ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Ebymect 5 mg/850 mg film-coated tablets
Ebymect 5 mg/1,000 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ebymect 5 mg/850 mg film-coated tablets
Each tablet contains dapagliflozin propanediol monohydrate equivalent to 5 mg dapagliflozin and 850 mg of metformin hydrochloride.

Ebymect 5 mg/1,000 mg film-coated tablets
Each tablet contains dapagliflozin propanediol monohydrate equivalent to 5 mg dapagliflozin and 1,000 mg of metformin hydrochloride.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Ebymect 5 mg/850 mg film-coated tablets
Brown, biconvex, 9.5 x 20 mm oval, film-coated tablets engraved with "5/850" on one side and "1067" engraved on the other side.

Ebymect 5 mg/1,000 mg film-coated tablets
Yellow, biconvex, 10.5 x 21.5 mm oval, film-coated tablets engraved with "5/1000" on one side and "1069" engraved on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

4.2 Posology and method of administration

Posology
Adults with normal renal function (GFR ≥ 90 mL/min)

For patients inadequately controlled on metformin monotherapy or metformin in combination with other glucose-lowering medicinal products including insulin
The recommended dose is one tablet twice daily. Each tablet contains a fixed dose of dapagliflozin and metformin (see section 2). Patients not adequately controlled on metformin alone or in combination with other glucose-lowering medicinal products, including insulin, should receive a total daily dose of Ebymect equivalent to dapagliflozin 10 mg, plus the total daily dose of metformin, or the nearest therapeutically appropriate dose, already being taken. When Ebymect is used in combination with insulin or an insulin secretagogue such as sulphonylurea, a lower dose of insulin or sulphonylurea may be considered to reduce the risk of hypoglycaemia (see sections 4.5 and 4.8).

For patients switching from separate tablets of dapagliflozin and metformin
Patients switching from separate tablets of dapagliflozin (10 mg total daily dose) and metformin to Ebymect should receive the same daily dose of dapagliflozin and metformin already being taken or the nearest therapeutically appropriate dose of metformin.

Special populations
Renal impairment
No dose adjustment is recommended for patients with mild renal impairment, GFR 60 - 89 mL/min. The maximum daily dose is 3000 mg metformin and should preferably be divided into 2 - 3 daily doses. However, dose reduction may be considered in relation to declining renal function. If no adequate strength of Ebymect is available, individual mono-components should be used instead of the fixed dose combination.

A GFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter. In patients at increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.

Ebymect is not recommended for use in patients with GFR < 60 mL/min (see section 4.4). The efficacy of dapagliflozin 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.

Hepatic impairment
This medicinal product must not be used in patients with hepatic impairment (see sections 4.3, 4.4 and 5.2).

Elderly (≥ 65 years)
Because metformin is eliminated in part by the kidney, and because elderly patients are more likely to have decreased renal function, this medicinal product 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 elderly patients (see sections 4.3 and 4.4). Risk of volume depletion with dapagliflozin should also be taken into account (see sections 4.4 and 5.2). Due to the limited therapeutic experience with dapagliflozin in patients 75 years and older, initiation of therapy in this population is not recommended.

Paediatric population
The safety and efficacy of Ebymect in children and adolescents aged 0 to < 18 years have not yet been established. No data are available.

Method of administration
Ebymect should be given twice daily with meals to reduce the gastrointestinal adverse reactions associated with metformin.

4.3 Contraindications

Ebymect is contraindicated in patients with:

- hypersensitivity to the active substances or to any of the excipients listed in section 6.1;
- any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis);
- diabetic pre-coma;
- severe renal failure (GFR < 30 mL/min) (see sections 4.4 and 5.2);
- 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 (see sections 4.2, 4.4 and 5.2);
- acute alcohol intoxication, alcoholism (see section 4.5).

4.4 Special warnings and precautions for use

General
Ebymect should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

Lactic acidosis
Lactic acidosis, a very rare but serious metabolic complication, most often occurs at acute worsening of renal function or cardiorespiratory illness or sepsis. Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis.

In case of dehydration (severe diarrhoea or vomiting, fever or reduced fluid intake), Ebymect should be temporarily discontinued and contact with a health care professional is recommended.

Medicinal products that can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs) should be initiated with caution in metformin-treated patients. Other risk factors for lactic acidosis are excessive alcohol intake, hepatic insufficiency, inadequately controlled diabetes, ketosis, prolonged fasting and any conditions associated with hypoxia, as well as concomitant use of medicinal products that may cause lactic acidosis (see sections 4.3 and 4.5).

Patients and/or care-givers should be informed on the risk of lactic acidosis. Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. In case of suspected symptoms, the patient should stop taking Ebymect and seek immediate medical attention. Diagnostic laboratory findings are decreased blood pH (< 7.35), increased plasma lactate levels above 5 mmol/l, and an increased anion gap and lactate/pyruvate ratio.

Renal function
The efficacy of dapagliflozin, a component of this medicinal 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. Therefore, this medicinal product is not recommended for use in patients with moderate to severe renal impairment (patients with GFR < 60 mL/min) (see section 4.2).

Metformin is excreted by the kidney, and moderate to severe renal insufficiency increases the risk of lactic acidosis (see section 4.4).

Renal function should be assessed:
- Before initiation of treatment and regularly thereafter (see sections 4.2, 4.8, 5.1 and 5.2).
- For renal function with GFR levels approaching moderate renal impairment and in elderly patients, at least 2 to 4 times per year.
- Prior to initiation of concomitant medicinal products that may reduce renal function and periodically thereafter.
- If renal function falls below GFR < 60 mL/min, treatment should be discontinued.
- Metformin is contraindicated in patients with GFR of < 30 mL/min and should be temporarily discontinued in the presence of conditions that alter renal function (see section 4.3).

Decreased renal function in elderly 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 NSAID.

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 (see section 5.1), which may be more pronounced in patients with high blood glucose concentrations.

This medicinal product is not recommended for use in patients receiving loop diuretics (see section 4.5) 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 cardiovascular disease, patients on anti-hypertensive therapy with a history of hypotension or elderly patients.

For patients receiving this medicinal product, in case of intercurrent conditions that may lead to volume depletion, careful monitoring of volume status (e.g. physical examination, blood pressure measurements, laboratory tests including haematocrit) and electrolytes is recommended. Temporary interruption of treatment with this medicinal product is recommended for patients who develop volume depletion until the depletion is corrected (see section 4.8).

Diabetic ketoacidosis
Rare cases of diabetic ketoacidosis (DKA), including life-threatening cases, have been reported in clinical trials and post-marketing in patients treated with SGLT2 inhibitors, including dapagliflozin. In a number of cases, the presentation of the condition was atypical with only moderately increased blood glucose values, below 14 mmol/l (250 mg/dl). It is not known if DKA is more likely to occur with higher doses of dapagliflozin.

The risk of diabetic ketoacidosis must be considered in the event of non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness. Patients should be assessed for ketoacidosis immediately if these symptoms occur, regardless of blood glucose level.

In patients where DKA is suspected or diagnosed, treatment with dapagliflozin should be discontinued immediately.

Treatment should be interrupted in patients who are hospitalised for major surgical procedures or acute serious medical illnesses. In both cases, treatment with dapagliflozin may be restarted once the patient's condition has stabilised.

Before initiating dapagliflozin, factors in the patient history that may predispose to ketoacidosis should be considered.

Patients who may be at higher risk of DKA include patients with a low beta-cell function reserve (e.g. type 2 diabetes patients with low C-peptide or latent autoimmune diabetes in adults (LADA) or patients with a history of pancreatitis), patients with conditions that lead to restricted food intake or severe dehydration, patients for whom insulin doses are reduced and patients with increased insulin requirements due to acute medical illness, surgery or alcohol abuse. SGLT2 inhibitors should be used with caution in these patients.

Restarting SGLT2 inhibitor treatment in patients with previous DKA while on SGLT2 inhibitor treatment is not recommended, unless another clear precipitating factor is identified and resolved.

The safety and efficacy of dapagliflozin in patients with type 1 diabetes have not been established and dapagliflozin should not be used for treatment of patients with type 1 diabetes. Limited data from clinical trials suggest that DKA occurs with common frequency when patients with type 1 diabetes are treated with SGLT2 inhibitors.

Urinary tract infections
Urinary tract infections were more frequently reported for dapagliflozin compared to placebo in a pooled analysis up to 24 weeks (see section 4.8). 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.

Elderly (≥ 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 inhibitors (ACE-I) and angiotensin II type 1 receptor blockers (ARB). The same recommendations for renal function apply to elderly patients as to all patients (see sections 4.2, 4.4, 4.8 and 5.1).

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 (see section 4.8).

Elderly 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 (see section 4.8).

Therapeutic experience in patients 75 years and older is limited. Initiation of therapy in this population is not recommended (see sections 4.2 and 5.2).

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.

Use in patients treated with pioglitazone
While a causal relationship between dapagliflozin and bladder cancer is unlikely (see sections 4.8 and 5.3), as a precautionary measure, this medicinal product 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.

Elevated haematocrit
Haematocrit increase was observed with dapagliflozin treatment (see section 4.8); therefore, caution in patients with already elevated haematocrit is warranted.

Lower limb amputations
An increase in cases of lower limb amputation (primarily of the toe) has been observed in ongoing long-term, clinical studies with another SGLT2 inhibitor. It is unknown whether this constitutes a class effect. Like for all diabetic patients it is important to counsel patients on routine preventative foot care.

Combinations not studied
Dapagliflozin has not been studied in combination with glucagon-like peptide 1 (GLP-1) analogues.

Urine laboratory assessments
Due to its mechanism of action, patients taking this medicinal product will test positive for glucose in their urine.

Administration of iodinated contrast agents
Intravascular administration of iodinated contrast agents may lead to contrast induced nephropathy, resulting in metformin accumulation and increased risk of lactic acidosis. Ebymect should be discontinued prior to, or at the time of, the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable (see sections 4.2 and 4.5).

Surgery
Ebymect must be discontinued at the time of surgery with general, spinal or epidural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and provided that renal function has been re-evaluated and found to be stable.

Change in clinical status of patients with previously controlled type 2 diabetes
As this medicinal product contains metformin, a patient with type 2 diabetes previously well-controlled on it who 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, treatment must be stopped immediately and other appropriate corrective measures initiated.

4.5 Interaction with other medicinal products and other forms of interaction

Coadministration of multiple doses of dapagliflozin and metformin does not meaningfully alter the pharmacokinetics of either dapagliflozin or metformin in healthy subjects.

No interaction studies have been performed for Ebymect. The following statements reflect the information available on the individual active substances.

Dapagliflozin

Pharmacodynamic interactions

Diuretics

This medicinal product may add to the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension (see section 4.4).

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 dapagliflozin (see sections 4.2 and 4.8).

Pharmacokinetic interactions

The metabolism of dapagliflozin is primarily via glucuronide conjugation mediated by UDP-glucuronosyltransferase 1A9 (UGT1A9).

In *in vitro* studies, dapagliflozin neither inhibited cytochrome P450 (CYP) 1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, nor induced CYP1A2, CYP2B6 or CYP3A4. Therefore, this medicinal product is not expected to alter the metabolic clearance of coadministered medicinal products that are metabolised by these enzymes.

Effect of other medicinal products on dapagliflozin

Interaction studies conducted in healthy subjects, using mainly a single-dose design, suggest that the pharmacokinetics of dapagliflozin are not altered by pioglitazone, sitagliptin, glimepiride, voglibose, hydrochlorothiazide, bumetanide, valsartan, or simvastatin.

Following coadministration of dapagliflozin with rifampicin (an inducer of various active transporters and drug-metabolising enzymes) a 22 % decrease in dapagliflozin systemic exposure (AUC) was observed, but with no clinically meaningful effect on 24-hour urinary glucose excretion. No dose adjustment is recommended. A clinically relevant effect with other inducers (e.g. carbamazepine, phenytoin, phenobarbital) is not expected.

Following coadministration of dapagliflozin with mefenamic acid (an inhibitor of UGT1A9), a 55 % increase in dapagliflozin systemic exposure was seen, but with no clinically meaningful effect on 24-hour urinary glucose excretion. No dose adjustment is recommended.

Effect of dapagliflozin on other medicinal products

In interaction studies conducted in healthy subjects, using mainly a single-dose design, dapagliflozin did not alter the pharmacokinetics of pioglitazone, sitagliptin, glimepiride, hydrochlorothiazide, bumetanide, valsartan, digoxin (a P-gp substrate) or warfarin (S-warfarin, a CYP2C9 substrate), or the anti-coagulatory effects of warfarin as measured by INR. Combination of a single dose of dapagliflozin 20 mg and simvastatin (a CYP3A4 substrate) resulted in a 19 % increase in AUC of simvastatin and 31 % increase in AUC of simvastatin acid. The increase in simvastatin and simvastatin acid exposures are not considered clinically relevant**.**

Other interactions

The effects of smoking, diet, herbal products and alcohol use on the pharmacokinetics of dapagliflozin have not been studied.

Interference with 1,5-anhydroglucitol (1,5-AG) assay

Monitoring glycaemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycaemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycaemic control.

Paediatric population
Interaction studies have only been performed in adults.

Metformin
Concomitant use not recommended
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 C_{max} by 81 %. Therefore, close monitoring of glycaemic 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.

Alcohol
Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in the case of fasting, malnutrition or hepatic impairment due to the metformin active substance of this medicinal product (see section 4.4). Consumption of alcohol and medicinal products containing alcohol should be avoided.

Iodinated contrast agents
Intravascular administration of iodinated contrast agents may lead to contrast induced nephropathy, resulting in metformin accumulation and increased risk of lactic acidosis. Ebymect must be discontinued prior to, or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable (see sections 4.2 and 4.4).

Combination requiring precautions for use
Glucocorticoids (given by systemic and local routes), beta-2 agonists, and diuretics have intrinsic hyperglycaemic activity. The patient should be informed and more frequent blood glucose monitoring perfomed, 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.

Some medicinal products can adversely affect renal function which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting or using such products in combination with metformin, close monitoring of renal function is necessary.

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 metformin (see sections 4.2 and 4.8)

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no data from the use of Ebymect 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 (see section 5.3). Therefore, the use of this medicinal 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 (see section 5.3).

When the patient plans to become pregnant, and during pregnancy, it is recommended that diabetes is not treated with this medicinal product, 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 this medicinal product or dapagliflozin (and/or its metabolites) are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of dapagliflozin/metabolites in milk, as well as pharmacologically-mediated effects in nursing offspring (see section 5.3). Metformin is excreted in human milk in small amounts. A risk to the newborns/infants cannot be excluded.

This medicinal product should not be used while breast-feeding.

Fertility
The effect of this medicinal product or dapagliflozin on fertility in humans has not been studied. In male and female rats, dapagliflozin showed no effects on fertility at any dose tested. For metformin, studies in animals have not shown reproductive toxicity (see section 5.3).

4.7 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 this medicinal product is used in combination with other glucose-lowering medicinal products known to cause hypoglycaemia.

4.8 Undesirable effects

Ebymect has been demonstrated to be bioequivalent with coadministered dapagliflozin and metformin (see section 5.2). There have been no therapeutic clinical trials conducted with Ebymect tablets.

Dapagliflozin plus metformin
Summary of the safety profile
In an analysis of 5 placebo-controlled dapagliflozin add-on to metformin studies, the safety results were similar to that of the pre-specified pooled analysis of 12 placebo-controlled dapagliflozin studies (see Dapagliflozin, *Summary of the safety profile* below). No additional adverse reactions were identified for the dapagliflozin plus metformin group compared with those reported for the individual components. In the separate dapagliflozin add-on to metformin pooled analysis, 623 subjects were treated with dapagliflozin 10 mg as add-on to metformin and 523 were treated with placebo plus metformin.

Dapagliflozin
Summary of the safety profile
In a pre-specified pooled analysis of 13 placebo-controlled studies, 2,360 subjects were treated with dapagliflozin 10 mg and 2,295 were treated with placebo.

The most frequently reported adverse reaction was hypoglycaemia, which depended on the type of background therapy used in each study. The frequency of minor episodes of hypoglycaemia was similar between treatment groups, including placebo, with the exceptions of studies with add-on sulphonylurea (SU) and add-on insulin therapies. Combination therapies with sulphonylurea and add-on insulin had higher rates of hypoglycaemia (see *Hypoglycaemia* below).

Tabulated list of adverse reactions

The following adverse reactions have been identified in the placebo-controlled dapagliflozin plus metformin clinical trials, dapagliflozin clinical trials and metformin clinical trials and post-marketing experience. None were found to be dose-related. Adverse reactions listed below are classified according to frequency and system organ class. Frequency categories are defined according to the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data).

Table 1. Adverse reactions in dapagliflozin and metformin immediate-release clinical trial and postmarketing data[a]

System organ class	Very common	Common	Uncommon	Rare	Very rare
Infections and infestations		Vulvovaginitis, balanitis and related genital infections[*,b,c] Urinary tract infection[*,b,d]	Fungal infection[**]		
Metabolism and nutrition disorders	Hypoglycaemia (when used with SU or insulin)[b]		Volume depletion[b,e] Thirst[**]	Diabetic ketoacidosis[k]	Lactic acidosis Vitamin B12 deficiency[h,§]
Nervous system disorders		Taste disturbance[§] Dizziness			
Gastrointestinal disorders	Gastrointestinal symptoms[i,§]		Constipation[**] Dry mouth[**]		
Hepatobiliary disorders					Liver function disorders[§] Hepatitis[§]
Skin and subcutaneous tissue disorders					Urticaria[§] Erythema[§] Pruritus[§]
Musculoskeletal and connective tissue disorders		Back pain[*]			
Renal and urinary disorders		Dysuria Polyuria[*,f]	Nocturia[**] Renal impairment[**,b]		

System organ class	Very common	Common	Uncommon	Rare	Very rare
Reproductive system and breast disorders			Vulvovaginal pruritus[**] Pruritus genital[**]		
Investigations		Haematocrit increased[g] Creatinine renal clearance decreased[b] Dyslipidaemia[j]	Blood creatinine increased[**,b] Blood urea increased[**] Weight decreased[**]		

[a]The table shows adverse reactions identified from up to 24-week (short-term) data regardless of glycaemic rescue, except those marked with §, for which adverse reaction and frequency categories are based on information from the metformin Summary of Product Characteristics available in the European Union.

[b]See corresponding subsection below for additional information.

[c]Vulvovaginitis, balanitis and related genital infections includes, e.g. the predefined preferred terms: vulvovaginal mycotic infection, vaginal infection, balanitis, genital infection fungal, vulvovaginal candidiasis, vulvovaginitis, balanitis candida, genital candidiasis, genital infection, genital infection male, penile infection, vulvitis, vaginitis bacterial, vulval abscess.

[d]Urinary tract infection includes the following preferred terms, listed in order of frequency reported: urinary tract infection, cystitis, Escherichia urinary tract infection, genitourinary tract infection, pyelonephritis, trigonitis, urethritis, kidney infection and prostatitis.

[e]Volume depletion includes, e.g. the predefined preferred terms: dehydration, hypovolaemia, hypotension.

[f]Polyuria includes the preferred terms: pollakiuria, polyuria, urine output increased.

[g]Mean changes from baseline in haematocrit were 2.30 % for dapagliflozin 10 mg versus –0.33 % for placebo. Haematocrit values > 55 % were reported in 1.3 % of the subjects treated with dapagliflozin 10 mg versus 0.4 % of placebo subjects.

[h]Long-term treatment with metformin has been associated with a decrease in vitamin B12 absorption which may very rarely result in clinically significant vitamin B12 deficiency (e.g. megaloblastic anaemia).

[i]Gastrointestinal symptoms such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite occur most frequently during initiation of therapy and resolve spontaneously in most cases.

[j]Mean percent change from baseline for dapagliflozin 10 mg versus placebo, respectively, was: total cholesterol 2.5 % versus 0.0 %; HDL cholesterol 6.0 % versus 2.7 %; LDL cholesterol 2.9 % versus –1.0 %; triglycerides -2.7 % versus –0.7 %.

[k]See section 4.4

[*]Reported in ≥ 2 % of subjects and ≥ 1 % more and at least 3 more subjects treated with dapagliflozin 10 mg compared to placebo.

[**]Reported by the investigator as possibly related, probably related or related to study treatment and reported in ≥ 0.2 % of subjects and ≥ 0.1 % more and at least 3 more subjects treated with dapagliflozin 10 mg compared to placebo.

Description of selected adverse reactions

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 of hypoglycaemia were reported.

In an add-on to metformin and a sulphonylurea study, up to 24 weeks, minor episodes of hypoglycaemia were reported in 12.8 % of subjects who received dapagliflozin 10 mg plus metformin and a sulphonylurea and in 3.7 % of subjects who received placebo plus metformin and a sulphonylurea. No major events 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 (see section 4.5).

In an add-on to insulin study up to 104 weeks, episodes of major hypoglycaemia were reported in 0.5 % 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.

Volume depletion
Reactions related to volume depletion (including, reports of dehydration, hypovolaemia or hypotension) were reported in 1.1 % and 0.7 % 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 (see section 4.4).

Vulvovaginitis, balanitis and related genital infections
Vulvovaginitis, balanitis and related genital infections were reported in 5.5 % and 0.6 % 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 (8.4 % and 1.2 % for dapagliflozin and placebo, respectively), and subjects with a prior history were more likely to have a recurrent infection.

Urinary tract infections
Urinary tract infections were more frequently reported for dapagliflozin compared with placebo (4.7 % versus 3.5 %, respectively; see section 4.4). 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.

Increased creatinine
Adverse drug reactions related to increased creatinine were grouped (e.g. decreased renal creatinine clearance, renal impairment, increased blood creatinine and decreased glomerular filtration rate). This grouping of reactions was reported in 3.2 % and 1.8 % of patients who received dapagliflozin 10 mg and placebo, respectively. In patients with normal renal function or mild renal impairment (baseline eGFR $\geq$ 60 mL/min/1.73 m^2) this grouping of reactions were reported in 1.3 % and 0.8 % of patients who received dapagliflozin 10 mg and placebo, respectively. These reactions were more common in patients with baseline eGFR $\geq$ 30 and < 60 mL/min/1.73 m^2 (18.5 % dapagliflozin 10 mg vs. 9.3 % placebo).

Further evaluation of patients who had renal-related adverse events showed that most had serum creatinine changes of $\leq$ 0.5 mg/dl from baseline. The increases in creatinine were generally transient during continuous treatment or reversible after discontinuation of treatment.

Parathyroid hormone (PTH)
Small increases in serum PTH levels were observed with increases being larger in subjects with higher baseline PTH concentrations. Bone mineral density measurements in patients with normal or mildly impaired renal function did not indicate bone loss over a treatment period of two years.

Malignancies
During clinical trials, the overall proportion of subjects with malignant or unspecified tumours was similar between those treated with dapagliflozin (1.50 %) and placebo/comparator (1.50 %), and there was no carcinogenicity or mutagenicity signal in animal data (see section 5.3). 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.

Special populations
Elderly (≥ 65 years)
In subjects ≥ 65 years of age, adverse reactions related to renal impairment or failure were reported in 7.7 % of subjects treated with dapagliflozin and 3.8 % of subjects treated with placebo (see section 4.4). 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 1.7 % and 0.8 % of dapagliflozin-treated subjects and placebo-treated subjects, respectively (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Removal of dapagliflozin by haemodialysis has not been studied. The most effective method to remove metformin and lactate is haemodialysis.

Dapagliflozin
Dapagliflozin did not show any toxicity in healthy subjects at single oral doses up to 500 mg (50 times the maximum recommended human dose). These subjects had detectable glucose in the urine for a dose-related period of time (at least 5 days for the 500 mg dose), with no reports of dehydration, hypotension or electrolyte imbalance, and with no clinically meaningful effect on QTc interval. The incidence of hypoglycaemia was similar to placebo. In clinical studies where once daily doses of up to 100 mg (10 times the maximum recommended human dose) were administered for 2 weeks in healthy subjects and type 2 diabetes subjects, the incidence of hypoglycaemia was slightly higher than placebo and was not dose-related. Rates of adverse events including dehydration or hypotension were similar to placebo, and there were no clinically meaningful dose-related changes in laboratory parameters, including serum electrolytes and biomarkers of renal function.

In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status.

Metformin
High overdose or concomitant risks of metformin may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in hospital.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, Combinations of oral blood glucose-lowering drugs, ATC code: A10BD15

Mechanism of action
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.

Dapagliflozin
Dapagliflozin is a highly potent (K_i: 0.55 nM), selective and reversible inhibitor of sodium-glucose co-transporter 2 (SGLT2).

The SGLT2 is selectively expressed in the kidney with no expression detected in more than 70 other tissues including liver, skeletal muscle, adipose tissue, breast, bladder and brain. SGLT2 is the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. Despite the presence of hyperglycaemia in type 2 diabetes, reabsorption of filtered glucose continues. 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. 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.

Urinary glucose excretion (glucuresis) induced by dapagliflozin is associated with caloric loss and reduction in weight. Inhibition of glucose and sodium co-transport by dapagliflozin is also associated with mild diuresis and transient natriuresis.

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
Metformin is a biguanide with anti-hyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

Metformin may act via three mechanisms:
- by reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis;
- by modestly increasing insulin sensitivity, improving peripheral glucose uptake and utilisation in muscle;
- by delaying intestinal glucose absorption.

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase. Metformin increases the transport capacity of specific types of membrane glucose transporters (GLUT-1 and GLUT-4).

Pharmacodynamic effects

Dapagliflozin

Increases in the amount of glucose excreted in the urine were observed in healthy subjects and in subjects with type 2 diabetes mellitus following the administration of dapagliflozin. Approximately 70 g of glucose was excreted in the urine per day (corresponding to 280 kcal/day) at a dapagliflozin dose of 10 mg/day in subjects with type 2 diabetes mellitus for 12 weeks. Evidence of sustained glucose excretion was seen in subjects with type 2 diabetes mellitus given dapagliflozin 10 mg/day for up to 2 years.

This urinary glucose excretion with dapagliflozin also results in osmotic diuresis and increases in urinary volume in subjects with type 2 diabetes mellitus. Urinary volume increases in subjects with type 2 diabetes mellitus treated with dapagliflozin 10 mg were sustained at 12 weeks and amounted to approximately 375 mL/day. The increase in urinary volume was associated with a small and transient increase in urinary sodium excretion that was not associated with changes in serum sodium concentrations.

Urinary uric acid excretion was also increased transiently (for 3-7 days) and accompanied by a sustained reduction in serum uric acid concentration. At 24 weeks, reductions in serum uric acid concentrations ranged from -48.3 to -18.3 micromoles/l (-0.87 to -0.33 mg/dl).

The pharmacodynamics of 5 mg dapagliflozin twice daily and 10 mg dapagliflozin once daily were compared in healthy subjects. The steady-state inhibition of renal glucose reabsorption and the amount of urinary glucose excretion over a 24-hour period was the same for both dosing regimens.

Metformin

In humans, independently of its action on glycaemia, metformin has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: metformin reduces total cholesterol, LDL cholesterol and triglyceride levels.

In clinical studies, use of metformin was associated with either a stable body weight or modest weight loss.

Clinical efficacy and safety

The coadministration of dapagliflozin and metformin has been studied in subjects with type 2 diabetes inadequately controlled on metformin alone or in combination with a DPP-4 inhibitor (sitagliptin), sulphonylurea or insulin. Treatment with dapagliflozin plus metformin at all doses produced clinically relevant and statistically significant improvements in HbA1c and fasting plasma glucose compared with placebo in combination with metformin. These clinically relevant glycaemic effects were sustained in long-term extensions up to 104 weeks. HbA1c reductions were seen across subgroups including gender, age, race, duration of disease, and baseline body mass index (BMI). Additionally, at Week 24, clinically relevant and statistically significant improvements in mean changes from baseline in body weight were seen with dapagliflozin and metformin combination treatments compared with control. Body weight reductions were sustained in long-term extensions up to 208 weeks. Additionally, dapagliflozin twice-daily treatment added to metformin was shown to be effective and safe in type 2 diabetic subjects. Furthermore, two 12-week, placebo-controlled studies were conducted in patients with inadequately controlled type 2 diabetes and hypertension.

Glycaemic control

In a 52-week, active-controlled non-inferiority study (with 52- and 104-week extension periods), dapagliflozin 10 mg was evaluated as add-on therapy to metformin compared with a sulphonylurea

(glipizide) as add-on therapy to metformin in subjects with inadequate glycaemic control (HbA1c > 6.5 % and ≤ 10 %). The results showed a similar mean reduction in HbA1c from baseline to Week 52, compared with glipizide, thus demonstrating non-inferiority (Table 2). At Week 104, adjusted mean change from baseline in HbA1c was -0.32 % for dapagliflozin and -0.14 % for glipizide, respectively. At Week 208, adjusted mean change from baseline in HbA1c was -0.10 % for dapagliflozin and 0.20 % for glipizide, respectively. At 52, 104 and 208 weeks, a significantly lower proportion of subjects in the group treated with dapagliflozin (3.5 %, 4.3 % and 5.0 %, respectively) experienced at least one event of hypoglycaemia compared with the group treated with glipizide (40.8 %, 47 % and 50.0 %, respectively). The proportion of subjects remaining in the study at Week 104 and Week 208 was 56.2 % and 39.7 % for the group treated with dapagliflozin and 50.0 % and 34.6 % for the group treated with glipizide.

Table 2. Results at Week 52 (LOCF[a]) in an active-controlled study comparing dapagliflozin with glipizide as add-on to metformin

Parameter	Dapagliflozin + metformin	Glipizide + metformin
N[b]	400	401
HbA1c (%)		
Baseline (mean)	7.69	7.74
Change from baseline[c]	-0.52	-0.52
Difference from glipizide + metformin[c]	0.00[d]	
(95 % CI)	(-0.11, 0.11)	
Body weight (kg)		
Baseline (mean)	88.44	87.60
Change from baseline[c]	-3.22	1.44
Difference from glipizide + metformin[c]	-4.65[*]	
(95 % CI)	(-5.14, -4.17)	

[a]LOCF: Last observation carried forward
[b]Randomised and treated subjects with baseline and at least 1 post-baseline efficacy measurement
[c]Least squares mean adjusted for baseline value
[d]Non-inferior to glipizide + metformin
[*]p-value < 0.0001

Dapagliflozin as an add-on with either metformin alone, metformin in combination with sitagliptin, sulphonylurea or insulin (with or without additional oral glucose-lowering medicinal products, including metformin) resulted in statistically significant mean reductions in HbA1c at 24 weeks compared with subjects receiving placebo (p < 0.0001; Tables 3, 4 and 5). Dapagliflozin 5 mg twice daily provided statistically significant reductions in HbA1c at 16 weeks compared with subjects receiving placebo (p < 0.0001; Table 3).

The reductions in HbA1c observed at Week 24 were sustained in the add-on combination studies. For the add-on to metformin study, HbA1c reductions were sustained through Week 102 (-0.78 % and 0.02 % adjusted mean change from baseline for dapagliflozin 10 mg and placebo, respectively). At Week 48 for metformin plus sitagliptin, the adjusted mean change from baseline for dapagliflozin 10 mg and placebo was -0.44 % and 0.15 %, respectively. At Week 104 for insulin (with or without additional oral glucose-lowering medicinal products, including metformin), the HbA1c reductions were -0.71 % and -0.06 % adjusted mean change from baseline for dapagliflozin 10 mg and placebo, respectively. At Weeks 48 and 104, the insulin dose remained stable compared to baseline in subjects treated with dapagliflozin 10 mg at an average dose of 76 IU/day. In the placebo group there was an increase of 10.5 IU/day and 18.3 IU/day from baseline (mean average dose of 84 and 92 IU/day) at Weeks 48 and 104, respectively. The proportion of subjects remaining in the study at Week 104 was 72.4 % for the group treated with dapagliflozin 10 mg and 54.8 % for the placebo group.

In a separate analysis of subjects on insulin plus metformin, similar reductions in HbA1C to those seen in the total study population were seen in subjects treated with dapagliflozin with insulin plus metformin. At Weeks 24, HbA1c change from baseline in subjects treated with dapagliflozin plus insulin with metformin was -0.93 %.

Table 3. Results of (LOCF[a]) placebo-controlled studies up to 24 weeks of dapagliflozin in add-on combination with metformin or metformin plus sitagliptin

	Add-on combination					
	Metformin[1]		**Metformin[1, b]**		**Metformin[1] + Sitagliptin[2]**	
	Dapagliflozin 10 mg QD	**Placebo QD**	**Dapagliflozin 5 mg BID**	**Placebo BID**	**Dapagliflozin 10 mg QD**	**Placebo QD**
N[c]	135	137	99	101	113	113
HbA1c (%)						
Baseline (mean)	7.92	8.11	7.79	7.94	7.80	7.87
Change from baseline[d]	-0.84	-0.30	-0.65	-0.30	-0.43	-0.02
Difference from placebo[d] (95 % CI)	-0.54* (-0.74, -0.34)		-0.35* (-0.52, -0.18)		-0.40* (-0.58, -0.23)	
Subjects (%) achieving: HbA1c < 7 %						
Adjusted for baseline	40.6**	25.9	38.2** (N=90)	21.4 (N=87)		
Body weight (kg)						
Baseline (mean)	86.28	87.74	93.62	88.82	93.95	94.17
Change from baseline[d]	-2.86	-0.89	-2.74	-0.86	-2.35	-0.47
Difference from placebo[d] (95 % CI)	-1.97* (-2.63, -1.31)		-1.88*** (-2.52, -1.24)		-1.87* (-2.61, -1.13)	

Abbreviations: QD: once daily; BID: twice daily
[1]Metformin ≥ 1500 mg/day;
[2]Sitagliptin 100 mg/day
[a]LOCF: Last observation (prior to rescue for rescued subjects) carried forward
[b]Placebo-controlled 16-week study
[c]All randomised subjects who took at least one dose of double-blind study medicinal product during the short-term double-blind period
[d]Least squares mean adjusted for baseline value
*p-value < 0.0001 versus placebo + oral glucose-lowering medicinal product
**p-value < 0.05 versus placebo + oral glucose-lowering medicinal product
***The percent change in body weight was analysed as a key secondary endpoint (p < 0.0001); absolute body weight change (in kg) was analysed with a nominal p-value (p < 0.0001).

Table 4. Results of a 24-week placebo-controlled study of dapagliflozin in add-on combination with metformin and a sulphonylurea

	Add-on combination	
	Sulphonylurea + Metformin[1]	
	Dapagliflozin 10 mg	**Placebo**
N[a]	108	108
HbA1c (%)[b]		
Baseline (mean)	8.08	8.24
Change from Baseline[c]	-0.86	-0.17
Difference from Placebo[c]	−0.69*	
(95 % CI)	(−0.89, −0.49)	
Subjects (%) achieving:		
HbA1c < 7 %		
Adjusted for baseline	31.8*	11.1
Body weight (kg)		
Baseline (mean)	88.57	90.07
Change from Baseline[c]	-2.65	-0.58
Difference from Placebo[c]	−2.07*	
(95 % CI)	(−2.79, −1.35)	

[1]Metformin (immediate- or extended-release formulations) ≥ 1500 mg/day plus maximum tolerated dose, which must be at least half maximum dose, of a sulphonylurea for at least 8 weeks prior to enrolment.

[a]Randomised and treated patients with baseline and at least 1 post-baseline efficacy measurement.

[b]HbA1c analysed using LRM (Longitudinal repeated measures analysis)

[c]Least squares mean adjusted for baseline value

*p-value < 0.0001 versus placebo + oral glucose-lowering medicinal product(s)

Table 5. Results at Week 24 (LOCF[a]) in a placebo-controlled study of dapagliflozin in combination with insulin (alone or with oral glucose-lowering medicinal products, including metformin)

Parameter	Dapagliflozin 10 mg + insulin ± oral glucose-lowering medicinal products[2]	Placebo + insulin ± oral glucose-lowering medicinal products[2]
N[b]	194	193
HbA1c (%)		
Baseline (mean)	8.58	8.46
Change from baseline[c]	-0.90	-0.30
Difference from placebo[c]	-0.60[*]	
(95 % CI)	(-0.74, -0.45)	
Body weight (kg)		
Baseline (mean)	94.63	94.21
Change from baseline[c]	-1.67	0.02
Difference from placebo[c]	-1.68[*]	
(95 % CI)	(-2.19, -1.18)	
Mean daily insulin dose (IU)[1]		
Baseline (mean)	77.96	73.96
Change from baseline[c]	-1.16	5.08
Difference from placebo[c]	-6.23[*]	
(95 % CI)	(-8.84, -3.63)	
Subjects with mean daily insulin dose reduction of at least 10 % (%)	19.7[**]	11.0

[a]LOCF: Last observation (prior to or on the date of the first insulin up-titration, if needed) carried forward
[b]All randomised subjects who took at least one dose of double-blind study medicinal product during the short-term double-blind period
[c]Least squares mean adjusted for baseline value and presence of oral glucose-lowering medicinal product
[*]p-value < 0.0001 versus placebo + insulin ± oral glucose-lowering medicinal product
[**]p-value < 0.05 versus placebo + insulin ± oral glucose-lowering medicinal product
[1]Up-titration of insulin regimens (including short-acting, intermediate, and basal insulin) was only allowed if subjects met pre-defined FPG criteria.
[2]Fifty percent of subjects were on insulin monotherapy at baseline; 50 % were on 1 or 2 oral glucose-lowering medicinal product(s) in addition to insulin: Of this latter group, 80 % were on metformin alone, 12 % were on metformin plus sulphonylurea therapy, and the rest were on other oral glucose-lowering medicinal products.

Fasting plasma glucose
Treatment with dapagliflozin as an add-on to either metformin alone (dapagliflozin 10 mg QD or dapagliflozin 5 mg BID) or metformin plus sitagliptin, sulphonylurea or insulin resulted in statistically significant reductions in fasting plasma glucose (-1.90 to -1.20 mmol/l [-34.2 to -21.7 mg/dl]) compared with placebo (-0.58 to 0.18 mmol/l [-10.4 to 3.3 mg/dl]) at Week 16 (5 mg BID) or Week 24. This effect was observed at Week 1 of treatment and maintained in studies extended through Week 104.

Post-prandial glucose
Treatment with dapagliflozin 10 mg as an add-on to sitagliptin plus metformin resulted in reductions in 2-hour post-prandial glucose at 24 weeks that were maintained up to Week 48.

Body weight
Dapagliflozin as an add-on to metformin alone or metformin plus sitagliptin, sulphonylurea or insulin (with or without additional oral glucose-lowering medicinal products, including metformin) resulted in statistically significant body weight reduction up to 24 weeks ($p < 0.0001$, Tables 3, 4 and 5). These effects were sustained in longer-term trials. At 48 weeks, the difference for dapagliflozin as add-on to metformin plus sitagliptin compared with placebo was -2.07 kg. At 102 weeks, the difference for

dapagliflozin as add-on to metformin compared with placebo or as add-on to insulin compared with placebo was -2.14 and -2.88 kg, respectively.

As an add-on therapy to metformin in an active-controlled non-inferiority study, dapagliflozin resulted in a statistically significant body weight change compared with glipizide of -4.65 kg at 52 weeks ($p < 0.0001$, Table 2) that was sustained at 104 and 208 weeks (-5.06 kg and -4.38 kg, respectively).

A 24-week study in 182 diabetic subjects using dual energy X-ray absorptiometry (DXA) to evaluate body composition demonstrated reductions with dapagliflozin 10 mg plus metformin compared with placebo plus metformin, respectively, in body weight and body fat mass as measured by DXA rather than lean tissue or fluid loss. Treatment with dapagliflozin 10 mg plus metformin showed a numerical decrease in visceral adipose tissue compared with placebo plus metformin treatment in a magnetic resonance imaging substudy.

Blood pressure
In a pre-specified pooled analysis of 13 placebo-controlled studies, treatment with dapagliflozin 10 mg resulted in a systolic blood pressure change from baseline of –3.7 mmHg and diastolic blood pressure of –1.8 mmHg versus –0.5 mmHg systolic and -0.5 mmHg diastolic blood pressure for placebo group at Week 24. Similar reductions were observed at up to 104 weeks.

In two 12-week, placebo-controlled studies a total of 1,062 patients with inadequately controlled type 2 diabetes and hypertension (despite pre-existing stable treatment with an ACE-I or ARB in one study and an ACE-I or ARB plus one additional antihypertensive treatment in another study) were treated with dapagliflozin 10 mg or placebo. At Week 12 for both studies, dapagliflozin 10 mg plus usual antidiabetic treatment provided improvement in HbA1c and decreased the placebo-corrected systolic blood pressure on average by 3.1 and 4.3 mmHg, respectively.

Cardiovascular safety
A meta-analysis of cardiovascular events in the clinical program was performed. In the clinical program, 34.4 % of subjects had a history of cardiovascular disease (excluding hypertension) at baseline and 67.9 % had hypertension. Cardiovascular episodes were adjudicated by an independent adjudication committee. The primary end point was the time-to-first event of one of the following outcomes: cardiovascular death, stroke, myocardial infarction (MI) or hospitalisation for unstable angina. Primary episodes occurred at a rate of 1.62 % per patient-year in subjects treated with dapagliflozin and 2.06 % in comparator-treatment subjects, per patient-year. The hazard ratio comparing dapagliflozin to comparator was 0.79 (95 % Confidence interval [CI]: 0.58, 1.07), indicating that in this analysis dapagliflozin is not associated with an increase in cardiovascular risk in patients with type 2 diabetes mellitus. Cardiovascular death, MI and stroke were observed with a hazard ratio of 0.77 (95 % CI: 0.54, 1.10).

Patients with baseline HbA1c ≥ 9 %
In a pre-specified analysis of subjects with baseline HbA1c ≥ 9.0 %, treatment with dapagliflozin 10 mg resulted in statistically significant reductions in HbA1c at Week 24 as an add-on to metformin (adjusted mean change from baseline: -1.32 % and -0.53 % for dapagliflozin and placebo, respectively).

Metformin
The prospective randomised (UKPDS) study has established the long-term benefit of intensive blood glucose control in type 2 diabetes. Analysis of the results for overweight patients treated with metformin after failure of diet alone showed:

- a significant reduction of the absolute risk of any diabetes-related complication in the metformin group (29.8 events/1,000 patient-years) versus diet alone (43.3 events/1,000 patient-years), p=0.0023, and versus the combined sulphonylurea and insulin monotherapy groups (40.1 events/1,000 patient-years), p=0.0034;
- a significant reduction of the absolute risk of any diabetes-related mortality: metformin 7.5 events/1,000 patient-years, diet alone 12.7 events/1,000 patient-years, p=0.017;
- a significant reduction of the absolute risk of overall mortality: metformin 13.5 events/1,000 patient-years versus diet alone 20.6 events/1,000 patient-years, (p=0.011), and versus the combined sulphonylurea and insulin monotherapy groups 18.9 events/1,000 patient-years (p=0.021);
- a significant reduction in the absolute risk of myocardial infarction: metformin 11 events/1,000 patient-years, diet alone 18 events/1,000 patient-years, (p=0.01).

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Ebymect in all subsets of the paediatric population in the treatment of type 2 diabetes (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Ebymect combination tablets are considered to be bioequivalent to coadministration of corresponding doses of dapagliflozin and metformin hydrochloride administered together as individual tablets.

The pharmacokinetics of 5 mg dapagliflozin twice daily and 10 mg dapagliflozin once daily were compared in healthy subjects. Administration of 5 mg dapagliflozin twice daily gave similar overall exposures (AUC_{ss}) over a 24-hour period as 10 mg dapagliflozin administered once daily. As expected, dapagliflozin 5 mg administered twice daily compared with 10 mg dapagliflozin once daily resulted in lower peak dapagliflozin plasma concentrations (C_{max}) and higher trough plasma dapagliflozin concentrations (C_{min}).

Interaction with food
The administration of this medicinal product in healthy volunteers after a high fat meal compared to after the fasted state resulted in the same extent of exposure for both dapagliflozin and metformin. The meal resulted in a delay of 1 to 2 hours in the peak concentrations and a decrease in the maximum plasma concentration of 29 % of dapagliflozin and 17 % of metformin. These changes are not considered to be clinically meaningful.

Paediatric population
Pharmacokinetics in the paediatric population have not been studied.

The following statements reflect the pharmacokinetic properties of the individual active substances of this medicinal product.

Dapagliflozin
Absorption
Dapagliflozin was rapidly and well absorbed after oral administration. Maximum dapagliflozin plasma concentrations (C_{max}) were usually attained within 2 hours after administration in the fasted state. Geometric mean steady-state dapagliflozin C_{max} and AUC_{τ} values following once daily 10 mg doses of dapagliflozin were 158 ng/mL and 628 ng h/mL, respectively. The absolute oral bioavailability of dapagliflozin following the administration of a 10 mg dose is 78 %.

Distribution
Dapagliflozin is approximately 91 % protein bound. Protein binding was not altered in various disease states (e.g. renal or hepatic impairment). The mean steady-state volume of distribution of dapagliflozin was 118 liters.

Biotransformation
Dapagliflozin is extensively metabolised, primarily to yield dapagliflozin 3-O-glucuronide, which is an inactive metabolite. Dapagliflozin 3-O-glucuronide or other metabolites do not contribute to the glucose-lowering effects. The formation of dapagliflozin 3-O-glucuronide is mediated by UGT1A9, an enzyme present in the liver and kidney, and CYP-mediated metabolism was a minor clearance pathway in humans.

Elimination
The mean plasma terminal half-life ($t_{1/2}$) for dapagliflozin was 12.9 hours following a single oral dose of dapagliflozin 10 mg to healthy subjects. The mean total systemic clearance of dapagliflozin administered intravenously was 207 mL/min. Dapagliflozin and related metabolites are primarily eliminated via urinary excretion with less than 2 % as unchanged dapagliflozin. After administration of a 50 mg [^{14}C]-dapagliflozin dose, 96 % was recovered, 75 % in urine and 21 % in feces. In feces, approximately 15 % of the dose was excreted as parent drug.

Linearity
Dapagliflozin exposure increased proportional to the increment in dapagliflozin dose over the range of 0.1 to 500 mg and its pharmacokinetics did not change with time upon repeated daily dosing for up to 24 weeks.

Special populations
Renal impairment
At steady-state (20 mg once-daily dapagliflozin for 7 days), subjects with type 2 diabetes mellitus and mild, moderate or severe renal impairment (as determined by iohexol plasma clearance) had mean systemic exposures of dapagliflozin of 32 %, 60 % and 87 % higher, respectively, than those of subjects with type 2 diabetes mellitus and normal renal function. The steady-state 24-hour urinary glucose excretion was highly dependent on renal function and 85, 52, 18 and 11 g of glucose/day was excreted by subjects with type 2 diabetes mellitus and normal renal function or mild, moderate or severe renal impairment, respectively. The impact of hemodialysis on dapagliflozin exposure is not known.

Hepatic impairment
In subjects with mild or moderate hepatic impairment (Child-Pugh classes A and B), mean C_{max} and 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. In subjects with severe hepatic impairment (Child-Pugh class C) mean C_{max} and AUC of dapagliflozin were 40 % and 67 % higher than matched healthy controls, respectively.

Elderly (≥ 65 years)
There is no clinically meaningful increase in exposure based on age alone in subjects up to 70 years old. However, an increased exposure due to age-related decrease in renal function can be expected. There are insufficient data to draw conclusions regarding exposure in patients > 70 years old.

Gender
The mean dapagliflozin AUC_{ss} in females was estimated to be about 22 % higher than in males.

Race
There were no clinically relevant differences in systemic exposures between White, Black or Asian races.

Body weight
Dapagliflozin exposure was found to decrease with increased weight. Consequently, low-weight patients may have somewhat increased exposure and patients with high weight somewhat decreased exposure. However, the differences in exposure were not considered clinically meaningful.

Paediatric population
Pharmacokinetics in the paediatric population have not been studied.

Metformin
Absorption
After an oral dose of metformin, t_{max} is reached in 2.5 h. Absolute bioavailability of a 500 mg or 850 mg metformin tablet is approximately 50-60 % in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces was 20-30 %.

After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption is non-linear. At the usual metformin doses and dosing schedules, steady-state plasma concentrations are reached within 24-48 hours and are generally less than 1 μg/mL. In controlled clinical trials, maximum metformin plasma levels (C_{max}) did not exceed 5 μg/mL, even at maximum doses.

Distribution
Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean V_d ranged between 63-276 l.

Biotransformation
Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.

Elimination
Renal clearance of metformin is > 400 mL/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 hours.

Special populations
Renal impairment
In patients with decreased renal function (based on measured creatinine clearance), the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance, leading to increased levels of metformin in plasma.

5.3 Preclinical safety data

Coadministration of dapagliflozin and metformin
Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity.

The following statements reflect the preclinical safety data of the individual active substances of Ebymect.

Dapagliflozin
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and fertility. Dapagliflozin did not induce tumours in either mice or rats at any of the doses evaluated in two-year carcinogenicity studies.

Reproductive and developmental toxicity
Direct administration of dapagliflozin to weanling juvenile rats and indirect exposure during late pregnancy (time periods corresponding to the second and third trimesters of pregnancy with respect to human renal maturation) and lactation are each associated with increased incidence and/or severity of renal pelvic and tubular dilatations in progeny.

In a juvenile toxicity study, when dapagliflozin was dosed directly to young rats from postnatal day 21 until postnatal day 90, renal pelvic and tubular dilatations were reported at all dose levels; pup exposures at the lowest dose tested were ≥ 15 times the maximum recommended human dose. These findings were associated with dose-related increases in kidney weight and macroscopic kidney enlargement observed at all doses. The renal pelvic and tubular dilatations observed in juvenile animals did not fully reverse within the approximate 1-month recovery period.

In a separate study of pre- and postnatal development, maternal rats were dosed from gestation day 6 through postnatal day 21, and pups were indirectly exposed *in utero* and throughout lactation. (A satellite study was conducted to assess dapagliflozin exposures in milk and pups.) Increased incidence or severity of renal pelvic dilatation was observed in adult offspring of treated dams, although only at the highest dose tested (associated maternal and pup dapagliflozin exposures were 1,415 times and 137 times, respectively, the human values at the maximum recommended human dose). Additional developmental toxicity was limited to dose-related reductions in pup body weights, and observed only at doses ≥ 15 mg/kg/day (associated with pup exposures that are ≥ 29 times the human values at the maximum recommended human dose). Maternal toxicity was evident only at the highest dose tested, and limited to transient reductions in body weight and food consumption at dose. The no observed adverse effect level (NOAEL) for developmental toxicity, the lowest dose tested, is associated with a maternal systemic exposure multiple that is approximately 19 times the human value at the maximum recommended human dose.

In additional studies of embryo-foetal development in rats and rabbits, dapagliflozin was administered for intervals coinciding with the major periods of organogenesis in each species. Neither maternal nor developmental toxicities were observed in rabbits at any dose tested; the highest dose tested is associated with a systemic exposure multiple of approximately 1,191 times the maximum recommended human dose. In rats, dapagliflozin was neither embryolethal nor teratogenic at exposures up to 1,441 times the maximum recommended human dose.

Metformin
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Hydroxypropyl cellulose (E463)
Microcrystalline cellulose (E460(i))
Magnesium stearate (E470b)
Sodium starch glycolate type A

Film-coating:
Polyvinyl alcohol (E1203)
Macrogol 3350 (E1520(iii))

Talc (E553b)
Titanium dioxide (E171)
Iron oxide yellow (E172)
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PCTFE/Alu blister.

Pack sizes:
14, 28, 56 and 60 film-coated tablets in non-perforated blisters.
60x1 film-coated tablets in perforated unit dose blisters.
Multipack containing 196 (2 packs of 98) film-coated tablets in non-perforated blisters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

Ebymect 5 mg/850 mg film-coated tablets
EU/1/15/1051/001 5 mg/850 mg 14 tablets
EU/1/15/1051/002 5 mg/850 mg 28 tablets
EU/1/15/1051/003 5 mg/850 mg 56 tablets
EU/1/15/1051/004 5 mg/850 mg 60 tablets
EU/1/15/1051/005 5 mg/850 mg 60 x 1 tablet (unit dose)
EU/1/15/1051/006 5 mg/850 mg 196 (2 x 98) tablets (multipack)

Ebymect 5 mg/1,000 mg film-coated tablets
EU/1/15/1051/007 5 mg/1000 mg 14 tablets
EU/1/15/1051/008 5 mg/1000 mg 28 tablets

EU/1/15/1051/009 5 mg/1000 mg 56 tablets
EU/1/15/1051/010 5 mg/1000 mg 60 tablets
EU/1/15/1051/011 5 mg/1000 mg 60 x 1 tablet (unit dose)
EU/1/15/1051/012 5 mg/1000 mg 196 (2 x 98) tablets (multipack)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16 November 2015

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

AstraZeneca GmbH
Tinsdaler Weg 183
22880 Wedel
Germany

Bristol Myers Squibb S.r.l.
Loc. Fontana del Ceraso
Anagni, 03012
Italy

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER 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.

D. 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.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON – WITH BLUE BOX

1. NAME OF THE MEDICINAL PRODUCT

Ebymect 5 mg/850 mg film-coated tablets
dapagliflozin/metformin hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains dapagliflozin propanediol monohydrate equivalent to 5 mg dapagliflozin and 850 mg of metformin hydrochloride.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
28 film-coated tablets
56 film-coated tablets
60 film-coated tablets
60xl film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1051/001
EU/1/15/1051/002
EU/1/15/1051/003
EU/1/15/1051/004
EU/1/15/1051/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ebymect 5 mg/850 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – PART OF MULTIPACK - WITH BLUE BOX

1. NAME OF THE MEDICINAL PRODUCT

Ebymect 5 mg/850 mg film-coated tablets
dapagliflozin/metformin hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains dapagliflozin propanediol monohydrate equivalent to 5 mg dapagliflozin and 850 mg of metformin hydrochloride.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack: 196 (2 packs of 98) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1051/006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ebymect 5 mg/850 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE INTERMEDIATE PACKAGING

INNER CARTON – PART OF MULTIPACK – WITHOUT BLUE BOX

1. NAME OF THE MEDICINAL PRODUCT

Ebymect 5 mg/850 mg film-coated tablets
dapagliflozin/metformin hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains dapagliflozin propanediol monohydrate equivalent to 5 mg dapagliflozin and 850 mg of metformin hydrochloride.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

98 film-coated tablets. Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1051/006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ebymect 5 mg/850 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON – WITH BLUE BOX

1. NAME OF THE MEDICINAL PRODUCT

Ebymect 5 mg/1,000 mg film-coated tablets
dapagliflozin/metformin hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains dapagliflozin propanediol monohydrate equivalent to 5 mg dapagliflozin and 1,000 mg of metformin hydrochloride.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
28 film-coated tablets
56 film-coated tablets
60 film-coated tablets
60x1 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1051/007
EU/1/15/1051/008
EU/1/15/1051/009
EU/1/15/1051/010
EU/1/15/1051/011

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ebymect 5 mg/1,000 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – PART OF MULTIPACK – WITH BLUE BOX

1. NAME OF THE MEDICINAL PRODUCT

Ebymect 5 mg/1,000 mg film-coated tablets
dapagliflozin/metformin hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains dapagliflozin propanediol monohydrate equivalent to 5 mg dapagliflozin and 1,000 mg of metformin hydrochloride.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack: 196 (2 packs of 98) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1051/012

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ebymect 5 mg/1,000 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE INTERMEDIATE PACKAGING

INNER CARTON – PART OF MULTIPACK – WITHOUT BLUE BOX

1. NAME OF THE MEDICINAL PRODUCT

Ebymect 5 mg/1,000 mg film-coated tablets
dapagliflozin/metformin hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains dapagliflozin propanediol monohydrate equivalent to 5 mg dapagliflozin and 1,000 mg of metformin hydrochloride.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

98 film-coated tablets. Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1051/012

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ebymect 5 mg/1,000 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS (PERFORATED)

1. NAME OF THE MEDICINAL PRODUCT

Ebymect 5 mg/850 mg tablets
dapagliflozin/metformin HCl

2. NAME OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca AB

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS (NON-PERFORATED)

1. NAME OF THE MEDICINAL PRODUCT

Ebymect 5 mg/850 mg tablets
dapagliflozin/metformin HCl

2. NAME OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca AB

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

10 tablets blister: {Sun/Moon symbol}
14 tablets blister: Mon. Tue. Wed. Thu. Fri. Sat. Sun.
{Sun/Moon symbol}

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS (PERFORATED)

1. NAME OF THE MEDICINAL PRODUCT

Ebymect 5 mg/1,000 mg tablets
dapagliflozin/metformin HCl

2. NAME OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca AB

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS (NON-PERFORATED)

1. NAME OF THE MEDICINAL PRODUCT

Ebymect 5 mg/1,000 mg tablets
dapagliflozin/metformin HCl

2. NAME OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca AB

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

10 tablets blister: {Sun/Moon symbol}
14 tablets blister: Mon. Tue. Wed. Thu. Fri. Sat. Sun.
{Sun/Moon symbol}

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Ebymect 5 mg/850 mg film-coated tablets
Ebymect 5 mg/1,000 mg film-coated tablets
dapagliflozin/metformin hydrochloride

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Ebymect is and what it is used for

This medicine contains two different substances called dapagliflozin and metformin. Both belong to a group of medicines called oral anti-diabetics.

This medicine is used for a type of diabetes called “type 2 diabetes” in adult patients (aged 18 years and older) and usually occurs when you are older. If you have type 2 diabetes, your pancreas does not make enough insulin or your body is not able to use the insulin it produces properly. This leads to a high level of sugar (glucose) in your blood. Dapagliflozin works by removing excess sugar from your body via your urine and lowers the amount of sugar in your blood. Metformin works mainly by inhibiting glucose production in the liver.

- These are medicines taken by mouth for diabetes.
- This medicine is taken in combination with diet and exercise.
- This medicine is used if your diabetes cannot be controlled with other medicines used to treat diabetes, along with diet and exercise.
- Your doctor may ask you to take this medicine on its own or together with other medicines to treat diabetes. This may be another medicine taken by mouth and/or insulin given by injection.
- If you are already taking both dapagliflozin and metformin as single tablets, your doctor may ask you to switch to this medicine. To avoid overdose, do not continue taking dapagliflozin and metformin tablets, if you are taking this medicine.

It is important to continue to follow the advice on diet and exercise given to you by your doctor, pharmacist or nurse.

2. What you need to know before you take Ebymect

Do not take Ebymect

- if you are allergic to dapagliflozin, metformin or any of the other ingredients of this medicine (listed in section 6).
- if you have ever had a diabetic coma.
- if you have uncontrolled diabetes, with, for example severe hyperglycaemia (high blood glucose), nausea, vomiting, diarrhoea, rapid weight loss, lactic acidosis (see "Risk of lactic acidosis" below) or ketoacidosis. Ketoacidosis is a condition in which substances called 'ketone bodies' accumulate in the blood and which can lead to a diabetic pre-coma. Symptoms include stomach pain, fast and deep breathing, sleepiness or your breath developing an unusual fruity smell.
- if you have severely reduced kidney function.
- if you have a severe infection.
- 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.
- 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.
- if you have problems with your liver.
- if you drink large amounts of alcohol, either every day or only from time to time (please see section "Ebymect with alcohol").

Do not take this medicine if any of the above apply to you.

Warnings and precautions

<u>Risk of lactic acidosis</u>

Ebymect may cause a very rare, but very serious side effect called lactic acidosis, particularly if your kidneys are not working properly. The risk of developing lactic acidosis is also increased with uncontrolled diabetes, serious infections, prolonged fasting or alcohol intake, dehydration (see further information below), liver problems and any medical conditions in which a part of the body has a reduced supply of oxygen (such as acute severe heart disease).
If any of the above apply to you, talk to your doctor for further instructions.

Stop taking Ebymect for a short time if you have a condition that may be associated with dehydration (significant loss of body fluids) such as severe vomiting, diarrhoea, fever, exposure to heat or if you drink less fluid than normal. Talk to your doctor for further instructions.

Stop taking Ebymect and contact a doctor or the nearest hospital immediately if you experience some of the symptoms of lactic acidosis, as this condition may lead to coma.
Symptoms of lactic acidosis include:

- vomiting
- stomach ache (abdominal pain)
- muscle cramps
- a general feeling of not being well with severe tiredness
- difficulty in breathing
- reduced body temperature and heartbeat

Lactic acidosis is a medical emergency and must be treated in a hospital.

Talk to your doctor, pharmacist or nurse before taking this medicine, and during treatment:
- if you have "type 1 diabetes" – the type that usually starts when you are young, and your body does not produce any insulin.
- if you experience rapid weight loss, feeling sick or being sick, stomach pain, excessive thirst, fast and deep breathing, confusion, unusual sleepiness or tiredness, a sweet smell to your breath, a sweet or metallic taste in your mouth, or a different odour to your urine or sweat, contact a doctor or the nearest hospital straight away. These symptoms could be a sign of "diabetic ketoacidosis" – a problem you can get with diabetes because of increased levels of "ketone bodies" in your urine or blood, seen in tests. The risk of developing diabetic ketoacidosis may be increased with prolonged fasting, excessive alcohol consumption, dehydration, sudden reductions in insulin dose, or a higher need of insulin due to major surgery or serious illness.
- if you have problems with your kidneys. Your doctor will check your kidney function.
- 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. Tell your doctor before you start taking this medicine if you have any of these signs.
- if you are taking 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 Ebymect'.
- if you have a history of serious heart disease or if you have had a stroke.
- 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.
- 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.
- if you have an increase in the amount of red blood cells in your blood, seen in tests.

If you need to have major surgery, you must stop taking Ebymect during and for some time after the procedure. Your doctor will decide when you must stop and when to restart your treatment with Ebymect.

Like for all diabetic patients it is important to check your feet regularly and adhere to any other advice regarding foot care given by your health care professional.

If any of the above applies to you (or you are not sure), talk to your doctor, pharmacist or nurse before taking this medicine.

Kidney function
During treatment with Ebymect, your doctor will check your kidney function at least once every year or more frequently if you are elderly and/or if you have worsening kidney function.

Urine glucose
Because of how this medicine works, your urine will test positive for sugar while you are on this medicine.

Children and adolescents
This medicine is not recommended for children and adolescents under 18 years of age, because it has not been studied in these patients.

Other medicines and Ebymect
If you need to have an injection of a contrast medium that contains iodine into your bloodstream, for example in the context of an X-ray or scan, you must stop taking Ebymect before or at the time of the injection. Your doctor will decide when you must stop and when to restart your treatment with Ebymect.

Tell your doctor if you are taking, have recently taken or might take any other medicines. You may need more frequent blood glucose and kidney function tests, or your doctor may adjust the dosage of Ebymect. It is especially important to mention the following:

- if you are taking medicines which increase urine production (diuretics). Your doctor may ask you to stop taking this medicine. Possible signs of losing too much fluid from your body are listed at the top of section 4 'Possible side effects'.
- 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).
- if you are taking cimetidine, a medicine used to treat stomach problems.
- if you are using bronchodilators (beta-2 agonists) which are used to treat asthma.
- if you are using corticosteroids, which are used to treat inflammation in diseases like asthma and arthritis.
- if you are using medicines used to treat pain and inflammation (NSAID and COX-2-inhibitors, such as ibuprofen and celecoxib).
- if you are using certain medicines for the treatment of high blood pressure (ACE inhibitors and angiotensin II receptor antagonists).

Ebymect with alcohol
Avoid excessive alcohol intake while taking Ebymect since this may increase the risk of lactic acidosis (see "Warnings and precautions").

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 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 this medicine if you are breast-feeding. It is not known if this medicine passes into human breast milk.

Driving and using machines
This medicine has no or negligible influence on the ability to drive and use machines. Taking it with other medicines that lower the amount of sugar in your blood, such as insulin or a "sulphonylurea" medicine, can cause too low blood sugar levels (hypoglycaemia), which may cause symptoms such as weakness, dizziness, increased sweating, fast heart beat, change in vision or difficulties concentrating, and may affect your ability to drive and use machines. Do not drive or use any tools or machines, if you start to feel these symptoms.

3. How to take Ebymect

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

How much to take

- The amount of this medicine that you will take varies depending on your condition and the doses you currently take of metformin and/or individual tablets of dapagliflozin and metformin. Your doctor will tell you exactly which strength of this medicine to take.
- The recommended dose is one tablet twice a day.

Taking this medicine
- Swallow the tablet whole with half a glass of water.
- Take your tablet with food. This is to reduce the risk of side effects in the stomach.
- Take your tablet twice daily, once in the morning (breakfast) and once in the evening (dinner).

Your doctor may prescribe this medicine together with other medicine(s) to lower the amount of sugar in your blood. These may be medicine(s) by mouth or insulin given by injection. Remember to take these other medicine(s) as your doctor has told you. This will help get the best results for your health.

Diet and exercise
To control your diabetes, you still need to keep to diet and exercise, even when you are taking this medicine. So it is important to keep following the advice about diet and exercise from your doctor, pharmacist or nurse. In particular, if you are following a diabetic weight control diet, continue to follow it while you are taking this medicine.

If you take more Ebymect than you should
If you take more Ebymect tablets than you should, you may experience lactic acidosis. Symptoms of lactic acidosis include feeling or being very sick, vomiting, stomach ache, muscular cramps, severe tiredness or difficulty breathing. If this happens to you, you may need immediate hospital treatment, as lactic acidosis may lead to coma. Stop taking this medicine immediately and contact a doctor or the nearest hospital straight away (see section 2). Take the medicine pack with you.

If you forget to take Ebymect
Do not take a double dose of this medicine to make up for a forgotten dose.

If you stop taking Ebymect
Do not stop taking this medicine without talking to your doctor first. Your blood sugar may increase without this medicine.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Stop taking Ebymect and see a doctor as soon as possible if you notice any of the following serious or potentially serious side effects:

- **Lactic acidosis,** seen very rarely (may affect up to 1 user in 10,000)

Ebymect may cause a very rare, but very serious side effect called lactic acidosis (see section "Warnings and precautions"). If this happens you must **stop taking Ebymect and contact a doctor or the nearest hospital immediately,** as lactic acidosis may lead to coma.

- **Dehydration: loss of too much fluid from your body,** 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.

- **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.

Contact a doctor or the nearest hospital straight away if you have any of the following side effects:

- diabetic ketoacidosis, seen rarely (may affect up to 1 in 1,000 people)

These are the signs of diabetic ketoacidosis (see also section 2 Warnings and precautions):
- increased levels of "ketone bodies" in your urine or blood
- rapid weight loss
- feeling sick or being sick
- stomach pain
- excessive thirst
- fast and deep breathing
- confusion
- unusual sleepiness or tiredness
- a sweet smell to your breath, a sweet or metallic taste in your mouth or a different odour to your urine or sweat.

This may occur regardless of blood glucose level. Your doctor may decide to temporarily or permanently stop your treatment with Ebymect.

Contact your doctor as soon as possible if you have any of the following side effects:

- **Low blood sugar levels (hypoglycaemia),** seen very commonly (may affect more than 1 in 10 people) - when taking this medicine with a sulphonylurea or other medicines that lower the amount of sugar in your blood, such as 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.

Other side effects include:
Very common (may affect more than 1 in 10 people)
- nausea, vomiting
- diarrhoea or stomach ache
- loss of appetite

Common (may affect up to 1 in 10 people)
- genital infection (thrush) of your penis or vagina (signs may include irritation, itching, unusual discharge or odour)
- back pain
- passing more water (urine) than usual or needing to pass water more often
- changes in the amount of cholesterol or fats in your blood (shown in tests)
- changes in the amount of red blood cells in your blood (shown in tests)
- changes in taste
- dizziness

Uncommon (may affect up to 1 in 100 people)
- thirst

- constipation
- discomfort when passing water (urine)
- awakening from sleep at night to pass urine
- dry mouth
- weight decreased
- changes in laboratory blood tests (creatinine or urea)
- decrease in kidney function

Very rare (may affect up to 1 in 10,000 people)
- decreased vitamin B12 levels in the blood
- abnormalities in liver function tests, inflammation of the liver (hepatitis)
- redness of the skin (erythema),itching or an itchy rash (hives)

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Ebymect

- Keep this medicine out of the sight and reach of children.

- Do not use this medicine after the expiry date which is stated on the blister or carton after 'EXP'. The expiry date refers to the last day of that month.

- This medicine does not require any special storage conditions.

- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Ebymect contains
- The active substances are dapagliflozin and metformin hydrochloride (metformin HCl).

Each Ebymect 5 mg/850 mg film-coated tablet (tablet) contains dapagliflozin propanediol monohydrate equivalent to 5 mg dapagliflozin and 850 mg metformin hydrochloride.
Each Ebymect 5 mg/1,000 mg film-coated tablet (tablet) contains dapagliflozin propanediol monohydrate equivalent to 5 mg dapagliflozin and 1,000 mg metformin hydrochloride.

- The other ingredients are:
  - tablet core: hydroxypropyl cellulose (E463), microcrystalline cellulose (E460(i)), magnesium stearate (E470b), sodium starch glycolate.
  - film-coating: polyvinyl alcohol (E1203), macrogol 3350 (E1520(iii)), talc (E553b), titanium dioxide (E171), iron oxides (E172).

What Ebymect looks like and contents of the pack
- Ebymect 5 mg/850 mg are 9.5 x 20 mm oval, brown film-coated tablets. They have "5/850" on one side and "1067" on the other side.

- Ebymect 5 mg/1,000 mg are 10.5 x 21.5 mm oval, yellow film-coated tablets. They have “5/1000” on one side and “1069” on the other side.

Ebymect 5 mg/850 mg film-coated tablets and Ebymect 5 mg/1,000 mg film-coated tablets are available in PVC/PCTFE/Alu blister. The pack sizes are 14, 28, 56 and 60 film-coated tablets in non-perforated blisters, 60x1 film-coated tablets in perforated unit dose blisters and multipack containing 196 (2 packs of 98) film-coated tablets in non-perforated blisters.

Not all pack sizes may be marketed in your country.

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

Annex IV

Scientific conclusions

Scientific conclusions

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are used together with diet and exercise in patients with type 2 diabetes, either alone or in combination with other diabetes medicines.

In March 2016 the EMA was informed by the Marketing authorization holder (MAH) of canagliflozin about an approximately 2-fold increase of lower limb amputations in canagliflozin-treated subjects compared to placebo in the MAH sponsored ongoing cardiovascular (CV) event study CANVAS. In addition, an analysis of the ongoing renal study CANVAS-R with a similar population as CANVAS showed a numerical imbalance with regards to amputation events.

Further to the information received by the EMA, the Independent Data Monitoring Committee (IDMC) for the CANVAS and CANVAS-R studies, which has access to all un-blinded CV outcome and safety data, recommended that the study should continue, that action to minimize this potential risk should be taken and that participants should be informed adequately about this risk.

The European Commission (EC) triggered a procedure under Article 20 of Regulation (EC) No 726/2004 on 15 April 2016; the PRAC was requested to assess the impact on the benefit-risk balance of canagliflozin containing medicinal products, to assess whether this is a class issue and to issue a recommendation by 31 March 2017 on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked and whether provisional measures are necessary to ensure the safe and effective use of these medicinal products.

A Direct Healthcare Professional Communication (DHPC) was circulated on 2 May 2016 to inform healthcare professionals that a two-fold higher incidence of lower limb amputation (primarily of the toe) had been seen in a clinical trial with canagliflozin; in addition, the need to counsel patients about the importance of routine preventative foot care was highlighted. The communication also asked healthcare professionals to consider treatment discontinuation in patients who develop amputation preceding events.

Furthermore, the PRAC considered that a class effect could not be excluded, as all SGLT2 inhibitors share the same mechanism of action, as the potential mechanism leading to an increased amputation risk is not known, and as an underlying cause specific to canagliflozin containing medicines only cannot be identified at the moment. Consequently, the EC requested on 6 July 2016 to extend the current procedure to include all of the authorised products of the class of SGLT2 inhibitors.

Overall summary of the scientific evaluation by the PRAC

Having considered all available data, the PRAC was of the view that the growing data on amputation in the CANVAS and CANVAS-R trial confirm an increased amputation risk for canagliflozin; it is unlikely that the difference in amputation risk seen with canagliflozin compared to placebo is a finding by chance. The PRAC also considered that data on amputation events from clinical trials and post-marketing surveillance for dapagliflozin and empagliflozin-containing medicines are either not available to the same extent as for canagliflozin-containing medicines or here were some limitations in the data collection.

The PRAC was also of the view that it is currently not possible to identify an underlying cause for the observed imbalances in amputation risk that would be specifically attributable to canagliflozin-containing medicines and not to the other products of the class. All members of the class share the same mode of action and there is no confirmed underlying mechanism that is canagliflozin-specific. The mechanism of action that would allow understanding which patients are at risk is therefore still unclear.

PRAC noted that an increased amputation risk has only become apparent with canagliflozin so far, but one large cardiovascular outcome study (DECLARE) is still on-going for dapagliflozin and amputation events

were not been systematically captured within the completed large cardiovascular outcome study conducted with empagliflozin (EMPA-REG). Hence, it is currently not possible to establish whether the increased amputation risk is a class effect or not.

Therefore, having considered all the data submitted, in view of the above, the PRAC concluded that the benefit-risk balance of the bove listed products remains positive, but considered that changes to the product information of all authorised SGLT2 inhibitors adding information on the risk of lower limb amputations, as well as additional pharmacovigilance activities to be reflected in the RMP, are warranted. The CANVAS and CANVAS-R studies and the CREDENCE and DECLARE Studies are planned to be completed in 2017 and 2020, respectively. Final analysis of these studies, after un-blinding, will provide further information on the benefit/risk of SGLT2 inhibitors particularly of the risk of lower limb amputations.

Grounds for PRAC recommendation

Whereas

- The PRAC considered the procedure under Article 20 of Regulation (EC) No 726/2004 for the products listed in Annex A;

- The PRAC reviewed the totality of the data submitted by the marketing authorisation holders in relation to the risk of lower limb amputation in patients treated with Sodium-glucose co-transporter 2 (SGLT2) inhibitors for type 2 diabetes mellitus;

- The PRAC considered that the available data on amputation in the CANVAS and CANVAS-R trials confirm that treatment with canagliflozin may contribute to an increased risk of amputation of the lower limb, mainly of the toe;

- The PRAC was also of the opinion that a mechanism of action, allowing to understand which patients are at risk, is still unclear;

- The PRAC was of the view that it is currently not possible to identify an underlying cause for the observed imbalances in amputation risk that would be specifically attributable to canagliflozin-containing medicines and not to the other products of the class;

- The PRAC noted that data on amputation events from clinical trials and post-marketing surveillance for dapagliflozin and empagliflozin-containing medicines are either not available to the same extent as for canagliflozin-containing medicines or there were some limitations in the data collection of these events;

- The PRAC therefore considered that the risk may constitute a possible class effect;

- Because no specific risk factors could be identified apart from general amputation risk factors potentially contributing to the events, the PRAC recommended that patients should be advised on routine preventative foot care and maintaining adequate hydration as a general advice to prevent amputation;

- The PRAC was therefore of the view that the risk of lower limb amputation should be included in the product information for all products listed in Annex A, with a warning highlighting to healthcare professional and patients the importance of routine preventative foot care. The warning for canagliflozin also includes information that, in patients developing amputation preceding events,

consideration may be given to discontinue treatment. For canagliflozin, lower limb amputations (mainly of the toe) have been also included, as an adverse drug reaction, in the product information;

- The PRAC also considered that additional information on amputation events should be collected through appropriate case report forms (CRFs) for clinical trials, follow-up questionnaires for post-marketing cases, use of common MedDRA preferred term (PT) lists for amputation preceding events, and appropriate meta-analyses of large studies including cardiovascular outcome studies. All RMPs should be updated accordingly via an appropriate variation to be submitted no later than one month of the European Commission decision;

The PRAC, as a consequence, concluded that the benefit-risk balance of the SGLT2 inhibitor containing products identified in Annex A remains favourable, subject to the agreed amendments to the product information and additional pharmacovigilance activities to be reflected in the RMP.
The PRAC therefore recommended that the variation to the terms of the marketing authorisation for the above listed products referred to in Annex A, for which the relevant sections of the summary of product characteristics and package leaflet are set out in Annex III of the PRAC recommendation, was warranted.

CHMP opinion

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.

Overall conclusion

The CHMP, as a consequence, considers that the benefit-risk balance of Invokana, Vokanamet, Forxiga, Edistride, Xigduo, Ebymect, Jardiance and Synjardy remain favourable subject to the amendments to the product information described above.

Therefore the CHMP recommends the variation to the terms of the marketing authorisations for Invokana, Vokanamet, Forxiga, Edistride, Xigduo, Ebymect, Jardiance and Synjardy.