EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 September 2015
EMA/679678/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Edistride

International non-proprietary name: dapagliflozin

Procedure No. EMEA/H/C/004161/0000

Note

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

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1. Background information on the procedure

1.1. Submission of the dossier

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

The applicant applied for the following indication:

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).

The legal basis for this application refers to:

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

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

This application is submitted as a multiple of Forxiga authorised on 12 November 2012 in accordance with Article 82.1 of Regulation (EC) No 726/2004.

Information on Paediatric requirements

Not applicable

Similarity

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

Licensing status

The cross-referred product Forxiga was given a Community Marketing Authorisation on 12 November 2012.

A new application was filed in the following countries: South Africa, China, Venezuela Republic of Bolivarian, Algeria, Egypt, Bahrain, Saudi Arabia, Jordan, Jamaica, Dominican Republic, Morocco, Uganda, Ghana, Nigeria, Ethiopia, Kenya and Peru.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Kristina Dunder Co-Rapporteur: Martina Weise

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

2. Scientific discussion

2.1. Introduction

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

Edistride is a film-coated tablet containing dapagliflozin (ATC code A10BX09 ; pharmacotherapeutic group: Drugs used in diabetes, Other blood glucose lowering drugs, excluding insulins). Dapagliflozin is a highly potent (K_i: 0.55 nM), selective and reversible inhibitor of sodium-glucose co-transporter 2 (SGLT2). Dapagliflozin improves both fasting and post-prandial plasma glucose levels by reducing renal glucose reabsorption leading to urinary glucose excretion.

The proposed indication is:

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).

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

2.2. Quality aspects

Edistride is submitted under an informed consent application, article 10(c) of directive 2001/83/EC. Module 3 of the present duplicate dossier cross-refers to the up-to-date module 3 of the original dossier (Forxiga), which has been assessed and authorised. The declaration submitted by the Applicant states that Edistride possesses the same qualitative and quantitative composition in terms of active substances and same pharmaceutical form as Forxiga.

2.3. Non-clinical aspects

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

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

2.3.1. Ecotoxicity / environmental risk assessment

An Environmental Risk Assessment (ERA) has been submitted for dapagliflozin in the context of the marketing authorisation application for Forxiga. According to its results, dapagliflozin is not predicted to present a risk to the environment. As the dose, indication and the patient population has not changed, marketing authorisation of Edistride would not add to the environmental impact.

2.3.2. Discussion on non-clinical aspects

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

2.3.3. Conclusion on the non-clinical aspects

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

2.4. Clinical aspects

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

2.4.1. Discussion on clinical efficacy

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

2.4.2. Conclusions on the clinical efficacy

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

2.5. Clinical safety

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

The most common side effects are hypoglycaemia (when used with a sulphonylurea or insulin), urinary tract infection, genital tract infection, dyslipidaemia, dysuria and polyuria. Specific safety issues regarding a tumour imbalance in dapagliflozin treated patients, the limited data available in patients > 75 years old, the use in patients at risk of volume depletion, hypotension and electrolytes imbalances have been evaluated and addressed in the Summary of Product Characteristics (SmPC) and in the Risk Management Plan discussion on clinical safety.

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

2.5.1. Discussion on the clinical safety

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

2.5.2. Conclusions on the clinical safety

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

2.6. Risk Management Plan

Safety concerns

Summary of safety concerns

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

Pharmacovigilance plan

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
MB102103: Comparison of the Risk of Severe Complications of UTI Between Patients with T2DM Exposed to Dapagliflozin and Those Exposed to Other Anti diabetic Treatments. Non-interventional and "3" Based on Classification	Primary objective: To compare, by insulin use at the index date, the sex-specific incidence of hospitalization or emergency department (ED) visit for severe complications of UTI, defined as pyelonephritis and urosepsis, among patients with T2DM who are new users of dapagliflozin with those who are new users of ADs in classes other than SGLT2 inhibitors, insulin monotherapy, metformin monotherapy, or sulfonylurea monotherapy.	Severe complications of UTI	Ongoing	Interim data cuts will occur 24 and 48 months after the US approval of dapagliflozin (Jan 2014). The final data cut will occur at 60 months post the US approval with the Final Report submission estimated to be 2019.
MB102104: Comparison of Risk of Acute Hepatic Failure Between Patients with T2DM Exposed to Dapagliflozin and Those Exposed to Other Anti-diabetic Treatments. Non-	Primary objective: To compare, by insulin use at the index date, the incidence of hospitalization for ALI among patients with T2DM who are new users of dapagliflozin with	Risk of Acute Hepatic Failure	Ongoing	Interim data cuts will occur 24 and 48 months after the US approval of dapagliflozin (Jan 2014). The final data cut will occur at 60 months post the US approval with the Final Report

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
interventional and “3” Based on Classification	those who are new users of ADs in classes other than SGLT2 inhibitors, insulin monotherapy, metformin monotherapy, or sulfonylurea monotherapy.			submission estimated to be 2019.
MB102110: Comparison of Risk of Acute Renal Failure Between Patients with T2DM Exposed to Dapagliflozin and Those Exposed to Other Antidiabetic Treatments. Non-interventional and “3” Based on Classification	Primary Objective: To compare, by insulin use at the index date, the incidence of hospitalization for acute kidney injury (AKI) among patients with T2DM who are new users of dapagliflozin with those who are new users of ADs in classes other than SGLT2 inhibitors, insulin monotherapy, metformin monotherapy, or sulfonylurea monotherapy.	Risk of Acute Renal Failure	Ongoing	Interim data cuts will occur 24 and 48 months after the US approval of dapagliflozin (Jan 2014). The final data cut will occur at 60 months post the US approval with the Final Report submission estimated to be 2019.
MB102118: Comparison of the Risk of Cancer Among Patients with T2DM Exposed to Dapagliflozin and Those Exposed to Other Antidiabetic	The primary objectives of this study are (1) to compare the incidence of breast cancer, by insulin use at cohort entry, among females	Risk of cancer	Ongoing	Interim data cuts will occur 24, 48, 72, and 96 months after the US approval of dapagliflozin (Jan 2014). The final data cut

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Therapies. Non-interventional and "3" Based on Classification	with T2DM who are new initiators of dapagliflozin and females who are new initiators of ADs in classes other than SGLT2 inhibitors, insulin, metformin monotherapy, or sulfonylurea monotherapy and (2) to compare the incidence of bladder cancer, by insulin use at cohort entry and pioglitazone use, among male and female patients with T2DM who are new initiators of dapagliflozin and those who are new initiators of ADs in classes other than SGLT2 inhibitors, insulin monotherapy, metformin monotherapy, or sulfonylurea monotherapy			will occur at 120 months post the US approval with the Final Report Submission estimated to be 2024.
MB102117 (D1693C00001) CV Outcome study : Dapagliflozin Effect on Cardiovascular Event Incidence in Patients with	The primary safety objective of this trial is to establish whether the upper bound of the 2-sided 95% confidence interval for the estimated risk	Cardiovascular risk, bladder cancer, liver injury	Ongoing	Final Report Submission estimated to be 2020

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Diabetes Mellitus: A Multicentre, Randomized, Double-Blind, Placebo-Controlled Phase IV Trial to Evaluate The Effect of Dapagliflozin on The Incidence of Cardiovascular Death, Myocardial Infarction or Ischemic Stroke in Patients with Type 2 Diabetes and “3” Based on Classification	ratio comparing the incidence of the composite endpoint of cardiovascular death, myocardial infarction or ischemic stroke, in patients with T2DM with either established cardiovascular disease or at least two cardiovascular risk factors in addition to T2DM, observed with dapagliflozin to that observed in the placebo group is less than 1.3.			

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Genital Infections	**Product Labeling:** Undesirable Effects Vulvovaginitis, balanitis and related genital infections are listed as a common adverse drug reaction (ADR). 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. **Patient information:** Yeast infection (thrush) of the penis or vagina is included as a common side effect. Unusual vaginal bleeding, discharge, itching or odour is included as uncommon side effects.	Not applicable
Urinary tract infections	**Product Labeling:** Special Warnings and Precautions for use 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. 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. Undesirable Effects Urinary tract infection is listed as a common ADR. Urinary tract infections Urinary tract infections were more frequently reported for dapagliflozin 10 mg compared to placebo (4.7% versus	Not applicable

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	3.5%, respectively). Most infections were mild to moderate, and subjects responded to an initial course of standard treatment and rarely resulted in discontinuation from dapagliflozin treatment. These infections were more frequent in females, and subjects with a prior history were more likely to have a recurrent infection. **Patient information:** Warnings and precautions Talk to your doctor, pharmacist or nurse before taking Forxiga if you often get infections of the urinary tract. This medicine may cause urinary tract infections and your doctor may want to monitor you more closely. Your doctor may consider temporarily changing your treatment if you develop a serious infection. Possible side effects Stop taking Forxiga and see a doctor as soon as possible if you notice any of the following serious side effects: Urinary tract infection, seen commonly (may affect up to 1 in 10 people). These are signs of a severe infection of the urinary tract: • fever and/or chills • burning sensation when passing water (urinating) • pain in your back or side. Although uncommon, if you see blood in your urine, tell your doctor immediately.	
Hypoglycemia	**Product Labeling:** Interaction with other medicinal products and other forms of interaction Pharmacodynamic interactions Insulin and insulin secretagogues Insulin and insulin secretagogues, such as sulphonylureas, cause hypoglycaemia. Therefore, a lower dose of insulin or an insulin secretagogue may be required to reduce the risk of hypoglycaemia when used in combination dapagliflozin.	Not applicable

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Effects on ability to drive and use machines Forxiga 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. Undesirable Effects Hypoglycemia is listed as a very common ADR (when used with sulfonylurea) dapagliflozin plus metformin Hypoglycaemia 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 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. 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).	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	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. **Patient Information:** Other medicines and Forxiga Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines. Especially tell your doctor if you are taking other medicines that lower the amount of sugar in your blood such as insulin or a “sulphonylurea” medicine. Your doctor may want to lower the dose of these other medicines, to prevent you from getting blood sugar levels that are too low (hypoglycaemia). Driving and using machines This medicine has no or negligible influence on the ability to drive and use machines. Taking Forxiga with other medicines called sulphonylureas or with insulin can cause too low blood sugar levels (hypoglycaemia), which may cause symptoms such as shaking, sweating and 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 Forxiga. Possible side effects Hypoglycaemia (low blood sugar levels) is a common event (may affect more than 1 in 10 people) occurring when taking this medicine with insulin.	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	These are the signs of low blood sugar: • shaking, sweating, feeling very anxious, fast heart beat • feeling hungry, headache, change in vision • a change in your mood or feeling confused. Your doctor will tell you how to treat low blood sugar levels and what to do if you get any of the signs above.	
Volume depletion	**Product Labeling:** Special Warnings and Precautions for use: Use in patients at risk for volume depletion, hypotension and/or electrolyte imbalances Due to its mechanism of action, dapagliflozin increases diuresis associated with a modest decrease in blood pressure, which may be more pronounced in patients with high blood glucose concentrations. Dapagliflozin is not recommended for use in patients receiving loop diuretics or who are volume depleted, e.g. due to acute illness (such as gastrointestinal illness). Caution should be exercised in patients for whom a dapagliflozin induced drop in blood pressure could pose a risk, such as patients with known 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 this medical product is recommended for patients who develop volume depletion until the depletion is corrected. Interaction with other medicinal products and other forms of interaction	Not applicable

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Pharmacodynamic interactions Diuretics Dapagliflozin may add to the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension. Undesirable Effects Volume depletion is listed as an uncommon ADR. Volume depletion Reactions related to volume depletion (including, reports of dehydration, hypovolaemia or hypotension) were reported in 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. **Patient Information:** What you need to know before you take Forxiga Do not take Forxiga if you have a severe infection or if you have lost a lot of water from your body (dehydration) (e.g., due to long-lasting or severe diarrhoea, or if you have vomited several times in a row). Warnings and precautions Talk to your doctor, pharmacist or nurse before taking Forxiga: • if you are on medicines to lower blood pressure (anti hypertensives) and have a history of low blood pressure (hypotension). More information is given below in 'Other medicines and Forxiga' • 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 Forxiga until you recover to prevent dehydration Other medicines and Forxiga Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines.	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	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 Forxiga. Possible signs of losing too much fluid from your body are listed as 'Possible side effects'. Possible side effects Stop taking Forxiga and see a doctor as soon as possible if you notice any of the following serious side effects: Loss of too much fluid from your body (dehydration), seen uncommonly (may affect up to 1 in 100 people). These are signs of dehydration: • very dry or sticky mouth, feeling very thirsty • feeling very sleepy or tired • passing little or no water (urine) • fast heart beat.	
Clinical Consequences of Increased Hematocrit	**Product Labeling:** Special Warnings and Precautions for use: Elevated haematocrit Haematocrit increase was observed with dapagliflozin treatment; therefore, caution in patients with already elevated haematocrit is warranted. Undesirable Effects Haematocrit increased is listed as a common ADR, with footnote: "Mean changes from baseline in haematocrit were 2.30% 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." **Patient information:** Warnings and precautions Talk to your doctor, pharmacist or nurse before taking Forxiga if you have an increase in the amount of red blood cells in your blood, seen in tests	Not applicable
Renal Impairment/	**Product labeling:**	Not applicable

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Failure	Special Warnings and Precautions for use 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. 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. Forxiga 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). Forxiga 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 treatment and at least yearly thereafter • Prior to initiation of concomitant medicinal products that may reduce renal function and periodically thereafter • For renal function approaching moderate renal impairment, at least 2 to 4 times per year. If renal function falls below CrCl < 60 mL/min or eGFR < 60 mL/min/1.73 m2, treatment must be discontinued. Elderly patients Elderly patients are more likely to have impaired renal function, and/or to be treated with anti hypertensive medicinal products that may cause changes in renal function such as angiotensin converting enzyme (ACE) inhibitors and angiotensin II type 1 receptor blockers (ARB). The same recommendations for renal function apply to older patients as to all patients. In subjects ≥ 65 years of age, a higher proportion of subjects treated with dapagliflozin had adverse reactions related to renal impairment or failure compared with placebo. The most commonly reported adverse reaction	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	related to renal function was serum creatinine increases, the majority of which were transient and reversible. 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. Therapeutic experience in patients 75 years and older is limited. Initiation of dapagliflozin therapy in this population is not recommended. Undesirable Effects Blood creatinine increased and blood urea increased are listed as uncommon ADRs. **Patient Information:** Patient instructed to inform doctor, pharmacist, or nurse if they have a kidney problem. Changes in laboratory tests (including creatinine or urea) included as an uncommon side effect	
Bone fracture	None proposed	Not applicable
Liver injury	None proposed	Not applicable
Hypersensitivity reactions	None proposed	Not applicable
Bladder cancer	**Product labeling:** Special Warnings and Precautions for use with regard to use of Dapagliflozin in combination with pioglitazone: Use in patients treated with pioglitazone While a causal relationship between dapagliflozin and bladder cancer is unlikely, as a precautionary measure, 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. Undesirable effects	Not applicable

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	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. 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.	
Breast cancer	**Product labeling:** Undesirable effects Malignancies During clinical trials, the overall proportion of subjects with malignant or unspecified tumours was similar between those treated with dapagliflozin (1.50%) and placebo/comparator (1.50%), and there was no carcinogenicity or mutagenicity signal in animal data. When considering the cases of tumours occurring in the different organ systems, the relative risk associated with dapagliflozin was above 1 for some tumours (bladder, prostate, breast) and below 1 for others (e.g. blood and lymphatic, ovary, renal tract), not resulting in an overall increased tumour risk associated with dapagliflozin. The increased/decreased risk was not statistically significant in any of the organ systems. Considering the lack of tumour findings in non clinical studies as well as the short latency between first drug exposure and tumour diagnosis, a causal relationship is considered unlikely. Since the numerical imbalance of breast, bladder and prostate tumours must be considered with caution, it will be further investigated in post authorisation studies.	Not applicable
Prostate cancer	**Product labeling:**	Not applicable

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Undesirable effects 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. 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.	
Off-label use of Dapagliflozin in Specific Populations	**Product labeling:** Therapeutic experience in patients 75 years and older is limited. Initiation of dapagliflozin therapy in this population is not recommended. Dapagliflozin is not recommended for use in patients receiving loop diuretics or who are volume depleted, e.g. due to acute illness (such as gastrointestinal illness). Use in patients treated with pioglitazone While a causal relationship between dapagliflozin and bladder cancer is unlikely, as a precautionary measure, 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. **Patient information:** Warnings and precautions If you are 75 years old or older, you should not start taking this medicine. This is because you may be more prone to some side effects.	Not applicable

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	If you are taking another medicine for diabetes that contains “pioglitazone”, you should not start taking this medicine.	
Pediatric population	**Product labeling:** Posology and method of administration: Paediatric population The safety and efficacy of dapagliflozin in children aged 0 to < 18 years have not yet been established. No data are available. **Patient information** Children and adolescents Forxiga is not recommended for children and adolescents under 18 years of age, because it has not been studied in these patients.	Not applicable
Pregnancy / Nursing mothers	**Product labeling:** Fertility, pregnancy and lactation Pregnancy There are no data from the use of in pregnant women. Studies in rats treated with dapagliflozin have shown toxicity to the developing kidney in the time period corresponding to the second and third trimesters of human pregnancy. Therefore, the use of this medical product is not recommended during the second and third trimesters of pregnancy. 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 have shown excretion of dapagliflozin/metabolites in animal milk, as well as pharmacologically mediated effects in nursing offspring. A risk to the newborns/infants cannot be excluded. Dapagliflozin should not be used while breast-feeding. **Patient information** Pregnancy and breast feeding If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor	Not applicable

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	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 Forxiga if you are breast-feeding. It is not known if this medicine passes into human breast milk.	
Elderly population	**Product labeling:** Posology and method of administration Older people (≥ 65 years) In general, no dosage adjustment is recommended based on age. Renal function and risk of volume depletion should be taken into account. Due to the limited therapeutic experience in patients 75 years and older, initiation of dapagliflozin therapy is not recommended. Special warnings and precautions for use Older patients (≥ 65 years) Older patients are more likely to have impaired renal function, and/or to be treated with anti hypertensive medicinal products that may cause changes in renal function such as angiotensin converting enzyme (ACE) inhibitors and angiotensin II type 1 receptor blockers (ARB). The same recommendations for renal function apply to older patients as to all patients. In subjects ≥ 65 years of age, a higher proportion of subjects treated with dapagliflozin had adverse reactions related to renal impairment or failure compared with placebo. The most commonly reported adverse reaction related to renal function was serum creatinine increases, the majority of which were transient and reversible. 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.	Not applicable

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Therapeutic experience in patients 75 years and older is limited. Initiation of dapagliflozin therapy in this population is not recommended. Undesirable effects Special populations Older patients (≥ 65 years) In subjects ≥ 65 years of age, adverse reactions related to renal impairment or failure were reported in 7.7% of subjects treated with dapagliflozin and 3.8% of subjects treated with placebo. The most commonly reported adverse reaction related to renal function was increased serum creatinine. The majority of these reactions were transient and reversible. In subjects ≥ 65 years of age, adverse reactions of volume depletion, most commonly reported as hypotension, were reported in 1.7% and 0.8% of dapagliflozin treated subjects and placebo treated subjects, respectively.	
Patient with severe renal impairment	**Product labeling:** 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. 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. Forxiga 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). Forxiga has not been studied in severe 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. Forxiga 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.	Not applicable

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Patient with moderate and severe hepatic impairment	**Product Labeling:** Posology and method of administration: 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. Special Warnings and Precautions for use: 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.	Not applicable
Patients with compromised cardiac function (CF) NYHA class III and IV	**Product Labeling:** Special warnings and precautions for use Cardiac failure Experience in NYHA class I II is limited, and there is no experience in clinical studies with dapagliflozin in NYHA class III IV.	Not applicable

Conclusion

The CHMP and PRAC considered that the risk management plan version 12 is acceptable.

2.7. Pharmacovigilance

Pharmacovigilance system

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

2.8. Product information

The Product information for Edistride is the same as for Forxiga , except for the invented name.

2.8.1. User consultation

Since the package leaflet included in this application is a duplicate of the currently authorised leaflet for the product Forxiga, with only changes to the product name made throughout, a user

testing has not been performed. This was considered acceptable by the CHMP.

2.8.2. Additional monitoring

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

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

3. Benefit-Risk Balance

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

The product of this application is a duplicate with identical composition and documentation as Forxiga (EU/1/12/795/001-010), authorized in the treatment of 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

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

4. Recommendations

Outcome

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

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),

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

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

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

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

- **Risk Management Plan (RMP)**

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

An updated RMP should be submitted:

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

Additional risk minimisation measures

Not applicable