EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 September 2015
EMA/679419/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ebymect

International non-proprietary name: dapagliflozin / metformin

Procedure No. EMEA/H/C/004162/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Submission of the dossier

The applicant AstraZeneca AB submitted on 3 July 2015 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Ebymect, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 26 February 2015.

The applicant applied for the following indication:

Ebymect 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 (see sections 4.4, 4.5 and 5.1 for available data on different combinations)
- in patients already being treated with the combination of dapagliflozin and metformin as separate tablets.

The legal basis for this application refers to:

Article 10(c) of Directive 2001/83/EC – relating to informed consent from a marketing authorisation holder for an authorised medicinal product.

The application submitted is composed of administrative information, quality, non-clinical and clinical data with a letter from AstraZeneca AB allowing the cross reference to relevant quality, non-clinical and/or clinical data.

Information on Paediatric requirements

Not applicable

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Licensing status

The cross-referred product Xigduo was given a Community Marketing Authorisation on 16 January 2014.

A new application was filed in the following country: Canada.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Kristina Dunder Co-Rapporteur: Agnes Gyurasics

- The application was received by the EMA on 3 July 2015.
- The procedure started on 27 July 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 1 September 2015. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 1 September 2015.
- PRAC RMP Advice and assessment overview as endorsed by PRAC on 10 September 2015.
- The Rapporteur circulated an updated Assessment Report to all CHMP members on 18 September 2015.
- During the meeting on 24 September 2015, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Ebymect.

2. Scientific discussion

2.1. Introduction

This application has been submitted by AstraZeneca AB as an informed consent application in accordance with Article 10c of Directive 2001/83/EC as amended.

Ebymect is a film-coated tablet containing a fixed dose of dapagliflozin and metformin (ATC code: A10BD15 ; pharmacotherapeutic group: Drugs used in diabetes, Combinations of oral blood glucose-lowering drugs). Ebymect combines two anti-hyperglycaemic medicinal products with different and complementary mechanisms of action to improve glycaemic control in patients with type 2 diabetes: dapagliflozin, a sodium glucose co-transporter 2 (SGLT2) inhibitor, and metformin hydrochloride, a member of the biguanide class.

The proposed indication is:

Ebymect 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 (see sections 4.4, 4.5 and 5.1 for available data on different combinations)
• in patients already being treated with the combination of dapagliflozin and metformin as separate tablets.

Following the granting of a marketing authorisation for Xigduo, the authorisation holder (AstaZeneca AB) has allowed use to be made of the pharmaceutical, preclinical and clinical documentation contained in the file on the medicinal product, with a view to examining subsequent applications relating to other medicinal products possessing the same qualitative and quantitative composition in terms of active substances and the same pharmaceutical form.

2.2. Quality aspects

Since this application is an informed consent of the Xigduo, the quality data in support of the Ebymect application are identical to the up-to-date quality data of the Xigduo dossier, which has been assessed and approved (including all post-marketing procedures).

2.3. Non-clinical aspects

The applicant has made reference to module 4 of the Xigduo marketing authorisation application.

Since the Ebymect application is an informed consent of the Xigduo application, the non-clinical data in support of the Ebymect application are identical to the up-to-date non-clinical data of the Xigduo dossier, which have been assessed and approved (including all post-marketing procedures).

2.3.1. Ecotoxicity / environmental risk assessment

An environmental risk assessment of the fixed dose combination dapagliflozin/metformin hydrochloride has been evaluated and approved in the frame of the initial market authorisation application of Xigduo(EMEA/H/C/002672). Based on this evaluation, neither dapagliflozin nor metformin hydrochloride are expected to pose a risk to the environment. As the dose, indication and the patient population has not changed, marketing authorisation of Ebymect would not add to the environmental impact.

2.3.2. Discussion on non-clinical aspects

No additional non-clinical studies have been provided as this application has been submitted under the legal basis Article 10(c) of Directive 2001/83/EC. For this reason, the proposed sections 4.6 and 5.3 of the SmPC are in agreement with the proposed and approved wording for Xigduo.

2.3.3. Conclusion on the non-clinical aspects

The CHMP considers the non-clinical data are acceptable to support the marketing authorisation.

2.4. Clinical aspects

The applicant makes reference to module 5 of the marketing authorisation application of Xigduo.

2.4.1. Discussion on clinical efficacy

No additional clinical studies to evaluate the efficacy of Ebymect have been provided by the applicant. This is acceptable for submissions under the legal basis Article 10(c) of Directive 2001/83/EC.

2.4.2. Conclusions on the clinical efficacy

The CHMP considers that the clinical data are acceptable to support the marketing authorisation.

2.5. Clinical safety

The applicant makes reference to module 5 of the marketing authorisation application of Xigduo.

The most common side effects are hypoglycaemia, nausea, vomiting, diarrhoea, abdominal pain, loss of appetite, vulvovaginitis, balanitis and related genital infections, urinary tract infection, dysuria and polyuria. Specific safety issues regarding a tumour imbalance in dapagliflozin treated patients, the limited data available in patients > 75 years old, the use in patients at risk of volume depletion, hypotension and electrolytes imbalances have been evaluated and addressed in the Summary of Product Characteristics (SmPC) and in the Risk Management Plan discussion on clinical safety.

No additional clinical studies to evaluate the safety of Ebymect have been provided by the applicant. This is acceptable for submissions under the legal basis Article 10(c) of Directive 2001/83/EC.

2.5.1. Discussion on the clinical safety

No additional clinical studies to evaluate the safety of Ebymect have been provided by the applicant. This is acceptable for submissions under the legal basis Article 10(c) of Directive 2001/83/EC.

2.5.2. Conclusions on the clinical safety

The CHMP considers that the safety data are acceptable to support the marketing authorisation.

2.6. Risk Management Plan

Safety concerns

Important identified risks	Genital infections, Urinary tract infections, Lactic acidosis
Important potential risks	Hypoglycemia, Volume depletion, Clinical consequences of increased hematocrit, Renal impairment/failure, Bone fracture, Liver injury, Hypersensitivity reactions, Bladder cancer, Breast cancer, Prostate cancer, Off-label use of dapagliflozin in specific populations
Missing information	Pediatric population, Pregnancy and lactation, Elderly (≥ 65 years), Severe renal impairment, Moderate and severe hepatic impairment, Congestive heart failure defined as NYHA class III and IV

Pharmacovigilance plan

Study/activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status (planned, started)**	**Date for submission of interim or final reports (planned or actual)**
MB102103: Comparison of the Risk of Severe Complications of UTI Between Patients with T2DM Exposed to Dapagliflozin and	Primary objective: To compare, by insulin use at the index date, the sex-specific incidence of hospitalization or emergency	Severe complications of UTI	Ongoing	Interim data cuts will occur 24 and 48 months after the US approval of dapagliflozin (Jan 2014). The final data cut will occur at 60

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Those Exposed to Other Anti diabetic Treatments. Non-interventiona l and "2" Based on Classification [a]	department (ED) 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 ADs in classes other than SGLT2 inhibitors, insulin monotherapy, metformin monotherapy, or sulfonylurea monotherapy.			months post the US approval with the Final Report submission estimated to be 2019.
MB102104: Comparison of Risk of Acute Hepatic Failure Between Patients with T2DM Exposed to Dapagliflozin and Those Exposed to Other Anti-diabetic Treatments. Non-interventiona l and "2" Based on Classification[a]	Primary objective: To compare, by insulin use at the index date, the incidence of hospitalization for ALI among patients with T2DM who are new users of dapagliflozin with those who are new users of ADs in classes other than SGLT2 inhibitors, insulin monotherapy, metformin monotherapy, or sulfonylurea monotherapy.	Risk of Acute Hepatic Failure	Ongoing	Interim data cuts will occur 24 and 48 months after the US approval of dapagliflozin (Jan 2014). The final data cut will occur at 60 months post the US approval with the Final Report submission estimated to be 2019.
MB102110: Comparison of Risk of Acute Renal Failure Between Patients with T2DM Exposed to	Primary Objective: To compare, by insulin use at the index date, the incidence of hospitalization for	Risk of Acute Renal Failure	Ongoing	Interim data cuts will occur 24 and 48 months after the US approval of dapagliflozin (Jan 2014). The final data cut

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Dapagliflozin and Those Exposed to Other Antidiabetic Treatments. Non-interventional and "2" Based on Classification[a]	acute kidney injury (AKI) among patients with T2DM who are new users of dapagliflozin with those who are new users of ADs in classes other than SGLT2 inhibitors, insulin monotherapy, metformin monotherapy, or sulfonylurea monotherapy.			will occur at 60 months post the US approval with the Final Report submission estimated to be 2019.
MB102118: Comparison of the Risk of Cancer Among Patients with T2DM Exposed to Dapagliflozin and Those Exposed to Other Antidiabetic Therapies. Non-interventional and "2" Based on Classification[a]	The primary objectives of this study are (1) to compare the incidence of breast cancer, by insulin use at cohort entry, among females with T2DM who are new initiators of dapagliflozin and females who are new initiators of ADs in classes other than SGLT2 inhibitors, insulin, metformin monotherapy, or sulfonylurea monotherapy and (2) to compare the incidence of bladder cancer, by insulin use at cohort entry and pioglitazone use, among male and female patients with T2DM who are new initiators of dapagliflozin and those who are	Risk of cancer	Ongoing	Interim data cuts will occur 24, 48, 72, and 96 months after the US approval of dapagliflozin (Jan 2014). The final data cut will occur at 120 months post the US approval with the Final Report Submission estimated to be 2024.

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
	new initiators of ADs in classes other than SGLT2 inhibitors, insulin monotherapy, metformin monotherapy, or sulfonylurea monotherapy			
MB102117 (D1693C00001) CV Outcome study : Dapagliflozin Effect on Cardiovascular Event Incidence in Patients with Diabetes Mellitus: A Multicentre, Randomized, Double-Blind, Placebo-Controlled Phase IV Trial to Evaluate The Effect of Dapagliflozin on The Incidence of Cardiovascular Death, Myocardial Infarction or Ischemic Stroke in Patients with Type 2 Diabetes	The primary safety objective of this trial is to establish whether the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of the composite endpoint of cardiovascular death, myocardial infarction or ischemic stroke, in patients with T2DM with either established cardiovascular disease or at least two cardiovascular risk factors in addition to T2DM, observed with dapagliflozin to that observed in the placebo group is less than 1.3.	Cardiovascular risk, bladder cancer, liver injury	Ongoing	Final Report Submission estimated to be 2020
MB102134 Observational Single-Cohort Database Study of Dapagliflozin Utilization in Europe Non-interventiona	Primary objective: To describe the characteristics of European patients prescribed dapagliflozin by age, sex, dapagliflozin	Off-label use	Ongoing	The first drug utilization study analysis report will be submitted in 2015 and annually thereafter, with the corresponding

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
l and "2" Based on Classification[a]	dose, country, selected comorbidities, and selected concomitant medications.			Periodic Safety Update Report (PSUR). Final Report Submission estimated to be 2017.

Risk minimisation measures

Table VI-1 Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Genital Infections	**Product Labeling:** Undesirable Effects Vulvovaginitis, balanitis and related genital infections are listed as a common ADR. Vulvovaginitis, balanitis and related genital infections Vulvovaginitis, balanitis and related genital infections were reported in 4.8% and 0.9% of subjects who received dapagliflozin 10 mg and placebo, respectively. Most infections were mild to moderate, and subjects responded to an initial course of standard treatment and rarely resulted in discontinuation from dapagliflozin treatment. These infections were more frequent in females (6.9% and 1.5% for dapagliflozin and placebo, respectively), and subjects with a prior history were more likely to have a recurrent infection. **Patient information:** Yeast infection (thrush) of the penis or vagina is included as a common side effect. Unusual vaginal bleeding, discharge, itching or odour are included as uncommon side effects.	Not applicable
Urinary tract infections	**Product Labeling:** Special Warnings and Precautions for use Urinary tract infections	Not applicable

Table VI-1 Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Urinary tract infections were more frequently reported for dapagliflozin compared to placebo in a pooled analysis up to 24 weeks. Pyelonephritis was uncommon and occurred at a similar frequency to control. Urinary glucose excretion may be associated with an increased risk of urinary tract infection; therefore, temporary interruption of treatment should be considered when treating pyelonephritis or urosepsis. Undesirable Effects Urinary tract infection is listed as a common ADR. Urinary tract infections Urinary tract infections were more frequently reported for dapagliflozin compared with placebo (4.3% versus 3.7%, respectively). Most infections were mild to moderate, and subjects responded to an initial course of standard treatment and rarely resulted in discontinuation from dapagliflozin treatment. These infections were more frequent in females, and subjects with a prior history were more likely to have a recurrent infection. **Patient information:** Warnings and precautions Talk to your doctor, pharmacist or nurse before taking Xigduo if you often get infections of the urinary tract. This medicine may cause urinary tract infections and your doctor may want to monitor you more closely. Your doctor may consider temporarily changing your treatment if you develop a serious infection. Possible side effects Stop taking Xigduo and see a doctor as soon as possible if you notice any of the following serious side effects: Urinary tract infection, seen commonly (may affect up to 1 in 10 people). These are signs of a severe infection of the urinary tract: • fever and/or chills • burning sensation when passing water (urinating) • pain in your back or side. Although uncommon, if you see blood in your urine, tell your doctor immediately.	

Table VI-1 Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Lactic acidosis	**Product labeling:** Contraindications Xigduo is contraindicated in patients with moderate and severe renal impairment (CrCl < 60 mL/min; eGFR < 60 mL/min/1.73 m2); acute conditions with the potential to alter renal function (such as dehydration, severe infection, shock); acute or chronic disease which may cause tissue hypoxia (such as cardiac or respiratory failure, recent myocardial infarction, shock); hepatic impairment; acute alcohol intoxication, alcoholism; Special warnings and precautions for use Lactic acidosis Lactic acidosis is a very rare, but serious (high mortality in the absence of prompt treatment), metabolic complication that can occur due to accumulation of metformin, a component of this medical product. Reported cases of lactic acidosis in patients on metformin have occurred primarily in diabetic patients with significant renal failure. The incidence of lactic acidosis can and should be reduced by also assessing other associated risk factors such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any conditions associated with hypoxia. Diagnosis The risk of lactic acidosis must be considered in the event of non-specific signs such as muscle cramps with digestive disorders, abdominal pain and severe asthenia. Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain and hypothermia followed by coma. Diagnostic laboratory findings are decreased blood pH, plasma lactate levels above 5 mmol/L, and an increased anion gap and lactate/pyruvate ratio. If metabolic acidosis is suspected, treatment with the medicinal product should be discontinued and the patient hospitalised immediately. Change in clinical status of patients with previously controlled type 2 diabetes As Xigduo contains metformin, a patient with type 2 diabetes previously well controlled on Xigduo who	Not applicable

Table VI-1 Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate, and metformin levels. If acidosis of either form occurs, Xigduo must be stopped immediately and other appropriate corrective measures initiated. Interaction with other medicinal products and other forms of interaction Combinations not recommended There is increased risk of lactic acidosis in acute alcohol intoxication (particularly in the case of fasting, malnutrition or hepatic impairment) due to the metformin active substance of Xigduo. Consumption of alcohol and medicinal products containing alcohol should be avoided. Cationic substances that are eliminated by renal tubular secretion (e.g., cimetidine) may interact with metformin by competing for common renal tubular transport systems. A study conducted in seven normal healthy volunteers showed that cimetidine, administered as 400 mg twice daily, increased metformin systemic exposure (AUC) by 50% and Cmax by 81%. Therefore, close monitoring of glycemic control, dose adjustment within the recommended posology and changes in diabetic treatment should be considered when cationic medicinal products that are eliminated by renal tubular secretion are coadministered. The intravascular administration of iodinated contrast agents in radiological studies may lead to renal failure, resulting in metformin accumulation and a risk of lactic acidosis. Therefore, Xigduo must be discontinued prior to, or at the time of the test and not reinstituted until 48 hours afterwards, and only after renal function has been re evaluated and found to be normal. Combination requiring precautions for use Glucocorticoids (given by systemic and local routes), beta 2 agonists, and diuretics have intrinsic hyperglycemic activity. The patient should be informed and more frequent blood glucose monitoring perfomed,	

Table VI-1 Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	especially at the beginning of treatment with such medicinal products. If necessary, the dose of the glucose lowering medicinal product should be adjusted during therapy with the other medicinal product and on its discontinuation. Diuretics, especially loop diuretics, may increase the risk of lactic acidosis due to their potential to decrease renal function. Undesirable Effects Lactic acidosis is listed as a very rare ADR. **Patient Information:** What you need to know before you take Xigduo Do not take Xigduo if you drink large amount of alcohol (either every day or only from time to time). Warnings and precautions Talk to your doctor, pharmacist or nurse before taking Xigduo if you experience some of the following symptoms of lactic acidosis: feeling cold or uncomfortable, feeling or being very sick, stomach pain, unexplained weight loss, muscular cramps, or rapid breathing. Metformin hydrochloride, one of the ingredients in Xigduo, can cause a rare but serious side effect called lactic acidosis (a build-up of lactic acid in the blood) that can lead to death. Lactic acidosis is a medical emergency and must be treated in a hospital. If you experience some of the symptoms of lactic acidosis stop taking Xigduo and consult a doctor immediately. Xigduo with alcohol Avoid alcohol, including medicines containing alcohol, while taking Xigduo since alcohol may increase the risk of lactic acidosis. Possible side effects Stop taking Xigduo and see a doctor as soon as possible if you notice any of the following serious side effects: Lactic acidosis. Metformin hydrochloride, one of the substances in this medicine, can cause a rare but serious side effect called lactic acidosis (a buildup of lactic acid in the blood) that can lead to death. Lactic acidosis is a medical emergency and must be treated immediately. If this happens to you, you need to seek immediate medical	

Table VI-1 Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	treatment as lactic acidosis can lead to coma. Stop taking this medicine immediately and contact a doctor or the nearest hospital straight away. Signs of 'lactic acidosis' are: • feeling or being very sick • vomiting, stomach pain • muscular cramps • severe tiredness • difficulty breathing.	
Hypoglycemia	**Product Labeling:** Interaction with other medicinal products and other forms of interaction Pharmacodynamic interactions Insulin and insulin secretagogues Insulin and insulin secretagogues, such as sulphonylureas, cause hypoglycaemia. Therefore, a lower dose of insulin or an insulin secretagogue may be required to reduce the risk of hypoglycaemia when used in combination with this medical product. Effects on ability to drive and use machines Dapagliflozin or metformin have no or negligible influence on the ability to drive and use machines. Patients should be alerted to the risk of hypoglycaemia when Xigduo is used in combination with a sulphonylurea or insulin. Undesirable Effects Hypoglycemia is listed as a very common ADR (when used with SU or insulin). *Dapagliflozin plus metformin* Hypoglycaemia In studies with dapagliflozin in add-on combination with metformin, minor episodes of hypoglycaemia were reported at similar frequencies in the group treated with dapagliflozin 10 mg plus metformin (6.9%) and in the placebo plus metformin group (5.5%). No major events	Not applicable

Table VI-1 Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	of hypoglycaemia were reported. *Dapagliflozin* Hypoglycaemia The frequency of hypoglycaemia depended on the type of background therapy used in each study. For studies of dapagliflozin as add on to metformin or as add on to sitagliptin (with or without metformin), the frequency of minor episodes of hypoglycaemia was similar (< 5%) between treatment groups, including placebo up to 102 weeks of treatment. Across all studies, major events of hypoglycaemia were uncommon and comparable between the groups treated with dapagliflozin or placebo. In a study with add on insulin therapy, higher rates of hypoglycaemia were observed. In an add on to insulin study up to 104 weeks, episodes of major hypoglycaemia were reported in0.5% and 1.0% of subjects in dapagliflozin 10 mg plus insulin at Weeks 24 and 104, respectively, and in 0.5% of subjects treated with placebo plus insulin groups at Weeks 24 and 104. At Weeks 24 and 104, minor episodes of hypoglycaemia were reported, respectively, in 40.3% and 53.1% of subjects who received dapagliflozin 10 mg plus insulin and in 34.0% and 41.6% of the subjects who received placebo plus insulin. **Patient Information:** Other medicines and Xigduo Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines. Especially tell your doctor if you are taking other medicines that lower the amount of sugar in your blood such as insulin or a “sulphonylurea” medicine. Your doctor may want to lower the dose of these other medicines, to prevent you from getting blood sugar levels that are too low (hypoglycaemia). Driving and using machines This medicine has no or negligible influence on the ability to drive and use machines. Taking Xigduo with other medicines called sulphonylureas or with insulin can cause too low blood sugar levels (hypoglycaemia), which may cause symptoms such as shaking, sweating and	

Table VI-1 Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	change in vision, and may affect your ability to drive and use machines. Do not drive or use any tools or machines, if you feel dizzy taking Xigduo. Possible side effects Contact your doctor as soon as possible if you have any of the following side effects: Hypoglycaemia (low blood sugar levels) is a common event (may affect more than 1 in 10 people) occurring when taking this medicine with insulin. These are the signs of low blood sugar: • shaking, sweating, feeling very anxious, fast heart beat • feeling hungry, headache, change in vision • a change in your mood or feeling confused. Your doctor will tell you how to treat low blood sugar levels and what to do if you get any of the signs above.	
Volume depletion	**Product Labeling:** Special Warnings and Precautions for use: Use in patients at risk for volume depletion, hypotension and/or electrolyte imbalances Due to its mechanism of action, dapagliflozin increases diuresis associated with a modest decrease in blood pressure, which may be more pronounced in patients with high blood glucose concentrations. This medical product is not recommended for use in patients receiving loop diuretics or who are volume depleted, e.g. due to acute illness (such as gastrointestinal illness). Caution should be exercised in patients for whom a dapagliflozin induced drop in blood pressure could pose a risk, such as patients with known CVD, patients on anti hypertensive therapy with a history of hypotension or elderly patients. For patients receiving this medical product, in case of intercurrent conditions that may lead to volume depletion, careful monitoring of volume status (e.g. physical examination, blood pressure measurements,	Not applicable

Table VI-1 Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	laboratory tests including haematocrit) and electrolytes is recommended. Temporary interruption of treatment with this medical product is recommended for patients who develop volume depletion until the depletion is corrected. Interaction with other medicinal products and other forms of interaction Pharmacodynamic interactions Diuretics This medical product may add to the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension. Undesirable Effects Volume depletion is listed as an uncommon ADR. Volume depletion Reactions related to volume depletion (including, reports of dehydration, hypovolaemia or hypotension) were reported in 0.8% and 0.4% of subjects who received dapagliflozin 10 mg and placebo, respectively; serious reactions occurred in < 0.2% of subjects balanced between dapagliflozin 10 mg and placebo. **Patient Information:** What you need to know before you take Xigduo Do not take Xigduo if you have a severe infection or if you have lost a lot of water from your body (dehydration) (e.g., due to long-lasting or severe diarrhoea, or if you have vomited several times in a row). Warnings and precautions Talk to your doctor, pharmacist or nurse before taking Xigduo: • if you have very high levels of glucose in your blood which may make you dehydrated (lose too much body fluid). Possible signs of dehydration are listed at the top of section 4, 'Possible side effects'. Tell your doctor before you start taking Xigduo if you have any of these signs • if you are on medicines to lower blood pressure (anti hypertensives) and have a history of low blood pressure (hypotension). More information is given below in 'Other medicines and Xigduo' • if you have or develop nausea (feeling sick),	

Table VI-1 Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	vomiting or fever or if you are not able to eat or drink. These conditions can cause dehydration. Your doctor may ask you to stop taking Xigduo until you recover to prevent dehydration Other medicines and Xigduo Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines. Especially tell your doctor if you are taking a medicine used to remove water from the body (diuretic). Your doctor may ask you to stop taking Xigduo. Possible signs of losing too much fluid from your body are listed at the top of section 4 'Possible side effects'. Possible side effects Stop taking Xigduo and see a doctor as soon as possible if you notice any of the following serious side effects: Loss of too much fluid from your body (dehydration), seen uncommonly (may affect up to 1 in 100 people). These are signs of dehydration: • very dry or sticky mouth, feeling very thirsty • feeling very sleepy or tired • passing little or no water (urine) • fast heart beat.	
Clinical Consequences of Increased Hematocrit	**Product Labeling:** Special Warnings and Precautions for use Elevated haematocrit Haematocrit increase was observed with dapagliflozin treatment; therefore, caution in patients with already elevated haematocrit is warranted. Undesirable Effects Haematocrit increased is listed as a common ADR, with footnote: "Mean changes from baseline in haematocrit were 2.15% for dapagliflozin 10 mg versus -0.40% for placebo." **Patient information:** Warnings and precautions Talk to your doctor, pharmacist or nurse before taking Xigduo if you have an increase in the amount of red blood cells in your blood, seen in tests	Not applicable

Table VI-1 Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Renal Impairment/ Failure	**Product labeling:** Posology and method of administration Special populations Renal impairment No dose adjustment is recommended for patients with mild renal impairment. This medical product must not be used in patients with moderate to severe renal impairment (patients with creatinine clearance [CrCl] < 60 ml/min or estimated glomerular filtration rate [eGFR] < 60 ml/min/1.73 m2). Contraindications Xigduo is contraindicated in patients with moderate and severe renal impairment (creatinine clearance < 60 ml/min; eGFR < 60 ml/min/1.73 m2), and acute conditions with the potential to alter renal function such as (dehydration, severe infection, shock) Special Warnings and Precautions for use Use in patients with renal impairment The efficacy of dapagliflozin, a component of this medical product, is dependent on renal function, and efficacy is reduced in patients who have moderate renal impairment and likely absent in patients with severe renal impairment. In addition, metformin is excreted by the kidney, and moderate to severe renal insufficiency increases the risk of lactic acidosis. Therefore, this medical product must not be used in patients with moderate to severe renal impairment (patients with CrCl < 60 ml/min or estimated glomerular filtration rate [eGFR] < 60 ml/min/1.73 m2). Monitoring of renal function is recommended as follows: • Prior to initiation of treatment and at least yearly thereafter. • Prior to initiation of concomitant medicinal products that may reduce renal function and periodically thereafter • For renal function approaching moderate renal impairment, at least 2 to 4 times per year. If renal function falls below CrCl < 60 ml/min or eGFR < 60 ml/min/1.73 m2, Xigduo treatment must be discontinued. Decreased renal function in older patients is frequent and asymptomatic. Special caution should be exercised in situations where renal function may become impaired, for example when initiating anti hypertensive or diuretic	Not applicable

Table VI-1 Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	therapy or when starting treatment with a nonsteroidal anti inflammatory drug (NSAID). Elderly patients (≥ 65 years) Elderly patients are more likely to have impaired renal function, and/or to be treated with anti hypertensive medicinal products that may cause changes in renal function such as angiotensin converting enzyme (ACE) inhibitors and angiotensin II type 1 receptor blockers (ARB). The same recommendations for renal function apply to older patients as to all patients. In subjects ≥ 65 years of age, a higher proportion of subjects treated with dapagliflozin had adverse reactions related to renal impairment or failure compared with placebo. The most commonly reported adverse reaction related to renal function was serum creatinine increases, the majority of which were transient and reversible. Older patients may be at a greater risk for volume depletion and are more likely to be treated with diuretics. In subjects ≥ 65 years of age, a higher proportion of subjects treated with dapagliflozin had adverse reactions related to volume depletion. Therapeutic experience in patients 75 years and older is limited. Initiation of Xigduo therapy in this population is not recommended. Undesirable Effects Blood creatinine increased and Blood urea increased are listed as an uncommon ADR. **Patient Information:** What you need to know before you take Xigduo Do not take Xigduo if you have problems with your kidneys. Warnings and precautions Talk to your doctor, pharmacist or nurse before taking Xigduo if you have problems with your kidneys. Your doctor will check your kidney function Kidney function Your kidneys should be checked before you start taking and at least once a year whilst you are on this medicine.	

Table VI-1 Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Bone fracture	None proposed	Not applicable
Liver injury	**Product Labeling:** Undesirable Effects Liver function disorders and hepatisis is included as a very rare ADR. **Patient Information:** What you need to know before you take Xigduo Do not take Xigduo if you have problems with your liver. Liver problems (hepatitis) is included as a very rare side effect	Not applicable
Hypersensitivity reactions	None proposed	Not applicable
Bladder cancer	**Product labeling:** Special Warnings and Precautions for use with regard to use of Dapagliflozin in combination with pioglitazone: Use in patients treated with pioglitazone While a causal relationship between dapagliflozin and bladder cancer is unlikely, as a precautionary measure, Xigduo is not recommended for use in patients concomitantly treated with pioglitazone. Available epidemiological data for pioglitazone suggest a small increased risk of bladder cancer in diabetic patients treated with pioglitazone. Undesirable effects Malignancies During clinical trials, the overall proportion of subjects with malignant or unspecified tumours was similar between those treated with dapagliflozin (1.47%) and placebo/comparator (1.35%), and there was no carcinogenicity or mutagenicity signal in animal data. When considering the cases of tumours occurring in the different organ systems, the relative risk associated with dapagliflozin was above 1 for some tumours (bladder, prostate, breast) and below 1 for others (e.g., blood and lymphatic, ovary, renal tract), not resulting in an overall increased tumour risk associated with dapagliflozin. The increased/decreased risk was not statistically significant in any of the organ systems. Considering the lack of tumour findings in non clinical studies as well as the short latency between first drug exposure and tumour	Not applicable

Table VI-1 Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	diagnosis, a causal relationship is considered unlikely. Since the numerical imbalance of breast, bladder and prostate tumours must be considered with caution, it will be further investigated in post authorisation studies.	
Breast cancer	**Product labeling:** Undesirable effects Malignancies During clinical trials, the overall proportion of subjects with malignant or unspecified tumours was similar between those treated with dapagliflozin (1.47%) and placebo/comparator (1.35%), and there was no carcinogenicity or mutagenicity signal in animal data. When considering the cases of tumours occurring in the different organ systems, the relative risk associated with dapagliflozin was above 1 for some tumours (bladder, prostate, breast) and below 1 for others (e.g. blood and lymphatic, ovary, renal tract), not resulting in an overall increased tumour risk associated with dapagliflozin. The increased/decreased risk was not statistically significant in any of the organ systems. Considering the lack of tumour findings in non clinical studies as well as the short latency between first drug exposure and tumour diagnosis, a causal relationship is considered unlikely. Since the numerical imbalance of breast, bladder and prostate tumours must be considered with caution, it will be further investigated in post authorisation studies.	Not applicable
Prostate cancer	**Product labeling:** Undesirable effects Malignancies During clinical trials, the overall proportion of subjects with malignant or unspecified tumours was similar between those treated with dapagliflozin (1.47%) and placebo/comparator (1.35%), and there was no carcinogenicity or mutagenicity signal in animal data. When considering the cases of tumours occurring in the different organ systems, the relative risk associated with dapagliflozin was above 1 for some tumours (bladder, prostate, breast) and below 1 for others (e.g. blood and lymphatic, ovary, renal tract), not resulting in an overall increased tumour risk associated with dapagliflozin. The increased/decreased risk was not statistically significant in any of the organ systems. Considering the lack of tumour findings in non clinical studies as well as the short latency between first drug exposure and tumour diagnosis, a causal relationship is considered unlikely.	Not applicable

Table VI-1 Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Since the numerical imbalance of breast, bladder and prostate tumours must be considered with caution, it will be further investigated in post authorisation studies.	
Off-label use of Dapagliflozin in Specific Populations	**Product labeling:** Therapeutic experience in patients 75 years and older is limited. Initiation of Xigduo therapy in this population is not recommended. This medical product is not recommended for use in patients receiving loop diuretics or who are volume depleted, e.g. due to acute illness (such as gastrointestinal illness). Use in patients treated with pioglitazone While a causal relationship between dapagliflozin and bladder cancer is unlikely, as a precautionary measure, Xigduo is not recommended for use in patients concomitantly treated with pioglitazone. Available epidemiological data for pioglitazone suggest a small increased risk of bladder cancer in diabetic patients treated with pioglitazone. **Patient information:** Warnings and precautions If you are 75 years old or older, you should not start taking this medicine. This is because you may be more prone to some side effects. If you are taking another medicine for diabetes that contains “pioglitazone”, you should not start taking this medicine.	Not applicable
Pediatric population	**Product labeling:** Posology and method of administration: Paediatric population The safety and efficacy of Xigduo in children aged 0 to < 18 years have not yet been established. No data are available. **Patient information** Children and adolescents Xigduo is not recommended for children and adolescents under 18 years of age, because it has not been studied in	Not applicable

Table VI-1 Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	these patients.	
Pregnancy / Nursing mothers	**Product labeling:** Fertility, pregnancy and lactation Pregnancy There are no data from the use of Xigduo or dapagliflozin in pregnant women. Studies in rats treated with dapagliflozin have shown toxicity to the developing kidney in the time period corresponding to the second and third trimesters of human pregnancy. Therefore, the use of this medical product is not recommended during the second and third trimesters of pregnancy. A limited amount of data from the use of metformin in pregnant women does not indicate an increased risk of congenital malformations. Animal studies with metformin do not indicate harmful effects with respect to pregnancy, embryonic or foetal development, parturition or postnatal development. When the patient plans to become pregnant and during pregnancy, it is recommended that diabetes is not treated with Xigduo, but insulin be used to maintain blood glucose levels as close to normal as possible to reduce the risk of malformations of the foetus associated with abnormal blood glucose levels. Breast feeding It is unknown whether Xigduo or dapagliflozin (and/or its metabolites) are excreted in human milk. Available pharmacodynamic/toxicological data have shown excretion of dapagliflozin/metabolites in animal milk, as well as pharmacologically mediated effects in nursing offspring. Metformin is excreted in human milk in small amounts. A risk to the newborns/infants cannot be excluded. Xigduo should not be used while breast feeding. **Patient information** Pregnancy and breast feeding If you are pregnant or breast feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. You should stop taking this medicine if you become pregnant, since it is not recommended during the second and third trimesters (the last six months) of pregnancy. Talk to your doctor about the best way to control your	Not applicable

Table VI-1 Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	blood sugar while you are pregnant. Talk to your doctor if you would like to or are breast feeding before taking this medicine. You should not use Xigduo if you are breast feeding. It is not known if this medicine passes into human breast milk.	
Elderly population	Product labeling: Posology and method of administration Older people (≥ 65 years) Because metformin is eliminated in part by the kidney, and because older patients are more likely to have decreased renal function, Xigduo should be used with caution as age increases. Monitoring of renal function is necessary to aid in prevention of metformin associated lactic acidosis, particularly in older people. Risk of volume depletion with dapagliflozin should also be taken into account. Due to the limited therapeutic experience with dapagliflozin in patients 75 years and older, initiation of Xigduo therapy in this population is not recommended. Special warnings and precautions for use Decreased renal function in older patients is frequent and asymptomatic. Special caution should be exercised in situations where renal function may become impaired, for example when initiating anti hypertensive or diuretic therapy or when starting treatment with a nonsteroidal anti inflammatory drug (NSAID). Older patients (≥ 65 years) Older patients are more likely to have impaired renal function, and/or to be treated with anti hypertensive medicinal products that may cause changes in renal function such as angiotensin converting enzyme (ACE) inhibitors and angiotensin II type 1 receptor blockers (ARB). The same recommendations for renal function apply to older patients as to all patients. In subjects ≥ 65 years of age, a higher proportion of subjects treated with dapagliflozin had adverse reactions related to renal impairment or failure compared with placebo. The most commonly reported adverse reaction related to renal function was serum creatinine increases, the majority of which were transient and reversible. Older patients may be at a greater risk for volume	Not applicable

Table VI-1 Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	depletion and are more likely to be treated with diuretics. In subjects ≥ 65 years of age, a higher proportion of subjects treated with dapagliflozin had adverse reactions related to volume depletion. Therapeutic experience in patients 75 years and older is limited. Initiation of Xigduo therapy in this population is not recommended. Undesirable effects Special populations Older patients (≥ 65 years) In subjects ≥ 65 years of age, adverse reactions related to renal impairment or failure were reported in 2.5% of subjects treated with dapagliflozin and 1.1% of subjects treated with placebo. The most commonly reported adverse reaction related to renal function was increased serum creatinine. The majority of these reactions were transient and reversible. In subjects ≥ 65 years of age, adverse reactions of volume depletion, most commonly reported as hypotension, were reported in 1.5% and 0.4% of dapagliflozin treated subjects and placebo treated subjects, respectively.	
Patient with severe renal impairment	Product labeling: Contraindications Xigduo is contraindicated in patients with moderate and severe renal impairment (creatinine clearance < 60 ml/min; eGFR < 60 ml/min/1.73 m2), and acute conditions with the potential to alter renal function such as (dehydration, severe infection, shock) **Patient Information:** What you need to know before you take Xigduo Do not take Xigduo if you have problems with your kidneys. Warnings and precautions Talk to your doctor, pharmacist or nurse before taking Xigduo if you have problems with your kidneys. Your doctor will check your kidney function Kidney function Your kidneys should be checked before you start taking	Not applicable

Table VI-1 Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	and at least once a year whilst you are on this medicine.	
Patient with moderate and severe hepatic impairment	**Product Labeling:** Posology and method of administration This medical product must not be used in patients with hepatic impairment. Contraindications Xigduo is contraindicated in patients with hepatic impairment. **Patient Information:** What you need to know before you take Xigduo Do not take Xigduo if you have problems with your liver.	Not applicable
Patients with compromised cardiac function (CF) NYHA class III and IV	**Product Labeling:** Contraindications Xigduo is contraindicated in patients with acute or chronic disease which may cause tissue hypoxia such as cardiac or respiratory failure, recent myocardial infarction, shock. Special warnings and precausions for use Cardiac failure Experience in NYHA class I II is limited, and there is no experience in clinical studies with dapagliflozin in NYHA class III IV. **Patient Information:** What you need to know before you take Xigduo Do not take Xigduo if you have recently had a heart attack or if you have heart failure or serious problems with your blood circulation or difficulties in breathing which could be a sign of heart problems.	Not applicable

Conclusion

The CHMP and PRAC considered that the risk management plan version 7 is acceptable.

2.7. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8. Product information

The Product information for Ebymect is the same as for Xigduo, except for the invented name.

2.8.1. User consultation

Since the package leaflet included in this application is a duplicate of the currently authorised leaflet for the product Xigduo, with only changes to the product name made throughout, a user testing has not been performed. This was considered acceptable by the CHMP.

2.8.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Ebymect (DAPAGLIFLOZIN / METFORMIN) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

This is an informed consent application in accordance with article 10c of Directive 2001/83/EC.

The product of this application is a duplicate with identical composition and documentation as Xigduo (EU/1/13/900/001-12), authorized in the treatment of 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

available data on different combinations)

• in patients already being treated with the combination of dapagliflozin and metformin as separate tablets.

Based on the previous review of data on quality, safety and efficacy for Xigduo, the benefit/risk balance for Ebymect is considered favourable.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Ebymect in the indication:

"Ebymect 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 (see sections 4.4, 4.5 and 5.1 for available data on different combinations)
- in patients already being treated with the combination of dapagliflozin and metformin as separate tablets",

is favourable and therefore recommends the granting of the marketing subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.