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

Edistride 5 mg film-coated tablets
Edistride 10 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Edistride 5 mg film-coated tablets
Each tablet contains dapagliflozin propanediol monohydrate equivalent to 5 mg dapagliflozin.

Excipient with known effect:
Each 5 mg tablet contains 25 mg of lactose anhydrous.

Edistride 10 mg film-coated tablets
Each tablet contains dapagliflozin propanediol monohydrate equivalent to 10 mg dapagliflozin.

Excipient with known effect:
Each 10 mg tablet contains 50 mg of lactose anhydrous.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Edistride 5 mg film-coated tablets
Yellow, biconvex, 0.7 cm diameter round, film-coated tablets with "5" engraved on one side and "1427" engraved on the other side.

Edistride 10 mg film-coated tablets
Yellow, biconvex, approximately 1.1 x 0.8 cm diagonally diamond-shaped, film-coated tablets with "10" engraved on one side and "1428" engraved on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Edistride is indicated in adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control as:

Monotherapy
When diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance.

Add-on combination therapy
In combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control (see sections 4.4, 4.5 and 5.1 for available data on different combinations).

4.2 Posology and method of administration

Posology
Monotherapy and add-on combination therapy
The recommended dose is 10 mg dapagliflozin once daily for monotherapy and add-on combination therapy with other glucose-lowering medicinal products including insulin. When dapagliflozin is used in combination with insulin or an insulin secretagogue, such as a sulphonylurea, a lower dose of insulin or insulin secretagogue may be considered to reduce the risk of hypoglycaemia (see sections 4.5 and 4.8).

Special populations
Renal impairment
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. Edistride is not recommended for use in patients with moderate to severe renal impairment (patients with creatinine clearance [CrCl] < 60 ml/min or estimated glomerular filtration rate [eGFR] < 60 ml/min/1.73 m^2, see sections 4.4, 4.8, 5.1 and 5.2).

No dosage adjustment is indicated in patients with mild renal impairment.

Hepatic impairment
No dosage adjustment is necessary for patients with mild or moderate hepatic impairment. In patients with severe hepatic impairment, a starting dose of 5 mg is recommended. If well tolerated, the dose may be increased to 10 mg (see sections 4.4 and 5.2).

Elderly (≥ 65 years)
In general, no dosage adjustment is recommended based on age. Renal function and risk of volume depletion should be taken into account (see sections 4.4 and 5.2). Due to the limited therapeutic experience in patients 75 years and older, initiation of dapagliflozin therapy is not recommended.

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

Method of administration
Edistride can be taken orally once daily at any time of day with or without food. Tablets are to be swallowed whole.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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

Use in patients with renal impairment
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 (see section 4.2). In subjects with moderate renal impairment (patients with CrCl < 60 ml/min or eGFR < 60 ml/min/1.73 m^2), a higher proportion of subjects treated with dapagliflozin had adverse reactions of increase in creatinine, phosphorus, parathyroid hormone (PTH) and hypotension, compared with placebo. Edistride is not recommended for use in patients with moderate to severe renal impairment (patients with CrCl < 60 ml/min or eGFR < 60 ml/min/1.73 m^2). Edistride has not

been studied in severe renal impairment (CrCl < 30 ml/min or eGFR < 30 ml/min/1.73 m^2) or end-stage renal disease (ESRD).

Monitoring of renal function is recommended as follows:
- Prior to initiation of dapagliflozin and at least yearly, thereafter (see sections 4.2, 4.8, 5.1 and 5.2)
- Prior to initiation of concomitant medicinal products that may reduce renal function and periodically thereafter
- For renal function approaching moderate renal impairment, at least 2 to 4 times per year. If renal function falls below CrCl < 60 ml/min or eGFR < 60 ml/min/1.73 m^2, dapagliflozin treatment should be discontinued.

Use in patients with hepatic impairment
There is limited experience in clinical trials in patients with hepatic impairment. Dapagliflozin exposure is increased in patients with severe hepatic impairment (see sections 4.2 and 5.2).

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 very high blood glucose concentrations.

Dapagliflozin 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 dapagliflozin, 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 dapagliflozin 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 10 mg 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 dapagliflozin 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 dapagliflozin 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, dapagliflozin 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 Edistride will test positive for glucose in their urine.

Lactose
The tablets contain lactose anhydrous. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions
Diuretics
Dapagliflozin 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, dapagliflozin 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 metformin, 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 metformin, pioglitazone, sitagliptin, glimepiride, hydrochlorothiazide, bumetanide, valsartan, digoxin (a P-gp substrate) or warfarin (S-warfarin, a CYP2C9 substrate), or the anticoagulatory 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.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no data from the use of dapagliflozin in pregnant women. Studies in rats 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 dapagliflozin is not recommended during the second and third trimesters of pregnancy.

When pregnancy is detected, treatment with dapagliflozin should be discontinued.

Breast-feeding
It is unknown whether 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). A risk to the newborns/infants cannot be excluded. Dapagliflozin should not be used while breast-feeding.

Fertility
The effect of dapagliflozin on fertility in humans has not been studied. In male and female rats, dapagliflozin showed no effects on fertility at any dose tested.

4.7 Effects on ability to drive and use machines

Edistride has no or negligible influence on the ability to drive and use machines. Patients should be alerted to the risk of hypoglycaemia when dapagliflozin is used in combination with a sulphonylurea or insulin.

4.8 Undesirable effects

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 clinical trials. None were found to be dose-related. Adverse reactions listed below are classified according to frequency and system organ class (SOC). 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 placebo-controlled studies[a]

System organ class	Very common	Common[*]	Uncommon[**]	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[i]
Nervous system disorders		Dizziness		
Gastrointestinal disorders			Constipation[**] Dry mouth[**]	
Musculoskeletal and connective tissue disorders		Back pain[*]		
Renal and urinary disorders		Dysuria Polyuria[*,f]	Nocturia[**] Renal impairment[**,b]	
Reproductive system and breast disorders			Vulvovaginal pruritus[**] Pruritus genital[**]	
Investigations		Haematocrit increased[g] Creatinine renal clearance decreased[b] Dyslipidaemia[h]	Blood creatinine increased[**,b] Blood urea increased[**] Weight decreased[**]	

[a]The table shows up to 24-week (short-term) data regardless of glycaemic rescue.

[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]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 %.

[i]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

Hypoglycaemia

The frequency of hypoglycaemia depended on the type of background therapy used in each study.

For studies of dapagliflozin in monotherapy, 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. Studies with add-on sulphonylurea and add-on insulin therapies had higher rates of hypoglycaemia (see section 4.5).

In an add-on to glimepiride study, at weeks 24 and 48, minor episodes of hypoglycaemia were reported more frequently in the group treated with dapagliflozin 10 mg plus glimepiride (6.0 % and 7.9 %, respectively) than in the placebo plus glimepiride group (2.1 % and 2.1 %, respectively).

In an add-on to insulin study, episodes of major hypoglycaemia were reported in 0.5 % and 1.0 % of subjects treated with 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.

In an add-on to metformin and a sulphonylurea study, up to 24 weeks, no episodes of major hypoglycaemia were reported. 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.

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 10 mg compared to 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 ≥ 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 ≥ 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 ≤ 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

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. The removal of dapagliflozin by haemodialysis has not been studied.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, Other blood glucose lowering drugs, excluding insulins, ATC code: A10BX09

Mechanism of action
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 Edistride.

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.

Pharmacodynamic effects
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).

Clinical efficacy and safety

Thirteen double-blind, randomised, controlled clinical trials were conducted with 6,362 subjects with type 2 diabetes to evaluate the efficacy and safety of Edistride; 4,273 subjects in these studies were treated with dapagliflozin. Twelve studies had a treatment period of 24 weeks duration, 8 with long-term extensions ranging from 24 to 80 weeks (up to a total study duration of 104 weeks), and one study was 52 weeks in duration with long-term extensions of 52 and 104 weeks (total study duration of 208 weeks). Mean duration of diabetes ranged from 1.4 to 16.9 years. Fifty-two percent (52 %) had mild renal impairment and 11 % had moderate renal impairment. Fifty-one percent (51 %) of the subjects were men, 84 % were White, 9 % were Asian, 3 % were Black and 4 % were of other racial groups. Eighty percent (80 %) of the subjects had a body mass index (BMI) ≥ 27. Furthermore, two 12-week, placebo-controlled studies were conducted in patients with inadequately controlled type 2 diabetes and hypertension.

Glycaemic control

Monotherapy

A double-blind, placebo-controlled study of 24-week duration (with an additional extension period) was conducted to evaluate the safety and efficacy of monotherapy with Edistride in subjects with inadequately controlled type 2 diabetes mellitus. Once-daily treatment with dapagliflozin resulted in statistically significant ($p < 0.0001$) reductions in HbA1c compared to placebo (Table 2).

In the extension period, HbA1c reductions were sustained through Week 102 (-0.61 %, and -0.17 % adjusted mean change from baseline for dapagliflozin 10 mg and placebo, respectively).

Table 2. Results at Week 24 (LOCF[a]) of a placebo-controlled study of dapagliflozin as monotherapy

	Monotherapy	
	Dapagliflozin 10 mg	**Placebo**
N[b]	70	75
HbA1c (%)		
Baseline (mean)	8.01	7.79
Change from baseline[c]	-0.89	-0.23
Difference from placebo[c]	-0.66[*]	
(95 % CI)	(-0.96, -0.36)	
Subjects (%) achieving:		
HbA1c < 7 %		
Adjusted for baseline	50.8[§]	31.6
Body weight (kg)		
Baseline (mean)	94.13	88.77
Change from baseline[c]	-3.16	-2.19
Difference from placebo[c]	-0.97	
(95 % CI)	(-2.20, 0.25)	

[a]LOCF: Last observation (prior to rescue for rescued subjects) carried forward

[b]All randomised subjects who took at least one dose of double-blind study medication during the short-term double-blind period

[c]Least squares mean adjusted for baseline value

[*]p-value < 0.0001 versus placebo

[§] Not evaluated for statistical significance as a result of the sequential testing procedure for secondary end points

Combination therapy

In a 52-week, active-controlled non-inferiority study (with 52- and 104-week extension periods), Edistride 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 to glipizide, thus demonstrating non-inferiority (Table 3). At Week 104, adjusted mean change from baseline in HbA1c was -0.32 % for dapagliflozin and -0.14 % for glipizide. At Week 208, adjusted mean change from baseline in HbA1c was -0.10 % for dapagliflozin and 0.20 % for glipizide. 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 to the group treated with glipizide (40.8 %, 47.0 % 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 3. Results at Week 52 (LOCF[a]) in an active-controlled study comparing dapagliflozin to 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, glimepiride, metformin and a sulphonylurea, sitagliptin (with or without metformin) or insulin resulted in statistically significant reductions in HbA1c at 24 weeks compared with subjects receiving placebo ($p < 0.0001$; Tables 4, 5 and 6).

The reductions in HbA1c observed at Week 24 were sustained in add-on combination studies (glimepiride and insulin) with 48-week data (glimepiride) and up to 104-week data (insulin). At Week 48 when added to sitagliptin (with or without metformin), the adjusted mean change from baseline for dapagliflozin 10 mg and placebo was -0.30 % and 0.38 %, respectively. 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 10 mg and placebo, respectively). At Week 104 for insulin (with or without additional oral glucose-lowering medicinal products), 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 a mean 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.

Table 4. Results of 24-week (LOCF[a]) placebo-controlled studies of dapagliflozin in add-on combination with metformin or sitagliptin (with or without metformin)

	Add-on combination			
	Metformin[1]		DPP-4 Inhibitor (sitagliptin[2]) ± Metformin[1]	
	Dapagliflozin 10 mg	**Placebo**	**Dapagliflozin 10 mg**	**Placebo**
N[b]	135	137	223	224
HbA1c (%)				
Baseline (mean)	7.92	8.11	7.90	7.97
Change from baseline[c]	-0.84	-0.30	-0.45	0.04
Difference from placebo[c]	-0.54*		-0.48*	
(95 % CI)	(-0.74, -0.34)		(-0.62, -0.34)	
Subjects (%) achieving: HbA1c < 7 % Adjusted for baseline	40.6**	25.9		
Body weight (kg)				
Baseline (mean)	86.28	87.74	91.02	89.23
Change from baseline[c]	-2.86	-0.89	-2.14	-0.26
Difference from placebo[c]	-1.97*		-1.89*	
(95 % CI)	(-2.63, -1.31)		(-2.37, -1.40)	

[1]Metformin ≥ 1500 mg/day;

[2]sitagliptin 100 mg/day

[a]LOCF: Last observation (prior to rescue for rescued subjects) 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

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

**p-value < 0.05 versus placebo + oral glucose-lowering medicinal product

Table 5. Results of 24-week placebo-controlled studies of dapagliflozin in add-on combination with sulphonylurea (glimepiride) or metformin and a sulphonylurea

	Add-on combination			
	Sulphonylurea (glimepiride[1])		Sulphonylurea + Metformin[2]	
	Dapagliflozin 10 mg	Placebo	Dapagliflozin 10 mg	Placebo
N[a]	151	145	108	108
HbA1c (%)[b]				
Baseline (mean)	8.07	8.15	8.08	8.24
Change from baseline[c]	-0.82	-0.13	-0.86	-0.17
Difference from placebo[c] (95 % CI)	-0.68* (-0.86, -0.51)		−0.69* (−0.89, −0.49)	
Subjects (%) achieving: HbA1c < 7 % (LOCF)[d]				
Adjusted for baseline	31.7*	13.0	31.8*	11.1
Body weight (kg) (LOCF)[d]				
Baseline (mean)	80.56	80.94	88.57	90.07
Change from baseline[c]	-2.26	-0.72	-2.65	-0.58
Difference from placebo[c] (95 % CI)	-1.54* (-2.17, -0.92)		−2.07* (−2.79, −1.35)	

[1]glimepiride 4 mg/day;

[2]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]Columns 1 and 2, HbA1c analysed using LOCF (see footnote d); Columns 3 and 4, HbA1c analysed using LRM (see footnote e)

[c]Least squares mean adjusted for baseline value

[d]LOCF: Last observation (prior to rescue for rescued subjects) carried forward

[e]LRM: Longitudinal repeated measures analysis

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

Table 6. 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)

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 10 mg as a monotherapy or as an add-on to either metformin, glimepiride, metformin and a sulphonylurea, sitagliptin (with or without metformin) 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 to placebo (-0.33 to 0.21 mmol/l [-6.0 to 3.8 mg/dl]). 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 glimepiride resulted in statistically significant reductions in 2-hour post-prandial glucose at 24 weeks that were maintained up to Week 48.

Treatment with dapagliflozin 10 mg as an add-on to sitagliptin (with or without metformin) resulted in reductions in 2-hour post-prandial glucose at 24 weeks that were maintained up to Week 48.

Body weight
Dapagliflozin 10 mg as an add-on to metformin, glimepiride, metformin and a sulphonylurea, sitagliptin (with or without metformin) or insulin resulted in statistically significant body weight reduction at 24 weeks ($p < 0.0001$, Tables 4 and 5). These effects were sustained in longer-term trials. At 48 weeks, the difference for dapagliflozin as add-on to sitagliptin (with or without metformin) compared with placebo was -2.22 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 reduction compared with glipizide of -4.65 kg at 52 weeks ($p < 0.0001$, Table 3) 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 Edistride 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 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 Edistride 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 renal impairment
Moderate renal impairment (eGFR ≥ 30 to < 60 ml/min/1.73 m^2)
The efficacy of dapagliflozin was also assessed separately in a dedicated study of diabetic subjects with moderate renal impairment (252 subjects with mean eGFR 45 ml/min/1.73 m^2). The mean change from baseline in HbA1c at 24 weeks was -0.44 % and -0.33 %, for dapagliflozin 10 mg and placebo, respectively.

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 a monotherapy (adjusted mean change from baseline: -2.04 % and 0.19 % for dapagliflozin 10 mg and placebo, respectively) and as an add-on to metformin (adjusted mean change from baseline: -1.32 % and -0.53 % for dapagliflozin and placebo, respectively).

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with dapagliflozin in one or more 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

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 %. Administration with a high-fat meal decreased dapagliflozin C_{max} by up to 50 % and prolonged T_{max} by approximately 1 hour, but did not alter AUC as compared with the fasted state. These changes are not considered to be clinically meaningful. Hence, Edistride can be administered with or without food.

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 to 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.

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

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.

5.3 Preclinical safety data

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Microcrystalline cellulose (E460i)
Lactose, anhydrous
Crospovidone (E1202)
Silicon dioxide (E551)
Magnesium stearate (E470b)

Film-coating
Polyvinyl alcohol (E1203)
Titanium dioxide (E171)
Macrogol 3350
Talc (E553b)
Iron oxide yellow (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

Alu/Alu blister
Pack sizes of 14, 28 and 98 film-coated tablets in non-perforated calendar blisters
Pack sizes of 30x1 and 90x1 film-coated tablets in perforated unit dose 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)

Edistride 5 mg film-coated tablets
EU/1/15/1052/001 14 film-coated tablets
EU/1/15/1052/002 28 film-coated tablets
EU/1/15/1052/003 98 film-coated tablets
EU/1/15/1052/004 30 x 1 (unit dose) film-coated tablets
EU/1/12/1052/005 90 x 1 (unit dose) film-coated tablets

Edistride 10 mg film-coated tablets
EU/1/15/1052/006 14 film-coated tablets
EU/1/15/1052/007 28 film-coated tablets
EU/1/15/1052/008 98 film-coated tablets
EU/1/15/1052/009 30 x 1 (unit dose) film-coated tablets
EU/1/15/1052/010 90 x 1 (unit dose) film-coated tablets

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

09 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

AstraZeneca UK Limited
Silk Road Business Park
Macclesfield
SK10 2NA
United Kingdom

Bristol-Myers Squibb S.r.l.
Contrada Fontana del Ceraso
IT-03012 Anagni (FR)
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

OUTER CARTON 5 mg

1. NAME OF THE MEDICINAL PRODUCT

Edistride 5 mg film-coated tablets
dapagliflozin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains dapagliflozin propanediol monohydrate equivalent to 5 mg dapagliflozin.

3. LIST OF EXCIPIENTS

Contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
28 film-coated tablets
30x1 film-coated tablets
90x1 film-coated tablets
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/1/15/1052/001 14 film-coated tablets
EU/1/15/1052/002 28 film-coated tablets
EU/1/15/1052/003 98 film-coated tablets
EU/1/15/1052/004 30 x 1 (unit dose) film-coated tablets
EU/1/15/1052/005 90 x 1 (unit dose) film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

edistride 5 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 10 mg

1. NAME OF THE MEDICINAL PRODUCT

Edistride 10 mg film-coated tablets
dapagliflozin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains dapagliflozin propanediol monohydrate equivalent to10 mg dapagliflozin.

3. LIST OF EXCIPIENTS

Contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
28 film-coated tablets
30x1 film-coated tablets
90x1 film-coated tablets
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/1/15/1052/006 14 film-coated tablets
EU/1/15/1052/007 28 film-coated tablets
EU/1/15/1052/008 98 film-coated tablets
EU/1/15/1052/009 30 x 1 (unit dose) film-coated tablets
EU/1/15/1052/010 90 x 1 (unit dose) film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

edistride 10 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 UNIT DOSE 5 mg

1. NAME OF THE MEDICINAL PRODUCT

Edistride 5 mg tablets
dapagliflozin

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 PERFORATED UNIT DOSE 10 mg

1. NAME OF THE MEDICINAL PRODUCT

Edistride 10 mg tablets
dapagliflozin

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

CALENDAR BLISTERS NON-PERFORATED 5 mg

1. NAME OF THE MEDICINAL PRODUCT

Edistride 5 mg tablets
dapagliflozin

2. NAME OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca AB

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Monday Tuesday Wednesday Thursday Friday Saturday Sunday

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

CALENDAR BLISTERS NON-PERFORATED 10 mg

1. NAME OF THE MEDICINAL PRODUCT

Edistride 10 mg tablets
dapagliflozin

2. NAME OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca AB

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Monday Tuesday Wednesday Thursday Friday Saturday Sunday

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Edistride 5 mg film-coated tablets
Edistride 10 mg film-coated tablets
dapagliflozin

▼This medicine 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 Edistride is and what it is used for

Edistride contains the active substance dapagliflozin. It belongs to a group of medicines called "oral anti-diabetics".
- These are medicines taken by mouth for diabetes.
- They work by lowering the amount of sugar (glucose) in your blood.

Edistride is used for a type of diabetes called "type 2 diabetes mellitus" in adult patients (aged 18 years and older). "Type 2 diabetes mellitus" is the type of diabetes that usually starts 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 in your blood. Edistride works by removing excess sugar from your body via your urine.
- Edistride is used if your diabetes cannot be controlled with other medicines for diabetes, diet and exercise.
- Your doctor may ask you to take Edistride on its own if you are intolerant to metformin or together with other medicines to treat diabetes. This may be another medicine taken by mouth and/or insulin given by injection.

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 Edistride

Do not take Edistride:
- if you are allergic to dapagliflozin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor, pharmacist or nurse before taking Edistride, 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 a kidney problem – your doctor may ask you to take a different medicine.
- if you have a liver problem – your doctor may start you on a lower dose.
- if you have a history of serious heart disease or if you have had a stroke.
- if you are are on medicines to lower your blood pressure (anti-hypertensives) and have a history of low blood pressure (hypotension). More information is given below in **Other medicines and Edistride.**
- if you have very high levels of glucose in your blood which may make you dehydrated (lose too much body fluid). Possible signs of dehydration are listed at the top of section 4, 'Possible side effects'. Tell your doctor before you start taking Edistride if you have any of these signs.
- if you have or develop nausea (feeling sick), vomiting or fever or if you are not able to eat or drink. These conditions can cause dehydration. Your doctor may ask you to stop taking Edistride until you recover to prevent dehydration.
- if you often get infections of the urinary tract.
- if you are 75 years old or older, you should not start taking Edistride.
- if you are taking another medicine for diabetes that contains "pioglitazone", you should not start taking Edistride.
- if you have an increase in the amount of red blood cells in your blood, seen in tests.

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 Edistride.

Kidney function
Your kidneys should be checked before you start taking and whilst you are on this medicine.

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

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

Other medicines and Edistride
Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines.

Especially tell your doctor:
- if you are taking a medicine used to remove water from the body (diuretic). Your doctor may ask you to stop taking Edistride. 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 low blood sugar levels (hypo-glycaemia).

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

Driving and using machines
Edistride has no or negligible influence on the ability to drive and use machines. Taking this medicine with other medicines called sulphonylureas or with insulin can cause too low blood sugar levels (hypo-glycaemia), which may cause symptoms such as shaking, sweating and change in vision, and may affect your ability to drive and use machines. Do not drive or use any tools or machines, if you feel dizzy taking Edistride.

Edistride contains lactose
Edistride contains lactose (milk sugar). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take Edistride

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

How much to take
- The recommended dose is one 10 mg tablet each day.
- Your doctor may start you on a 5 mg dose if you have a liver problem.
- Your doctor will prescribe the strength that is right for you.

Taking this medicine
- Swallow the tablet whole with half a glass of water.
- You can take your tablet with or without food.
- You can take the tablet at any time of the day. However, try to take it at the same time each day. This will help you to remember to take it.

Your doctor may prescribe Edistride 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 Edistride.

If you take more Edistride than you should
If you take more Edistride tablets than you should, talk to a doctor or go to a hospital immediately. Take the medicine pack with you.

If you forget to take Edistride
What to do if you forget to take a tablet depends on how long it is until your next dose.
- If it is 12 hours or more until your next dose, take a dose of Edistride as soon as you remember. Then take your next dose at the usual time.
- If it is less than 12 hours until your next dose, skip the missed dose. Then take your next dose at the usual time.
- Do not take a double dose of Edistride to make up for a forgotten dose.

If you stop taking Edistride
Do not stop taking Edistride 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 Edistride and see a doctor as soon as possible if you notice any of the following serious side effects:

- loss of too much fluid from your body (dehydration), seen uncommonly.

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.

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 Edistride.

Contact your doctor as soon as possible if you have any of the following side effects:
Very common (may affect more than 1 in 10 people)
- low blood sugar levels (hypo-glycaemia) - when taking this medicine with a sulphonylurea or 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 when taking Edistride:
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)
- dizziness

Uncommon (may affect up to 1 in 100 people)
- thirst
- constipation
- awakening from sleep at night to pass urine
- dry mouth
- weight decreased
- changes in laboratory blood tests (for example creatinine or urea)
- decrease in kidney function

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 Edistride

- 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 to protect the environment.

6. Contents of the pack and other information

What Edistride contains

- The active substance is dapagliflozin.

Each Edistride 5 mg film-coated tablet (tablet) contains dapagliflozin propanediol monohydrate equivalent to 5 mg dapagliflozin.
Each Edistride 10 mg film-coated tablet (tablet) contains dapagliflozin propanediol monohydrate equivalent to 10 mg dapagliflozin.

- The other ingredients are:
  - tablet core: microcrystalline cellulose (E460i), anhydrous lactose (see section 2 'Edistride contains lactose'), crospovidone (E1202), silicon dioxide (E551), magnesium stearate (E470b).
  - film-coating: polyvinyl alcohol (E1203), titanium dioxide (E171), macrogol 3350, talc (E553b), yellow iron oxide (E172).

What Edistride looks like and contents of the pack

- Edistride 5 mg film-coated tablets are yellow and round with diameter of 0.7 cm. They have "5" on one side and "1427" on the other side.
- Edistride 10 mg film-coated tablets are yellow and diamond-shaped approximately 1.1 x 0.8 cm diagonally. They have "10" on one side and "1428" on the other side.

Edistride 5 mg tablets and Edistride 10 mg tablets are available in aluminium blisters in pack sizes of 14, 28 or 98 film-coated tablets in non-perforated calendar blisters and 30x1 or 90x1 film-coated tablets in perforated unit dose blisters.

Not all pack sizes may be marketed in your country.

Marketing Authorisation Holder
AstraZeneca AB
SE-151 85 Södertälje
Sweden

Manufacturer
AstraZeneca GmbH
Tinsdaler Weg 183
22880 Wedel
Germany

AstraZeneca UK Limited
Silk Road Business Park
Macclesfield
SK10 2NA
United Kingdom

Bristol-Myers Squibb Company
Contrada Fontana del Ceraso
IT-03012 Anagni (FR)
Italy

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
AstraZeneca S.A./N.V.
Tel: +32 2 370 48 11

Lietuva
UAB AstraZeneca Lietuva
Tel: +370 5 2660550

България
АстраЗенека България ЕООД
Тел.: +359 (2) 44 55 000

Luxembourg/Luxemburg
AstraZeneca S.A./N.V.
Tél/Tel: +32 2 370 48 11

Česká republika
AstraZeneca Czech Republic s.r.o.
Tel: +420 222 807 111

Magyarország
AstraZeneca Kft.
Tel.: +36 1 883 6500

Danmark
AstraZeneca A/S
Tlf: +45 43 66 64 62

Malta
Associated Drug Co. Ltd
Tel: +356 2277 8000

Deutschland
AstraZeneca GmbH
Tel: +49 41 03 7080

Nederland
AstraZeneca BV
Tel: +31 79 363 2222

Eesti
AstraZeneca
Tel: +372 6549 600

Norge
AstraZeneca AS
Tlf: +47 21 00 64 00

Ελλάδα
AstraZeneca A.E.
Τηλ: +30 2 106871500

Österreich
AstraZeneca Österreich GmbH
Tel: +43 1 711 31 0

España
Laboratorios Dr. Esteve, S.A.
Tel: +34 93 446 60 00

Laboratorio Tau, S. A.
Tel: +34 91 301 91 00

Polska
AstraZeneca Pharma Poland Sp. z o.o.
Tel.: +48 22 245 73 00

France
AstraZeneca
Tél: +33 1 41 29 40 00

Portugal
AstraZeneca Produtos Farmacêuticos, Lda.
Tel: +351 21 434 61 00

Hrvatska
AstraZeneca d.o.o.
Tel: +385 1 4628 000

România
AstraZeneca Pharma SRL
Tel: +40 21 317 60 41

Ireland
AstraZeneca Pharmaceuticals (Ireland) Ltd

Slovenija
AstraZeneca UK Limited

Tel: +353 1609 7100

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
AstraZeneca S.p.A.
Tel: +39 02 9801 1

Κύπρος
Αλέκτωρ Φαρμακευτική Λτδ
Τηλ: +357 22490305

Latvija
SIA AstraZeneca Latvija
Tel: +371 67377100

Tel: +386 1 51 35 600

Slovenská republika
AstraZeneca AB, o.z.
Tel: +421 2 5737 7777

Suomi/Finland
AstraZeneca Oy
Puh/Tel: +358 10 23 010

Sverige
AstraZeneca AB
Tel: +46 8 553 26 000

United Kingdom
AstraZeneca UK Ltd
Tel: +44 1582 836 836

This leaflet was last revised in

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.