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

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 long term use of the medicine).

Table I-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)
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 I-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 I-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.
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).

Table I-3 Important identified risk – Lactic acidosis

	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 I-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 I-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).

Table I-5 Important identified risk – Renal impairment

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 I-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 I-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
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 I-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 I-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 I-10 Important potential risk – Lower limb amputation

Evidence for linking the risk to the medicine	Clinical trial data for 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 Peripheral artery disease (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.
Additional pharmacovigilance activities	Dedicated eCRF for Lower Limb Amputation will be evaluated in relevant studies with duration >3 months Meta-analysis across studies D1690C00018, D1690C00019, and D1693C00001 (DECLARE). 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: Meta-analysis across studies D1690C00018, D1690C00019, and D1693C00001 [Meta-analysis across 3 interventional studies].

Purpose of the study: Determine the incidence of amputation and relevant preceding AEs over time by showing the cumulative proportion of subjects with events and numbers of subjects at risk at relevant time point.