016, D1691C00002 IR, D1691C00005 IR, D1691C00007 IR, and D1691C00011.

FDC, Fixed Dose Combination; IR, Immediate Release; XR, Extended Release

Cumulative summary tabulations of exposure by age/sex and by racial group are presented in Table 2-2 and Table 2-3, respectively.

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

	Number of subjects		
Age range (years)	**Male**	**Female**	**Total**
< 18 years	0	0	0
18 - 64 years	568	398	966
≥ 65 years	0	0	0
Total	568	398	966[a]

[a] Most subjects received both FDC and comparators due to the cross-over designs of all trials. Total excludes 13 patients who did not receive FDC treatment.

Data from completed clinical trials as of 15 January 2023 (Source: PBRER 16 January 2022 to 15 January 2023). The table includes data from trials: MB102-065, MB102-071, MB102-092, MB102-100, MB102-112, MB102-125, D1691C00008, D1691C00012, D1691C00016, D1691C00002 IR, D1691C00005 IR, D1691C00007 IR, and D1691C00011.

FDC, Fixed Dose Combination

Table 2-3 Estimated cumulative subject exposure to dapagliflozin/metformin FDC tablets from completed clinical trials by racial group

Racial group	**Number of subjects**
Caucasian	428
Black or African American	140
Asian	89
Other	177
Unknown	132
Total	966 [a]

[a] Most subjects received both FDC and comparators due to the cross-over designs of all trials. Total excludes 13 patients who did not receive FDC treatment.

Data from completed clinical trials as of 15 January 2024. The table includes data from trials: MB102-065, MB102-071, MB102-092, MB102-100, MB102-112, MB102-125, D1691C00008, D1691C00012, D1691C00016, D1691C00002 IR, D1691C00005 IR, D1691C00007 IR, and D1691C00011.

FDC, Fixed Dose Combination

2.4 MODULE SIV: Populations not studied in clinical trials

2.4.1 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.

2.4.2 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.

2.4.3 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.

2.5 MODULE SV: POST-AUTHORISATION EXPERIENCE

2.5.1 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.

2.5.2 Exposure

The regional cumulative sales figures are presented by patient-years in Table 2-4.

Table 2-4 Dapagliflozin/metformin FDC sales quantity by region

Region	**Estimated exposure (patient-years)[a]**
Europe	5704792
Rest of the world	10549380
Total	**16254172**

[b] Cumulative exposure as of 30 September 2025

2.6 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.

2.7 MODULE SVII: IDENTIFIED AND POTENTIAL RISKS

2.7.1 Identification of safety concerns in the initial RMP submission

Not applicable.

2.7.2 New safety concerns and reclassification with a submission of an updated RMP

2.7.2.1 New safety concern

There are no new safety concerns for XIGDUO. Safety concerns (Missing information) specific to the dapagliflozin mono-component indications, ie, 'Use in patients with NYHA class IV' and 'Long term safety in the paediatric population (aged 10 years and above)' do not apply for the XIGDUO approved indication.

2.7.2.2 Reclassification/removal of safety concerns

AstraZeneca has revised the list of safety concerns for dapagliflozin following the results from Cancer PASS. As a result, the following safety concerns are removed: breast cancer, bladder cancer and prostate cancer (important potential risks). There is robust evidence from multiple data sources with over 580,000 person-years of overall exposure demonstrating no increased risk of breast cancer, bladder cancer and prostate cancer. These findings are consistent across different populations, study designs, and analytical approaches.

A summary of the rationale for the removal of these risks are presented below.

2.7.2.2.1 Breast Cancer

The risk of breast cancer, previously categorised as an important potential risk is removed from the list of safety concerns.

The Cancer PASS, encompassing 130,358 person-years of dapagliflozin exposure across four international databases (CPRD, PHARMO, HIRD, Medicare), demonstrated that the propensity score–adjusted incidence rate of female breast cancer, in the overall cohorts, was comparable amongst dapagliflozin new users and comparator antidiabetic drug new users.

The pooled adjusted incidence rate ratio (IRR) of 1.01 across all databases show that dapagliflozin users had the same risk of female breast cancer as patients taking other diabetes medications, with no meaningful difference between treatment groups. Validated algorithms correctly identified breast cancer cases (positive predictive value [PPV] 81.5-99.0% of the time) and additional analyses confirmed that any potential errors in cancer diagnosis would not have masked an increased cancer risk with dapagliflozin.

These findings, corroborated by balanced results from the DECLARE cardiovascular outcomes trial where 17160 patients were randomised and analysed (dapagliflozin 36 [0.4%] vs placebo 35 [0.4%] cases) and the supportive meta-analyses (Spiazzi et al 2023) of 76

randomized controlled trials with SGLT2i that reported no increased risk of breast cancer with dapagliflozin (RR, 0.98; 95% CI, 0.66-1.47 from 23 dapagliflozin studies), provided robust evidence to support the removal of the safety concern. The review of the post-marketing data also does not indicate breast cancer as a safety signal for dapagliflozin

All post-approval commitments are completed; there are no planned clinical measures, additional risk minimisation measures or further additional pharmacovigilance activities for this risk. Based on the results from Cancer PASS and DECLARE study, breast cancer is removed as an important potential risk from the EU RMP and will be monitored through routine pharmacovigilance activities.

2.7.2.2.2 Bladder Cancer

The risk of bladder cancer, previously categorised as an important potential risk is removed from the list of safety concerns.

The Cancer PASS, encompassing 286,950 person-years of dapagliflozin exposure across four international databases (CPRD, PHARMO, HIRD, Medicare), demonstrated that dapagliflozin is not associated with increased bladder cancer risk.

The pooled adjusted IRR below 1.0 across all databases indicate that dapagliflozin users had lower bladder cancer risk compared to other diabetes treatments. Validated algorithms correctly identified bladder cancer cases (PPV 88.2-97.8% of the time) and additional analyses confirmed that any potential errors in cancer diagnosis would not have masked an increased cancer risk with dapagliflozin.

These findings, corroborated by balanced results from the DECLARE trial (dapagliflozin 26 [0.3%] vs placebo 45 [0.5%] cases), and the supportive meta-analyses (Spiazzi et al 2023) of 76 randomized controlled trials with SGLT2i that reported no increased risk of bladder cancer with dapagliflozin (RR 0.63; 95% CI: 0.42-0.95 from 23 dapagliflozin studies) provided robust evidence to support the removal of the safety concern. The review of the post-marketing data does not indicate bladder cancer as a safety signal for dapagliflozin.

All post-approval commitments are completed; there are no planned clinical measures, additional risk minimisation measures or further additional pharmacovigilance activities for this risk. Based on the results from Cancer PASS and DECLARE study, bladder cancer is removed as an important potential risk from the EU RMP and will be monitored through routine pharmacovigilance activities.

2.7.2.2.3 Prostate Cancer

The risk of prostate cancer, previously categorised as an important potential risk is removed from the list of safety concerns.

The Cancer PASS (165,308 person-years) demonstrated that dapagliflozin is not associated with increased risk of the male composite cancer endpoint (prostate, colon/rectum, lung, stomach, NHL, melanoma). The adjusted IRR of below 1.0 across all databases with associated 95% CIs crossing 1.0 indicated that dapagliflozin users had no increased risk of male composite cancer compared to other diabetes treatments, with almost 50% of the composite outcome composed of prostate cancer.

DECLARE trial results were concordant, showing similar prostate cancer rates between groups (dapagliflozin 73 [1.4%] vs placebo 63 [1.2%] cases). Cumulative review of Cancer PASS, DECLARE data, and AstraZeneca's global safety database do not support an association between prostate cancer and dapagliflozin.

All post-approval commitments are completed; there are no planned clinical measures, additional risk minimisation measures or further additional pharmacovigilance activities for this risk. Based on a comprehensive evidence review, prostate cancer is removed as an important potential risk from the EU RMP and will be monitored through routine pharmacovigilance activities.

2.7.3 Details of important identified risks, important potential risks and missing information

2.7.3.1 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.

2.7.3.2 Presentation of missing information

No missing information.

2.8 MODULE SVIII: SUMMARY OF THE SAFETY CONCERNS

2.8.1 Summary of the safety concerns

Table 2-5 Summary of safety concerns

Important identified risks	Diabetic Ketoacidosis including events with atypical presentation (dapagliflozin) Lactic acidosis (metformin)
Important potential risks	None

Table 2-5 Summary of safety concerns

Missing information	None

3 PART III: PHARMACOVIGILANCE PLAN

3.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

Specific adverse reaction follow-up questionnaires for safety concern

See Annex 4 for AE follow-up questionnaire for spontaneous reports of Lactic acidosis/Diabetic ketoacidosis including events with atypical presentation.

3.2 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.

There are no ongoing or planned additional pharmacovigilance activities for dapagliflozin.

3.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Not applicable

4 PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

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

5 PART V: RISK MINIMISATION MEASURES

5.1 ROUTINE RISK MINIMISATION MEASURES

Table 5-1 Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important identified risks	
Diabetic Ketoacidosis including events with atypical presentation	Routine risk communication: SmPC sections 4.4, 4.8. PL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: Symptoms of DKA included, and direction to assess patients immediately, regardless of blood glucose level, if these symptoms occur. Information included that dapagliflozin should be interrupted in relation to major surgical procedures or acute serious medical illnesses, or if DKA is suspected. (SmPC section 4.4, PL section 2). Before initiating dapagliflozin, factors in the patient history that may predispose to ketoacidosis should be considered. (SmPC section 4.4). Information on how to detect symptoms of DKA and instructions to seek medical attention (PL section 2, 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).
Important potential risks	
None	
Missing information	

None	

PL: Package leaflet; SmPC: Summary of product characteristics

5.2 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.

5.3 SUMMARY OF RISK MINIMISATION MEASURES

Table 5-2 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
Diabetic Ketoacidosis including events with atypical presentation (dapagliflozin)	Routine risk minimisations measures: 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).	Routine PV: AE follow-up forms for spontaneous reports

Lactic acidosis (metformin)	Routine risk minimisation measures: 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).	Routine PV: AE follow-up forms for spontaneous reports
Important potential risks		
None		
Missing information		
None		

6 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.

6.1 THE MEDICINE AND WHAT IT IS USED FOR

XIGDUO/EBYMECT is indicated in adults for the treatment of type 2 diabetes mellitus as an adjunct to diet and exercise (see SmPC for the full indication):

- 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

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

6.2 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*.

6.2.1 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 long-term use of the medicine).

Table 6-1 List of important risks and missing information

Type of safety concern	Safety concern
Important identified risks	Diabetic Ketoacidosis including events with atypical presentation (dapagliflozin) Lactic acidosis (metformin)
Important potential risks	None
Missing information	None

6.2.2 Summary of important risks

Table 6-2 Important identified risk – Diabetic Ketoacidosis Including Events with Atypical Presentation

Evidence for linking the risk to the medicine	Postmarketing experience with use of SGLT2 inhibitors, including dapagliflozin.
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 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, and 4).

Table 6-3 Important identified risk – Lactic acidosis

Evidence for linking the risk to the medicine	Postmarketing experience with use of metformin.

Table 6-3 Important identified risk – Lactic acidosis

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.
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).

6.2.3 Post-authorisation development plan

6.2.3.1 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.

6.2.3.2 Other studies in post-authorisation development plan

There are no studies required for XIGDUO/EBYMECT.

7 PART VII: ANNEXES

ANNEX 4: 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) - lactic-/ketoacidosis

ANNEX 6: Details of proposed additional risk minimisation activities

Not applicable

LIST OF REFERENCES

Spiazzi et al 2023
Spiazzi BF, Naibo RA, Wayerbacher LF, Piccoli GF, Farenzena LP, Londero TM, et al. Sodium-glucose cotransporter-2 inhibitors and cancer outcomes: A systematic review and meta-analysis of randomized controlled trials. Diabetes Res Clin Pract 2023;198:110621

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

Case ID #_____
Manufacturer Date of Receipt _____

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

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

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

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

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

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

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

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

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

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

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

Other relevant concomitant medications
Exclude drugs used to treat the event

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

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

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

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

Date and Signature

Date: _____

Signature (Reporting Physician): _____

Contact Information

Please return completed form to:

Fax:

E-mail:

Mail:

Thank you for completing this form.