ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Steglatro 5 mg film-coated tablets
Steglatro 15 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Steglatro 5 mg film-coated tablets

Each tablet contains ertugliflozin L-pyroglutamic acid, equivalent to 5 mg ertugliflozin.

Excipient with known effect
Each tablet contains 28 mg of lactose (as monohydrate).

Steglatro 15 mg film-coated tablets

Each tablet contains ertugliflozin L-pyroglutamic acid, equivalent to 15 mg ertugliflozin.

Excipient with known effect
Each tablet contains 85 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Steglatro 5 mg film-coated tablets

Pink, 6.4 x 6.6 mm, triangular-shaped, film-coated tablets debossed with "701" on one side and plain on the other side.

Steglatro 15 mg film-coated tablets

Red, 9.0 x 9.4 mm, triangular-shaped, film-coated tablets debossed with "702" on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Steglatro is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise:

- as monotherapy when metformin is considered inappropriate due to intolerance or contraindications.
- in addition to other medicinal products for the treatment of diabetes.

For study results with respect to combinations of therapies, effects on glycaemic control, cardiovascular events, and the populations studied, see sections 4.4, 4.5, and 5.1.

4.2 Posology and method of administration

Posology

The recommended starting dose of ertugliflozin is 5 mg once daily. In patients tolerating ertugliflozin 5 mg once daily, the dose can be increased to 15 mg once daily if additional glycaemic control is needed.

When ertugliflozin is used in combination with insulin or an insulin secretagogue, a lower dose of insulin or the insulin secretagogue may be required to reduce the risk of hypoglycaemia (see sections 4.4, 4.5, and 4.8).

In patients with volume depletion, correcting this condition prior to initiation of ertugliflozin is recommended (see section 4.4).

Missed dose

If a dose is missed, it should be taken as soon as the patient remembers. Patients should not take two doses of Steglatro on the same day.

Special populations

Renal impairment
Assessment of renal function is recommended prior to initiation of Steglatro and periodically thereafter (see section 4.4).

Initiation of this medicinal product is not recommended in patients with an estimated glomerular filtration rate (eGFR) less than 45 mL/min/1.73 m^2 or creatinine clearance (CrCl) less than 45 mL/min (see section 4.4).

In patients with an eGFR $\geq$ 45 to < 60 mL/min/1.73 m^2, Steglatro should be initiated at 5 mg and up-titrated to 15 mg as needed for glycaemic control.

Because the glycaemic lowering efficacy of ertugliflozin is reduced in patients with moderate renal impairment and likely absent in patients with severe renal impairment, if further glycaemic control is needed, the addition of other anti-hyperglycaemic agents should be considered (see section 4.4).

Steglatro should be discontinued when eGFR is persistently less than 30 mL/min/1.73 m^2 or CrCl is persistently less than 30 mL/min.

Steglatro should not be used in patients with severe renal impairment, with end-stage renal disease (ESRD), or receiving dialysis, as there is no clinical data to support effectiveness in these patients.

Hepatic impairment
No dose adjustment of ertugliflozin is necessary in patients with mild or moderate hepatic impairment. Ertugliflozin has not been studied in patients with severe hepatic impairment and is not recommended for use in these patients (see section 5.2).

Elderly
No dose adjustment of ertugliflozin is recommended based on age. Renal function and risk of volume depletion should be taken into account (see sections 4.4 and 4.8).

Paediatric population
The safety and efficacy of ertugliflozin in children under 18 years of age have not been established. No data are available.

Method of administration

Steglatro should be taken orally once daily in the morning, with or without food. In case of swallowing difficulties, the tablet could be broken or crushed as it is an immediate-release dosage form.

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

Steglatro should not be used in patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis (DKA) in these patients.

Hypotension/Volume depletion

Ertugliflozin causes an osmotic diuresis, which may lead to intravascular volume contraction. Therefore, symptomatic hypotension may occur after initiating Steglatro (see section 4.8), particularly in patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2 or CrCl less than 60 mL/min), elderly patients (≥ 65 years), patients on diuretics, or patients on anti-hypertensive therapy with a history of hypotension. Before initiating Steglatro, volume status should be assessed and corrected if indicated. Monitor for signs and symptoms after initiating therapy.

Due to its mechanism of action, ertugliflozin induces an osmotic diuresis and increases serum creatinine and decreases eGFR. Increases in serum creatinine and decreases in eGFR were greater in patients with moderate renal impairment (see section 4.8).

In case of conditions that may lead to fluid loss (e.g., gastrointestinal illness), careful monitoring of volume status (e.g., physical examination, blood pressure measurements, laboratory tests including haematocrit) and electrolytes is recommended for patients receiving ertugliflozin. Temporary interruption of treatment with ertugliflozin should be considered until the fluid loss is corrected.

Diabetic ketoacidosis

Rare cases of DKA, including life-threatening and fatal cases, have been reported in clinical trials and post-marketing in patients treated with sodium glucose co-transporter-2 (SGLT2) inhibitors, including ertugliflozin. 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 ertugliflozin.

The risk of DKA 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 ertugliflozin should be discontinued immediately.

Treatment should be interrupted in patients who are hospitalised for major surgical procedures or acute serious medical illnesses. Monitoring of ketones is recommended in these patients. Measurement of blood ketone levels is preferred to urine. Treatment with ertugliflozin may be restarted when the ketone values are normal and the patient's condition has stabilised.

Before initiating ertugliflozin, 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 ertugliflozin in patients with type 1 diabetes have not been established and ertugliflozin 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.

Lower limb amputations

In a long-term cardiovascular outcomes study VERTIS CV (eValuation of ERTugliflozin effIcacy and Safety, CardioVascular), a study in patients with type 2 diabetes mellitus and established atherosclerotic cardiovascular disease, non-traumatic lower limb amputations (primarily of the toe) were reported with an incidence of 2% (0.57 subjects with event per 100 patient-years), 2.1% (0.60 subjects with event per 100 patient-years) and 1.6% (0.47 subjects with event per 100 patient-years) for ertugliflozin 5 mg, ertugliflozin 15 mg and placebo groups. The event rates of lower limb amputations were 0.75 and 0.96 versus 0.74 events per 100 patient-years for ertugliflozin 5 mg and ertugliflozin 15 mg versus placebo, respectively. An increase in cases of lower limb amputation (primarily of the toe) has been observed in long-term clinical studies in type 2 diabetes mellitus with SGLT2 inhibitors. It is not known whether this constitutes a class effect. It is important to counsel patients with diabetes on routine preventative foot care.

Renal impairment

The efficacy of ertugliflozin for glycaemic control is dependent on renal function, and glycaemic efficacy is reduced in patients who have moderate renal impairment and likely absent in patients with severe renal impairment (see section 4.2).

Steglatro should not be initiated in patients with an eGFR below 45 mL/min/1.73 m^2 or CrCl below 45 mL/min. Steglatro should be discontinued when eGFR is persistently below 30 mL/min/1.73 m^2 or CrCl is persistently below 30 mL/min due to a reduction of efficacy.

Monitoring of renal function is recommended as follows:
- Prior to ertugliflozin initiation and periodically during treatment (see section 4.2).
- More frequently in patients with an eGFR below 60 mL/min/1.73 m^2 or a CrCl below 60 mL/min.

Hypoglycaemia with concomitant use with insulin and insulin secretagogues

Ertugliflozin may increase the risk of hypoglycaemia when used in combination with insulin and/or an insulin secretagogue, which are known to cause hypoglycaemia (see section 4.8). Therefore, a lower dose of insulin or insulin secretagogue may be required to minimise the risk of hypoglycaemia when used in combination with ertugliflozin (see sections 4.2 and 4.5).

Genital mycotic infections

Ertugliflozin increases the risk of genital mycotic infections. In trials with SGLT2 inhibitors, patients with a history of genital mycotic infections and uncircumcised males were more likely to develop genital mycotic infections (see section 4.8). Patients should be monitored and treated appropriately.

Urinary tract infections

Urinary glucose excretion may be associated with an increased risk of urinary tract infections (see section 4.8). Temporary interruption of ertugliflozin should be considered when treating pyelonephritis or urosepsis.

Necrotising fasciitis of the perineum (Fournier's gangrene)

Post-marketing cases of necrotising fasciitis of the perineum, (also known as Fournier's gangrene), have been reported in female and male patients taking SGLT2 inhibitors. This is a rare but serious and potentially life-threatening event that requires urgent surgical intervention and antibiotic treatment.

Patients should be advised to seek medical attention if they experience a combination of symptoms of pain, tenderness, erythema, or swelling in the genital or perineal area, with fever or malaise. Be aware that either urogenital infection or perineal abscess may precede necrotising fasciitis. If Fournier's gangrene is suspected, Steglatro should be discontinued and prompt treatment (including antibiotics and surgical debridement) should be instituted.

Elderly patients

Elderly patients may be at an increased risk of volume depletion and renal impairment. Patients 65 years and older treated with ertugliflozin had a higher incidence of adverse reactions related to volume depletion compared to younger patients. In a long-term cardiovascular outcomes study VERTIS CV, safety and efficacy were similar for patients age 65 years and older compared to patients younger than 65 (see sections 4.2 and 4.8).

Cardiac failure

There is no experience in clinical studies with ertugliflozin in New York Heart Association (NYHA) class IV.

Urine laboratory assessments

Due to its mechanism of action, patients taking Steglatro will test positive for glucose in their urine. Alternative methods should be used to monitor glycaemic control.

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. Alternative methods should be used to monitor glycaemic control.

Lactose

Steglatro contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

Diuretics
Ertugliflozin may add to the diuretic effect of 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. Ertugliflozin may increase the risk of hypoglycaemia when used in combination with insulin and/or an insulin secretagogue. Therefore, a lower dose of insulin or an insulin secretagogue may be required to reduce the risk of hypoglycaemia when used in combination with ertugliflozin (see sections 4.2, 4.4, and 4.8).

Pharmacokinetic interactions

Effects of other medicinal products on the pharmacokinetics of ertugliflozin
Metabolism by UGT1A9 and UGT2B7 is the primary clearance mechanism for ertugliflozin.

Interaction studies conducted in healthy subjects, using a single dose design, suggest that the pharmacokinetics of ertugliflozin are not altered by sitagliptin, metformin, glimepiride, or simvastatin.

Multiple-dose administration of rifampicin (a uridine 5'-diphospho-glucuronosyltransferase [UGT] and cytochrome P450 [CYP] inducer) decreases ertugliflozin area under the concentration-time curve (AUC) and maximum plasma concentration (C_{max}) by 39% and 15%, respectively. This decrease in exposure is not considered clinically relevant and therefore, no dose adjustment is recommended. A clinically relevant effect with other inducers (e.g., carbamazepine, phenytoin, phenobarbital) is not expected.

The impact of UGT inhibitors on the pharmacokinetics of ertugliflozin has not been studied clinically, but potential increase in ertugliflozin exposure due to UGT inhibition is not considered to be clinically relevant.

Effects of ertugliflozin on the pharmacokinetics of other medicinal products
Interaction studies conducted in healthy volunteers suggest that ertugliflozin had no clinically relevant effect on the pharmacokinetics of sitagliptin, metformin, and glimepiride.

Coadministration of simvastatin with ertugliflozin resulted in a 24% and 19% increase in AUC and C_{max} of simvastatin, respectively, and 30% and 16% increase in AUC and C_{max} of simvastatin acid, respectively. The mechanism for the small increases in simvastatin and simvastatin acid is unknown and is not perpetrated through organic anion transporting polypeptide (OATP) inhibition by ertugliflozin. These increases are not considered to be clinically meaningful.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited data from the use of ertugliflozin in pregnant women. Based on results from animal studies, ertugliflozin may affect renal development and maturation (see section 5.3). Therefore, Steglatro should not be used during pregnancy.

Breast-feeding

There is no information regarding the presence of ertugliflozin in human milk, the effects on the breast-fed infant, or the effects on milk production. Ertugliflozin is present in the milk of lactating rats and caused effects in the offspring of lactating rats. Pharmacologically-mediated effects were observed in juvenile rats (see section 5.3). Since human kidney maturation occurs in utero and during the first 2 years of life when exposure from breast-feeding may occur, a risk to newborns/infants cannot be excluded. Steglatro should not be used during breast-feeding.

Fertility

The effect of ertugliflozin on fertility in humans has not been studied. No effects on fertility were observed in animal studies (see section 5.3).

4.7 Effects on ability to drive and use machines

Ertugliflozin has no or negligible influence on the ability to drive and use machines. Patients should be alerted to the risk of hypoglycaemia when Steglatro is used in combination with insulin or an insulin secretagogue and to the elevated risk of adverse reactions related to volume depletion, such as postural dizziness (see sections 4.2, 4.4, and 4.8).

4.8 Undesirable effects

Summary of the safety profile

The safety and tolerability of ertugliflozin were assessed in 7 placebo- or active comparator-controlled studies with a total of 3 409 patients with type 2 diabetes mellitus treated with ertugliflozin 5 mg or 15 mg. In addition, the safety and tolerability of ertugliflozin in patients with type 2 diabetes and established atherosclerotic cardiovascular disease were assessed in VERTIS CV (see section 5.1) with a total of 5 493 patients treated with ertugliflozin 5 mg or 15 mg and a mean duration of exposure of 2.9 years.

Pool of placebo-controlled trials evaluating Steglatro 5 mg and 15 mg
The primary assessment of safety was conducted in a pool of three 26-week, placebo-controlled trials. Ertugliflozin was used as monotherapy in one trial and as add-on therapy in two trials (see section 5.1). These data reflect exposure of 1 029 patients to ertugliflozin with a mean exposure duration of approximately 25 weeks. Patients received ertugliflozin 5 mg (N=519), ertugliflozin 15 mg (N=510), or placebo (N=515) once daily.

The most commonly reported adverse reactions across the clinical program were urinary tract infections, vulvovaginal mycotic infection and other female genital mycotic infections. Serious DKA occurred rarely (see section 4.4).

Tabulated list of adverse reactions

Adverse reactions listed below are classified according to frequency and system organ class (SOC), within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness. 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 from placebo- and active comparator-controlled clinical trials and post-marketing experience

System organ class Frequency	**Adverse reaction**
Infections and infestations	
Very common	Urinary tract infections[†] Vulvovaginal mycotic infection and other female genital mycotic infections*[,†]
Common	Balanitis candida and other male genital mycotic infections*[,†]
Not known	Necrotising fasciitis of the perineum (Fournier's gangrene)*[,a]
Metabolism and nutrition disorders	
Common	Hypoglycaemia*[,†]
Rare	DKA*[,†]
Vascular disorders	
Common	Volume depletion*[,†]
Skin and subcutaneous tissue disorders	
Not known	Rash[a]
Renal and urinary disorders	
Common	Increased urination‡
Uncommon	Dysuria, Blood creatinine increased/Glomerular filtration rate decreased[†]
Reproductive system and breast disorders	
Common	Vulvovaginal pruritus
General disorders and administration site conditions	
Common	Thirst[§]
Investigations	
Common	Serum lipids changed[¶], Haemoglobin increased[**], BUN increased[¶¶]

* See section 4.4.

† See subsections below for additional information.

‡ Includes: pollakiuria, micturition urgency, polyuria, urine output increased, and nocturia.

§ Includes: thirst and polydipsia.

¶ Mean percent changes from baseline for ertugliflozin 5 mg and 15 mg versus placebo, respectively, were low-density lipoprotein cholesterol (LDL-C) 5.8% and 8.4% versus 3.2%; total cholesterol 2.8% and 5.7% versus 1.1%; however, high-density lipoprotein cholesterol (HDL-C) 6.2% and 7.6% versus 1.9%. Median percent changes from baseline for ertugliflozin 5 mg and 15 mg versus placebo, respectively, were triglycerides -3.9% and -1.7% versus 4.5%.

** The proportion of subjects having at least 1 increase in haemoglobin > 2.0 g/dL was higher in the ertugliflozin 5 mg and 15 mg groups (4.7% and 4.1%, respectively) compared to the placebo group (0.6%).

¶¶ The proportion of subjects having any occurrence of blood urea nitrogen (BUN) values ≥ 50% increase and value >upper limit of normal (ULN) was numerically higher in the ertugliflozin 5 mg group and higher in the 15 mg group (7.9% and 9.8%, respectively) relative to the placebo group (5.1%).

a Adverse reactions were identified through post-marketing surveillance.

Description of selected adverse reactions

Volume depletion
Ertugliflozin causes an osmotic diuresis, which may lead to intravascular volume contraction and adverse reactions related to volume depletion. In the pool of placebo-controlled studies, the incidence of adverse events related to volume depletion (dehydration, dizziness postural, presyncope, syncope, hypotension, and orthostatic hypotension) was low (< 2%) and not notably different across the ertugliflozin and placebo groups. In the subgroup analyses in the broader pool of phase 3 studies, subjects with eGFR < 60 mL/min/1.73 m^2, subjects ≥ 65 years of age and subjects on diuretics had a higher incidence of volume depletion in the ertugliflozin groups relative to the comparator group (see sections 4.2 and 4.4). In subjects with eGFR < 60 mL/min/1.73 m^2, the incidence was 5.1%, 2.6%, and 0.5% for ertugliflozin 5 mg, ertugliflozin 15 mg, and the comparator group and for subjects with eGFR 45 to < 60 mL/min/1.73 m^2, the incidence was 6.4%, 3.7%, and 0% respectively.

Hypoglycaemia
In the pool of placebo-controlled studies, the incidence of documented hypoglycaemia was increased for ertugliflozin 5 mg and 15 mg (5% and 4.5%) compared to placebo (2.9%). In this population, the incidence of severe hypoglycaemia was 0.4% in each group. When ertugliflozin was used as monotherapy, the incidence of hypoglycaemic events in the ertugliflozin groups was 2.6% in both groups and 0.7% in the placebo group. When used as add-on to metformin, the incidence of hypoglycaemic events was 7.2% in the ertugliflozin 5 mg group, 7.8% in the ertugliflozin 15 mg group and 4.3% in the placebo group.

When ertugliflozin was added to metformin and compared to sulphonylurea, the incidence of hypoglycaemia was higher for the sulphonylurea (27%) compared to ertugliflozin (5.6% and 8.2% for ertugliflozin 5 mg and 15 mg, respectively).

In the VERTIS CV sub-studies, when ertugliflozin was added to insulin with or without metformin, the incidences of documented hypoglycaemia were 39.4%, 38.9% and 37.5% for ertugliflozin 5 mg, ertugliflozin 15 mg and placebo, respectively. When ertugliflozin was added to a sulphonylurea, the incidences of hypoglycaemia were 7.3%, 9.3% and 4.2% for ertugliflozin 5 mg, ertugliflozin 15 mg and placebo, respectively. When ertugliflozin was added to metformin and a sulphonylurea, the incidences of hypoglycaemia were 20%, 26.5% and 14.5% for ertugliflozin 5 mg, ertugliflozin 15 mg and placebo, respectively.

In patients with moderate renal impairment taking insulins, sulphonylurea, or meglitinides as background medicinal products, documented hypoglycaemia was 36%, 27% and 36% for ertugliflozin 5 mg, ertugliflozin 15 mg, and placebo, respectively (see sections 4.2, 4.4, and 4.5).

Diabetic ketoacidosis
In VERTIS CV, ketoacidosis was identified in 19 (0.3%) ertugliflozin-treated patients and in 2 (0.1%) placebo-treated patients. Across 7 other phase 3 clinical trials in the ertugliflozin development program, ketoacidosis was identified in 3 (0.1%) ertugliflozin-treated patients and 0 (0%) of comparator-treated patients (see section 4.4).

Blood creatinine increased/Glomerular filtration rate decreased and renal-related events
Initial increases in mean creatinine and decreases in mean eGFR in patients treated with ertugliflozin were generally transient during continuous treatment. Patients with moderate renal impairment at baseline had larger mean changes that did not return to baseline at Week 26; these changes reversed after treatment discontinuation.

In VERTIS CV, treatment with ertugliflozin was associated with an initial decrease in mean eGFR (at Week 6, -2.7, -3.8 and -0.4 mL/min/1.73 m^2 in the ertugliflozin 5 mg, ertugliflozin 15 mg and placebo groups, respectively) followed by a return toward baseline. Long-term, continued treatment with ertugliflozin was associated with a slower decline in eGFR compared to placebo (up to week 260).

In VERTIS CV, the incidences of renal-related adverse reactions (e.g., acute kidney injury, renal impairment, acute prerenal failure) were 4.2%, 4.3% and 4.7% in patients treated with ertugliflozin 5 mg, ertugliflozin 15 mg and placebo respectively in the overall population; and were 9.7%, 10% and 10.2% in patients treated with ertugliflozin 5 mg, ertugliflozin 15 mg and placebo respectively in patients with an eGFR from 30 to less than 60 mL/min/1.73 m^2.

Genital mycotic infections
In the pool of three placebo-controlled clinical trials, female genital mycotic infections (e.g., genital candidiasis, genital infection fungal, vaginal infection, vulvitis, vulvovaginal candidiasis, vulvovaginal mycotic infection, vulvovaginitis) occurred in 9.1%, 12%, and 3% of females treated with ertugliflozin 5 mg, ertugliflozin 15 mg, and placebo, respectively. In females, discontinuation due to genital mycotic infections occurred in 0.6% and 0% of patients treated with ertugliflozin and placebo, respectively (see section 4.4).

In the same pool, male genital mycotic infections (e.g., balanitis candida, balanoposthitis, genital infection, genital infection fungal) occurred in 3.7%, 4.2%, and 0.4% of males treated with ertugliflozin 5 mg, ertugliflozin 15 mg, and placebo, respectively. Male genital mycotic infections occurred more commonly in uncircumcised males. In males, discontinuations due to genital mycotic infections occurred in 0.2% and 0% of patients treated with ertugliflozin and placebo, respectively. In rare instances, phimosis was reported and sometimes circumcision was performed (see section 4.4).

Urinary tract infections
In VERTIS CV, urinary tract infections occurred in 12.2%, 12% and 10.2% of patients treated with ertugliflozin 5 mg, ertugliflozin 15 mg and placebo, respectively. The incidences of serious urinary tract infections were 0.9%, 0.4%, and 0.8% with ertugliflozin 5 mg, ertugliflozin 15 mg and placebo, respectively.

Across 7 other phase 3 clinical trials in the ertugliflozin development program, the incidences of urinary tract infections were 4% and 4.1% for ertugliflozin 5 mg and 15 mg groups and 3.9% for placebo. Most of the events were mild or moderate, and no serious cases were reported.

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

Ertugliflozin did not show any toxicity in healthy subjects at single oral doses up to 300 mg and multiple doses up to 100 mg daily for 2 weeks. No potential acute symptoms and signs of overdose were identified.

In the event of an overdose, employ the usual supportive measures (e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment) as dictated by the patient's clinical status. Removal of ertugliflozin by haemodialysis has not been studied.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, sodium glucose co-transporter 2 (SGLT2) inhibitors, ATC code: A10BK04.

Mechanism of action

SGLT2 is the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. Ertugliflozin is a potent, selective, and reversible inhibitor of SGLT2. By inhibiting SGLT2, ertugliflozin reduces renal reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion.

Pharmacodynamic effects

Urinary glucose excretion and urinary volume
Dose-dependent increases in the amount of glucose excreted in urine were observed in healthy subjects and in patients with type 2 diabetes mellitus following single- and multiple-dose administration of ertugliflozin. Dose-response modelling indicates that ertugliflozin 5 mg and 15 mg result in near maximal urinary glucose excretion (UGE) in patients with type 2 diabetes mellitus, providing 87% and 96% of maximal inhibition, respectively.

Clinical efficacy and safety

Both improvement of glycaemic control and reduction of cardiovascular morbidity and mortality are integral parts of the treatment of type 2 diabetes mellitus.

Ertugliflozin has been studied as monotherapy and in combination with metformin, sitagliptin, a sulphonylurea, insulin (with or without metformin), metformin plus sitagliptin, metformin plus a sulphonylurea and compared to a sulphonylurea (glimepiride). Ertugliflozin has also been studied in patients with type 2 diabetes mellitus and moderate renal impairment.

The glycaemic efficacy and safety of ertugliflozin have been studied in 7 multi-centre, randomised, double-blind, placebo- or active comparator-controlled, phase 3 clinical studies involving 4 863 patients with type 2 diabetes, including a study of 468 patients with moderate renal impairment. The racial distribution was 76.8% White, 13.3% Asian, 5.0% Black and 4.8% other. Hispanic or Latino patients comprised 24.2% of the population. Patients had an average age of 57.8 years (range 21 years to 87 years), with 25.8% of patients ≥ 65 years of age and 4.5% ≥ 75 years of age.

In addition, a cardiovascular outcomes study (VERTIS CV) was conducted. VERTIS CV enrolled 8 246 patients with type 2 diabetes mellitus and established atherosclerotic cardiovascular disease including 1 776 patients with moderate renal impairment. VERTIS CV also included sub-studies to evaluate the glycaemic efficacy and safety of ertugliflozin added to other glycaemic treatments.

Glycaemic control

Monotherapy
A total of 461 patients with type 2 diabetes inadequately controlled on diet and exercise participated in a randomised, double-blind, multi-centre, 26-week, placebo-controlled study to evaluate the efficacy and safety of ertugliflozin monotherapy. These patients, who were not receiving any background anti-hyperglycaemic treatment, were randomised to ertugliflozin 5 mg, ertugliflozin 15 mg, or placebo administered once daily (see Table 2).

Table 2: Results at week 26 from a placebo-controlled monotherapy study of ertugliflozin*

	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Placebo
HbA1c (%)	**N = 156**	**N = 151**	**N = 153**
Baseline (mean)	8.2	8.4	8.1
Change from baseline (LS mean†)	-0.8	-1.0	0.2
Difference from placebo (LS mean†, 95% CI)	-1.0‡ (-1.2, -0.8)	-1.2‡ (-1.4, -0.9)	
Patients [N (%)] with HbA1c < 7%	44 (28.2)§	54 (35.8)§	20 (13.1)
Body weight (kg)	**N = 156**	**N = 152**	**N = 153**
Baseline (mean)	94.0	90.6	94.2
Change from baseline (LS mean†)	-3.2	-3.6	-1.4
Difference from placebo (LS mean†, 95% CI)	-1.8‡ (-2.6, -0.9)	-2.2‡ (-3.0, -1.3)	

* N includes all randomised, treated patients who had at least one measurement of the outcome variable.

† Least squares means adjusted for time, prior anti-hyperglycaemic medicinal products, baseline eGFR and the interaction of time by treatment.

‡ $p < 0.001$ compared to placebo.

§ $p < 0.001$ compared to placebo (based on adjusted odds ratio comparisons from a logistic regression model using multiple imputation for missing data values).

Ertugliflozin as add-on combination therapy with metformin

A total of 621 patients with type 2 diabetes inadequately controlled on metformin monotherapy (≥ 1 500 mg/day) participated in a randomised, double-blind, multi-centre, 26-week, placebo-controlled study to evaluate the efficacy and safety of ertugliflozin in combination with metformin. Patients were randomised to ertugliflozin 5 mg, ertugliflozin 15 mg, or placebo administered once daily in addition to continuation of background metformin therapy (see Table 3).

Table 3: Results at week 26 from a placebo-controlled study for ertugliflozin used in combination with metformin*

	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Placebo
HbA1c (%)	**N = 207**	**N = 205**	**N = 209**
Baseline (mean)	8.1	8.1	8.2
Change from baseline (LS mean†)	-0.7	-0.9	-0.0
Difference from placebo (LS mean†, 95% CI)	-0.7‡ (-0.9, -0.5)	-0.9‡ (-1.1, -0.7)	
Patients [N (%)] with HbA1c < 7%	73 (35.3)§	82 (40.0)§	33 (15.8)
Body weight (kg)	**N = 207**	**N = 205**	**N = 209**
Baseline (mean)	84.9	85.3	84.5
Change from baseline (LS mean†)	-3.0	-2.9	-1.3
Difference from placebo (LS mean†, 95% CI)	-1.7‡ (-2.2, -1.1)	-1.6‡ (-2.2, -1.0)	

* N includes all randomised, treated patients who had at least one measurement of the outcome variable.

† Least squares means adjusted for time, prior anti-hyperglycaemic medicinal products, baseline eGFR, menopausal status randomisation stratum, and the interaction of time by treatment.

‡ $p \leq 0.001$ compared to placebo.

§ $p < 0.001$ compared to placebo (based on adjusted odds ratio comparisons from a logistic regression model using multiple imputation for missing data values).

Active-controlled study of ertugliflozin versus glimepiride as add-on combination therapy with metformin

A total of 1 326 patients with type 2 diabetes inadequately controlled on metformin monotherapy participated in a randomised, double-blind, multi-centre, 52-week, active comparator-controlled study to evaluate the efficacy and safety of ertugliflozin in combination with metformin. These patients, who were receiving metformin monotherapy (≥ 1 500 mg/day), were randomised to ertugliflozin 5 mg, ertugliflozin 15 mg, or glimepiride administered once daily in addition to continuation of background metformin therapy. Glimepiride was initiated at 1 mg/day and titrated up to a maximum dose of 6 or 8 mg/day (depending on maximum approved dose in each country) or a maximum tolerated dose or down-titrated to avoid or manage hypoglycaemia. The mean daily dose of glimepiride was 3.0 mg (see Table 4).

Table 4: Results at week 52 from an active-controlled study comparing ertugliflozin to glimepiride as add-on therapy in patients inadequately controlled on metformin*

	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Glimepiride
HbA1c (%)	**N = 448**	**N = 440**	**N = 437**
Baseline (mean)	7.8	7.8	7.8
Change from baseline (LS mean†)	-0.6	-0.6	-0.7
Difference from glimepiride (LS mean†, 95% CI)	0.2 (0.1, 0.3)	0.1‡ (-0.0, 0.2)	
Patients [N (%)] with HbA1c < 7%	154 (34.4)	167 (38.0)	190 (43.5)
Body weight (kg)	**N = 448**	**N = 440**	**N = 437**
Baseline (mean)	87.9	85.6	86.8
Change from baseline (LS mean†)	-3.0	-3.4	0.9
Difference from glimepiride (LS mean†, 95% CI)	-3.9 (-4.4, -3.4)	-4.3§ (-4.8, -3.8)	

* N includes all randomised, treated patients who had at least one measurement of the outcome variable.

† Least squares means adjusted for time, prior anti-hyperglycaemic medicinal products, baseline eGFR and the interaction of time by treatment.

‡ Non-inferiority is declared when the upper bound of the two-sided 95% confidence interval (CI) for the mean difference is less than 0.3%.

§ $p < 0.001$ compared to glimepiride.

Factorial study with ertugliflozin and sitagliptin as add-on combination therapy with metformin
A total of 1 233 patients with type 2 diabetes participated in a randomised, double-blind, multi-centre, 26-week, active-controlled study to evaluate the efficacy and safety of ertugliflozin 5 mg or 15 mg in combination with sitagliptin 100 mg compared to the individual components. Patients with type 2 diabetes inadequately controlled on metformin monotherapy (≥ 1 500 mg/day) were randomised to one of five active-treatment arms: ertugliflozin 5 mg or 15 mg, sitagliptin 100 mg, or sitagliptin 100 mg in combination with 5 mg or 15 mg ertugliflozin administered once daily in addition to continuation of background metformin therapy (see Table 5).

Table 5: Results at week 26 from a factorial study with ertugliflozin and sitagliptin as add-on combination therapy with metformin compared to individual components alone*

	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Sitagliptin 100 mg	Ertugliflozin 5 mg + Sitagliptin 100 mg	Ertugliflozin 15 mg + Sitagliptin 100 mg
HbA1c (%)	**N = 250**	**N = 248**	**N = 247**	**N = 243**	**N = 244**
Baseline (mean)	8.6	8.6	8.5	8.6	8.6
Change from baseline (LS mean†)	-1.0	-1.1	-1.1	-1.5	-1.5
Difference from					
Sitagliptin				-0.4‡ (-0.6, -0.3)	-0.5‡ (-0.6, -0.3)
Ertugliflozin 5 mg				-0.5‡ (-0.6, -0.3)	
Ertugliflozin 15 mg					-0.4‡ (-0.6, -0.3)
(LS mean†, 95% CI)					
Patients [N (%)] with HbA1c < 7%	66 (26.4)	79 (31.9)	81 (32.8)	127 (52.3)§	120 (49.2)§
Body weight (kg)	**N = 250**	**N = 248**	**N = 247**	**N = 243**	**N = 244**
Baseline (mean)	88.6	88.0	89.8	89.5	87.5
Change from baseline (LS mean†)	-2.7	-3.7	-0.7	-2.5	-2.9
Difference from Sitagliptin (LS mean†, 95% CI)				-1.8‡ (-2.5, -1.2)	-2.3‡ (-2.9, -1.6)

* N includes all randomised, treated patients who had at least one measurement of the outcome variable.

† Least squares means adjusted for time, baseline eGFR and the interaction of time by treatment.

‡ $p < 0.001$ compared to control group.

§ $p < 0.001$ compared to corresponding dose of ertugliflozin or sitagliptin (based on adjusted odds ratio comparisons from a logistic regression model using multiple imputation for missing data values).

Ertugliflozin as add-on combination therapy with metformin and sitagliptin

A total of 463 patients with type 2 diabetes inadequately controlled on metformin (≥ 1 500 mg/day) and sitagliptin 100 mg once daily participated in a randomised, double-blind, multi-centre, 26-week, placebo-controlled study to evaluate the efficacy and safety of ertugliflozin. Patients were randomised to ertugliflozin 5 mg, ertugliflozin 15 mg, or placebo administered once daily in addition to continuation of background metformin and sitagliptin therapy (see Table 6).

Table 6: Results at week 26 from an add-on study of ertugliflozin in combination with metformin and sitagliptin*

	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Placebo
HbA1c (%)	**N = 156**	**N = 153**	**N = 153**
Baseline (mean)	8.1	8.0	8.0
Change from baseline (LS mean†)	-0.8	-0.9	-0.1
Difference from placebo (LS mean†, 95% CI)	-0.7‡ (-0.9, -0.5)	-0.8‡ (-0.9, -0.6)	
Patients [N (%)] with HbA1c < 7%	50 (32.1) §	61 (39.9) §	26 (17.0)
Body weight (kg)	**N = 156**	**N = 153**	**N = 153**
Baseline (mean)	87.6	86.6	86.5
Change from baseline (LS mean†)	-3.3	-3.0	-1.3
Difference from placebo (LS mean†, 95% CI)	-2.0‡ (-2.6, -1.4)	-1.7‡ (-2.3, -1.1)	

* N includes all randomised, treated patients who had at least one measurement of the outcome variable.

† Least squares means adjusted for time, prior anti-hyperglycaemic medicinal products, baseline eGFR, and the interaction of time by treatment.

‡ p< 0.001 compared to placebo.

§ p< 0.001 compared to placebo (based on adjusted odds ratio comparisons from a logistic regression model using multiple imputation for missing data values).

Combination therapy of ertugliflozin and sitagliptin

A total of 291 patients with type 2 diabetes inadequately controlled on diet and exercise participated in a randomised, double-blind, multi-centre, placebo-controlled 26-week study to evaluate the efficacy and safety of ertugliflozin in combination with sitagliptin. These patients, who were not receiving any background anti-hyperglycaemic treatment, were randomised to ertugliflozin 5 mg or ertugliflozin 15 mg in combination with sitagliptin (100 mg) or to placebo once daily (see Table 7).

Table 7: Results at Week 26 from a combination therapy study of ertugliflozin and sitagliptin*

	Ertugliflozin 5 mg + Sitagliptin	Ertugliflozin 15 mg + Sitagliptin	Placebo
HbA1c (%)	**N = 98**	**N = 96**	**N = 96**
Baseline (mean)	8.9	9.0	9.0
Change from baseline (LS mean†)	-1.6	-1.7	-0.4
Difference from placebo (LS mean† and 95% CI)	-1.2‡ (-1.5, -0.8)	-1.2‡ (-1.6, -0.9)	
Patients [N (%)] with HbA1c <7%	35 (35.7)§	30 (31.3)§	8 (8.3)
Body weight (kg)	**N = 98**	**N = 96**	**N = 97**
Baseline (mean)	90.8	91.3	95.0
Change from baseline (LS mean†)	-2.9	-3.0	-0.9
Difference from placebo (LS mean†, 95% CI)	-2.0‡ (-3.0, -1.0)	-2.1‡ (-3.1, -1.1)	

* N includes all patients who received at least one dose of study medication and had at least one measurement of the outcome variable.
† Least squares means adjusted for time, and the interaction of time by treatment.
‡ p< 0.001 compared to placebo.
§ p< 0.001 compared to placebo (based on adjusted odds ratio comparisons from a logistic regression model using multiple imputation for missing data values).

Ertugliflozin as add-on combination therapy with insulin (with or without metformin)
In an 18-week randomised, double-blind, multi-centre, placebo-controlled, glycaemic sub-study of VERTIS CV, a total of 1 065 patients with type 2 diabetes mellitus and established atherosclerotic cardiovascular disease with inadequate glycaemic control (haemoglobin A1c [HbA1c] between 7% and 10.5%) with background therapy of insulin ≥20 units/day (59% patients were also on metformin ≥1 500 mg/day) were randomised to ertugliflozin 5 mg, ertugliflozin 15 mg or placebo once daily (see Table 8).

Table 8: Results at Week 18 from an add-on study of ertugliflozin in combination with insulin (with or without metformin) in patients with type 2 diabetes mellitus*

	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Placebo
HbA1c (%)	**N = 348**	**N = 370**	**N = 347**
Baseline (mean)	8.4	8.4	8.4
Change from baseline (LS mean†)	-0.8	-0.8	-0.2
Difference from placebo (LS mean†, 95% CI)	-0.6‡ (-0.7, -0.4)	-0.6‡ (-0.8, -0.5)	
Patients [N (%)] with HbA1c <7%	72 (20.7) §	78 (21.1) §	37 (10.7)
Body weight (kg)	**N = 348**	**N = 370**	**N = 347**
Baseline (mean)	93.8	92.1	93.3
Change from baseline (LS mean†)	-1.9	-2.1	-0.2
Difference from placebo (LS mean†, 95% CI)	-1.6‡ (-2.1, -1.1)	-1.9‡ (-2.4, -1.4)	

* N includes all randomised, treated patients who had at least one measurement of the outcome variable.
† Least squares means adjusted for time, insulin stratum, baseline eGFR, and the interaction of time

by treatment.
‡ p< 0.001 compared to placebo.
§ p< 0.001 compared to placebo (based on adjusted odds ratio comparisons from a logistic regression model using multiple
imputation for missing data values).

Ertugliflozin as add-on combination therapy with metformin and sulphonylurea
In an 18-week randomised, double-blind, multi-centre, placebo-controlled, glycaemic sub-study of VERTIS CV, a total of 330 patients with type 2 diabetes mellitus and established atherosclerotic cardiovascular disease with inadequate glycaemic control (HbA1c between 7% and 10.5%) with background therapy of metformin ≥1 500 mg/day and a sulphonylurea were randomised to ertugliflozin 5 mg, ertugliflozin 15 mg or placebo once daily (see Table 9).

Table 9: Results at Week 18 from an add-on study of ertugliflozin in combination with metformin and a sulphonylurea in patients with type 2 diabetes mellitus*

	Ertugliflozin 5 mg	**Ertugliflozin 15 mg**	**Placebo**
HbA1c (%)	**N = 100**	**N = 113**	**N = 117**
Baseline (mean)	8.4	8.3	8.3
Change from baseline (LS mean†)	-0.9	-1.0	-0.2
Difference from placebo (LS mean†, 95% CI)	-0.7‡ (-0.9, -0.4)	-0.8‡ (-1.0, -0.5)	
Patients [N (%)] with HbA1c <7%	37 (37.0)§	37 (32.7)§	15 (12.8)
Body weight (kg)	**N = 100**	**N = 113**	**N = 117**
Baseline (mean)	92.1	92.9	90.5
Change from baseline (LS mean†)	-2.0	-2.4	-0.5
Difference from placebo (LS mean†, 95% CI)	-1.6‡ (-2.3, -0.8)	-1.9‡ (-2.6, -1.2)	

* N includes all randomised, treated patients who had at least one measurement of the outcome variable.
† Least squares means adjusted for time, baseline eGFR, and the interaction of time by treatment.
‡ p< 0.001 compared to placebo.
§ p< 0.001 compared to placebo (based on adjusted odds ratio comparisons from a logistic regression model using multiple imputation for missing data values).

Moderate renal impairment
26 week placebo-controlled study
The efficacy of ertugliflozin was also assessed separately in a dedicated study of diabetic patients with moderate renal impairment (468 patients with eGFR ≥ 30 to < 60 mL/min/1.73 m^2).

The least square (LS) mean (95% CI) changes from baseline in HbA1c were -0.26 (-0.42, -0.11), -0.29 (-0.44, -0.14), and -0.41 (-0.56, -0.27) in the placebo, ertugliflozin 5 mg, and ertugliflozin 15 mg groups, respectively. The HbA1c reductions in the ertugliflozin arms were not significantly different from placebo. The pre-specified analysis of glycaemic efficacy was confounded by use of prohibited concomitant anti-hyperglycaemic medicinal products. In a subsequent analysis excluding those subjects who used the prohibited medicinal products, ertugliflozin 5 mg and 15 mg were associated with placebo-corrected reductions in HbA1c of -0.14 (-0.36, 0.08) and -0.33 (-0.55, -0.11).

18 week placebo-controlled study
In the VERTIS CV study, 1 776 patients with type 2 diabetes mellitus and established atherosclerotic cardiovascular disease had moderate renal impairment (eGFR ≥30 to <60 mL/min/1.73 m^2). Among them, 1 319 patients had an eGFR ≥45 to <60 mL/min/1.73 m^2, including 879 patients exposed to

ertugliflozin (see Table 10), and 457 patients had an eGFR ≥30 to <45 mL/min/1.73 m^2, including 299 patients exposed to ertugliflozin.

Table 10: Results at Week 18 of ertugliflozin in patients with type 2 diabetes mellitus and cardiovascular disease with baseline eGFR ≥45 to <60 mL/min/1.73 m^2*

	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Placebo
HbA1c (%)	**N = 465**	**N = 413**	**N = 439**
Baseline (mean)	8.2	8.2	8.2
Change from baseline (LS mean†)	-0.5	-0.6	-0.3
Difference from placebo (LS mean†, 95% CI)	-0.3‡ (-0.4, -0.1)	-0.3‡ (-0.4, -0.2)	
Body weight (kg)	**N = 465**	**N = 413**	**N = 439**
Baseline (mean)	92.1	92.5	92.3
Change from baseline (LS mean†)	-1.8	-1.9	-0.5
Difference from placebo (LS mean†, 95% CI)	-1.3‡ (-1.7, -0.9)	-1.4‡ (-1.8, -1.0)	

* N includes all randomised, treated patients who had at least one measurement of the outcome variable.
† Least squares means adjusted for time, baseline eGFR, and the interaction of time by treatment.
‡ p< 0.001 compared to placebo.

In patients with an eGFR ≥30 to <45 mL/min/1.73 m^2, the HbA1c reduction from baseline to Week 18 was significantly different between placebo and ertugliflozin 5 mg but was not significantly different between placebo and ertugliflozin 15 mg.

Fasting plasma glucose
In three placebo-controlled studies, ertugliflozin resulted in statistically significant reductions in fasting plasma glucose (FPG). For ertugliflozin 5 mg and 15 mg, respectively, the placebo-corrected reductions in FPG were 1.92 and 2.44 mmol/L as monotherapy, 1.48 and 2.12 mmol/L as add-on to metformin, and 1.40 and 1.74 mmol/L as add-on to metformin and sitagliptin.

The combination of ertugliflozin and sitagliptin resulted in significantly greater reductions in FPG compared to sitagliptin or ertugliflozin alone or placebo. The combination of ertugliflozin 5 or 15 mg and sitagliptin resulted in incremental FPG reductions of 0.46 to 0.65 mmol/L compared to the ertugliflozin alone or 1.02 to 1.28 mmol/L compared to sitagliptin alone. The placebo-corrected reductions of ertugliflozin 5 or 15 mg in combination with sitagliptin were 2.16 and 2.56 mmol/L.

Efficacy in patients with baseline HbA1c ≥ 8%
In the monotherapy study conducted on a background of diet and exercise in patients with baseline HbA1c from 7-10.5%, the subgroup of patients in the study with a baseline HbA1c ≥ 8% had placebo-corrected reductions in HbA1c of 1.11% and 1.52% with ertugliflozin 5 or 15 mg, respectively.

In the study of ertugliflozin added-on to metformin in patients with baseline HbA1c from 7-10.5%, the placebo-corrected reductions in HbA1c for the subgroup of patients in the study with baseline HbA1c ≥ 9% were 1.31% and 1.43% with ertugliflozin 5 and 15 mg, respectively.

In the study of patients inadequately controlled on metformin with baseline HbA1c from 7.5-11%, among the subgroup of patients with a baseline HbA1c ≥ 10%, the combination of ertugliflozin 5 mg or 15 mg with sitagliptin resulted in reductions of HbA1c of 2.35% and 2.66% compared to 2.10%, 1.30%, and 1.82% for ertugliflozin 5 mg, ertugliflozin 15 mg and sitagliptin alone, respectively.

Post-prandial glucose
In the monotherapy study, ertugliflozin 5 and 15 mg resulted in statistically significant placebo-corrected reductions in 2-hour post-prandial glucose (PPG) of 3.83 and 3.74 mmol/L.

Blood pressure
In three 26-week, placebo-controlled studies, ertugliflozin reduced systolic blood pressure (SBP). For ertugliflozin 5 mg and 15 mg, the statistically significant placebo-corrected reductions in SBP ranged from 2.9 mmHg to 3.7 mmHg and 1.7 mmHg to 4.5 mmHg, respectively.

In a 52-week, active-controlled study versus glimepiride, reductions from baseline in SBP were 2.2 mmHg and 3.8 mmHg for ertugliflozin 5 mg and 15 mg respectively, while subjects treated with glimepiride had an increase in SBP from baseline of 1.0 mmHg.

Subgroup analysis
In patients with type 2 diabetes treated with ertugliflozin, clinically meaningful reductions in HbA1c were observed in subgroups defined by age, sex, race, ethnicity, geographic region, baseline body mass index (BMI), baseline HbA1c, and duration of type 2 diabetes mellitus.

Cardiovascular outcomes
The effect of ertugliflozin on cardiovascular risk in adult patients with type 2 diabetes mellitus and established atherosclerotic cardiovascular disease was evaluated in the VERTIS CV study, a multi-centre, multi-national, randomised, double-blind, placebo-controlled, event-driven trial. The study compared the risk of experiencing a major adverse cardiovascular event (MACE) between ertugliflozin and placebo when these were added to and used concomitantly with standard of care treatments for diabetes and atherosclerotic cardiovascular disease.

A total of 8 246 patients were randomised (placebo N=2 747, ertugliflozin 5 mg N=2 752, ertugliflozin 15 mg N=2 747) and followed for a median of 3 years. The mean age was 64 years and approximately 70% were male.

All patients in the study had inadequately controlled type 2 diabetes mellitus at baseline (HbA1c greater than or equal to 7%). The mean duration of type 2 diabetes mellitus was 13 years, the mean HbA1c at baseline was 8.2% and the mean eGFR was 76 mL/min/1.73 m^2. At baseline, patients were treated with one (32%) or more (67%) antidiabetic medicinal products including metformin (76%), insulin (47%), sulphonylureas (41%), dipeptidyl peptidase-4 (DPP-4) inhibitors (11%) and glucagon-like peptide-1 (GLP-1) receptor agonists (3%).

Almost all patients (99%) had established atherosclerotic cardiovascular disease at baseline. Approximately 24% patients had a history of heart failure. The primary endpoint in VERTIS CV was the time to first occurrence of MACE (cardiovascular death, non-fatal myocardial infarction (MI) or non-fatal stroke).

Ertugliflozin demonstrated non-inferiority versus placebo for MACE (see Table 11). Results for the individual 5 mg and 15 mg doses were consistent with results for the combined dose groups.

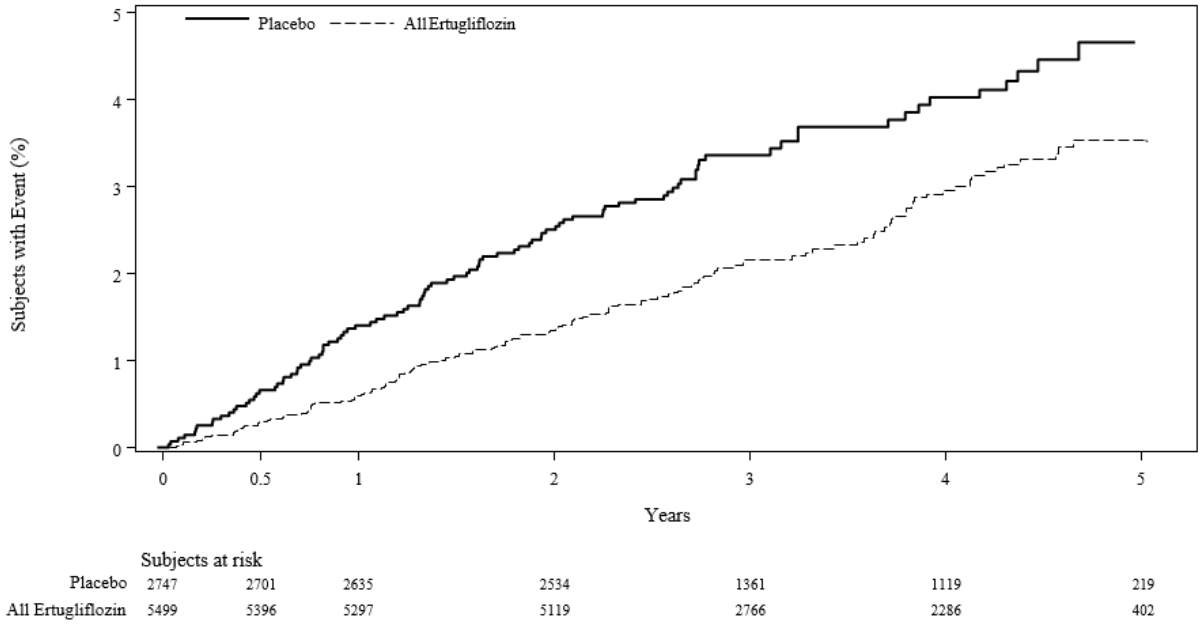
In patients treated with ertugliflozin, the rate of hospitalisation for heart failure was lower than in patients treated with placebo (see Table 11 and Figure 1).

Table 11: Analysis of MACE and its components and hospitalisation for heart failure from the VERTIS CV study*

Endpoint†	Placebo (N=2 747)		Ertugliflozin (N=5 499)		Hazard ratio vs placebo (CI)‡
	N (%)	Event rate (per 100 person-years)	N (%)	Event rate (per 100 person-years)	
MACE (CV death, non-fatal MI, or non-fatal stroke)	327 (11.9)	4.0	653 (11.9)	3.9	0.97 (0.85, 1.11)
Non-fatal MI	148 (5.4)	1.6	310 (5.6)	1.7	1.04 (0.86, 1.27)
Non-fatal stroke	78 (2.8)	0.8	157 (2.9)	0.8	1.00 (0.76, 1.32)
CV death	184 (6.7)	1.9	341 (6.2)	1.8	0.92 (0.77, 1.11)
Hospitalisation for heart failure#	99 (3.6)	1.1	139 (2.5)	0.7	0.70 (0.54, 0.90)

N=Number of patients, CI=Confidence interval, CV=Cardiovascular, MI=Myocardial infarction.
* Intent-to-treat analysis set.
† MACE was evaluated in subjects who took at least one dose of study medication and, for subjects who discontinued study medication prior to the end of the study, events that occurred more than 365 days after the last dose of study medication were censored. Other endpoints were evaluated using all randomised subjects and events that occurred any time after the first dose of study medication until the last contact date. The total number of first events was analysed for each endpoint.
‡ For MACE a 95.6% CI is presented, for other endpoints a 95% CI is presented.
#Not evaluated for statistical significance as it was not a part of the prespecified sequential testing procedure.

Figure 1: Time to first occurrence of hospitalisation for heart failure



Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with ertugliflozin in one or more subsets of the paediatric population in type 2 diabetes mellitus (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

General introduction

The pharmacokinetics of ertugliflozin are similar in healthy subjects and patients with type 2 diabetes. The steady state mean plasma AUC and C_{max} were 398 ng·hr/mL and 81 ng/mL, respectively, with 5 mg ertugliflozin once daily treatment, and 1 193 ng·hr/mL and 268 ng/mL, respectively, with 15 mg ertugliflozin once daily treatment. Steady-state is reached after 4 to 6 days of once-daily dosing with ertugliflozin. Ertugliflozin does not exhibit time-dependent pharmacokinetics and accumulates in plasma up to 10-40% following multiple dosing.

Absorption

Following single-dose oral administration of 5 mg and 15 mg of ertugliflozin, peak plasma concentrations (median time to maximum plasma concentration [T_{max}]) of ertugliflozin occur at 1 hour post-dose under fasted conditions. Plasma C_{max} and AUC of ertugliflozin increase in a dose-proportional manner following single doses from 0.5 mg to 300 mg and following multiple doses from 1 mg to 100 mg. The absolute oral bioavailability of ertugliflozin following administration of a 15 mg dose is approximately 100%.

Administration of ertugliflozin with a high-fat and high-calorie meal decreases ertugliflozin C_{max} by 29% and prolongs T_{max} by 1 hour but does not alter AUC as compared with the fasted state. The observed effect of food on ertugliflozin pharmacokinetics is not considered clinically relevant, and ertugliflozin may be administered with or without food. In phase 3 clinical trials, ertugliflozin was administered without regard to meals.

Ertugliflozin is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) transporters.

Distribution

The mean steady-state volume of distribution of ertugliflozin following an intravenous dose is 86 L. Plasma protein binding of ertugliflozin is 93.6% and is independent of ertugliflozin plasma concentrations. Plasma protein binding is not meaningfully altered in patients with renal or hepatic impairment. The blood-to-plasma concentration ratio of ertugliflozin is 0.66.

Ertugliflozin is not a substrate of organic anion transporters (OAT1, OAT3), organic cation transporters (OCT1, OCT2), or organic anion transporting polypeptides (OATP1B1, OATP1B3) *in vitro.*

Biotransformation

Metabolism is the primary clearance mechanism for ertugliflozin. The major metabolic pathway for ertugliflozin is UGT1A9 and UGT2B7-mediated O-glucuronidation to two glucuronides that are pharmacologically inactive at clinically relevant concentrations. CYP-mediated (oxidative) metabolism of ertugliflozin is minimal (12%).

Elimination

The mean systemic plasma clearance following an intravenous 100 µg dose was 11 L/hr. The mean elimination half-life in type 2 diabetic patients with normal renal function was estimated to be

17 hours based on the population pharmacokinetic analysis. Following administration of an oral [^{14}C]-ertugliflozin solution to healthy subjects, approximately 41% and 50% of the drug-related radioactivity was eliminated in faeces and urine, respectively. Only 1.5% of the administered dose was excreted as unchanged ertugliflozin in urine and 34% as unchanged ertugliflozin in faeces, which is likely due to biliary excretion of glucuronide metabolites and subsequent hydrolysis to parent.

Special populations

Renal impairment
In a phase 1 clinical pharmacology study in patients with type 2 diabetes and mild, moderate, or severe renal impairment (as determined by eGFR), following a single-dose administration of 15 mg ertugliflozin, the mean increases in AUC of ertugliflozin were ≤ 1.7-fold, compared to subjects with normal renal function. These increases in ertugliflozin AUC are not considered clinically relevant. There were no clinically meaningful differences in the ertugliflozin C_{max} values among the different renal function groups. The 24-hour urinary glucose excretion declined with increasing severity of renal impairment (see section 4.4). The plasma protein binding of ertugliflozin was unaffected in patients with renal impairment.

Hepatic impairment
Moderate hepatic impairment (based on the Child-Pugh classification) did not result in an increase in exposure of ertugliflozin. The AUC of ertugliflozin decreased by approximately 13%, and C_{max} decreased by approximately 21% compared to subjects with normal hepatic function. This decrease in ertugliflozin exposure is not considered clinically meaningful. There is no clinical experience in patients with Child-Pugh class C (severe) hepatic impairment. The plasma protein binding of ertugliflozin was unaffected in patients with moderate hepatic impairment.

Paediatric population
No studies with ertugliflozin have been performed in paediatric patients.

Effects of age, body weight, gender, and race
Based on a population pharmacokinetic analysis, age, body weight, gender, and race do not have a clinically meaningful effect on the pharmacokinetics of ertugliflozin.

Drug interactions

In vitro assessment of ertugliflozin
In *in vitro* studies, ertugliflozin and ertugliflozin glucuronides did not inhibit or inactivate CYPs 1A2, 2C9, 2C19, 2C8, 2B6, 2D6, or 3A4, and did not induce CYPs 1A2, 2B6, or 3A4. Ertugliflozin and ertugliflozin glucuronides did not inhibit the activity of UGTs 1A6, 1A9 or 2B7 *in vitro*. Ertugliflozin was a weak inhibitor of UGTs 1A1 and 1A4 *in vitro* at higher concentrations that are not clinically relevant. Ertugliflozin glucuronides had no effect on these isoforms. Overall, ertugliflozin is unlikely to affect the pharmacokinetics of concurrently administered medicinal products eliminated by these enzymes.

Ertugliflozin or ertugliflozin glucuronides do not meaningfully inhibit P-gp, OCT2, OAT1, or OAT3 transporters or transporting polypeptides OATP1B1 and OATP1B3 at clinically relevant concentrations *in vitro*. Overall, ertugliflozin is unlikely to affect the pharmacokinetics of concurrently administered medicinal products that are substrates of these transporters.

5.3 Preclinical safety data

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

General toxicity

Repeat-dose oral toxicity studies were conducted in mice, rats, and dogs for up to 13, 26, and 39 weeks, respectively. Signs of toxicity that were considered adverse were generally observed at exposures greater than or equal to 77 times the human unbound exposure (AUC) at the maximum recommended human dose (MRHD) of 15 mg/day. Most toxicity was consistent with pharmacology related to urinary glucose loss and included decreased body weight and body fat, increased food consumption, diarrhoea, dehydration, decreased serum glucose and increases in other serum parameters reflective of increased protein metabolism, gluconeogenesis and electrolyte imbalances, and urinary changes such as polyuria, glucosuria, and calciuria. Microscopic changes related to glucosuria and/or calciuria observed only in rodents included dilatation of renal tubules, hypertrophy of zona glomerulosa in adrenal glands (rats), and increased trabecular bone (rats). Except for emesis, there were no adverse toxicity findings in dogs at 379 times the human unbound exposure (AUC) at the MRHD of 15 mg/day.

Carcinogenesis

In the 2-year mouse carcinogenicity study, ertugliflozin was administered by oral gavage at doses of 5, 15, and 40 mg/kg/day. There were no ertugliflozin-related neoplastic findings at doses up to 40 mg/kg/day (approximately 41 times human unbound exposure at the MRHD of 15 mg/day based on AUC). In the 2-year rat carcinogenicity study, ertugliflozin was administered by oral gavage at doses of 1.5, 5, and 15 mg/kg/day. Ertugliflozin-related neoplastic findings included an increased incidence of benign adrenal medullary pheochromocytoma in male rats at 15 mg/kg/day. This finding was attributed to carbohydrate malabsorption leading to altered calcium homeostasis and was not considered relevant to human risk. The no-observed-effect level (NOEL) for neoplasia was 5 mg/kg/day (approximately 16 times human unbound exposure at the MRHD of 15 mg/day).

Mutagenesis

Ertugliflozin was not mutagenic or clastogenic with or without metabolic activation in the microbial reverse mutation, *in vitro* cytogenetic (human lymphocytes), and *in vivo* rat micronucleus assays.

Reproductive toxicology

In the rat fertility and embryonic development study, male and female rats were administered ertugliflozin at 5, 25, and 250 mg/kg/day. No effects on fertility were observed at 250 mg/kg/day (approximately 386 times human unbound exposure at the MRHD of 15 mg/day based on AUC comparisons). Ertugliflozin did not adversely affect developmental outcomes in rats and rabbits at maternal exposures that were 239 and 1 069 times, respectively, the human exposure at the maximum clinical dose of 15 mg/day, based on AUC. At a maternally toxic dose in rats (250 mg/kg/day), lower foetal viability and a higher incidence of a visceral malformation were observed at maternal exposure that was 510 times the maximum clinical dose of 15 mg/day.

In the pre- and postnatal development study, decreased postnatal growth and development were observed in rats administered ertugliflozin gestation day 6 through lactation day 21 at $\geq$ 100 mg/kg/day (estimated 239 times the human exposure at the maximum clinical dose of 15 mg/day, based on AUC). Sexual maturation was delayed in both sexes at 250 mg/kg/day (estimated 620 times the MRHD at 15 mg/day, based on AUC).

When ertugliflozin was administered to juvenile rats from postnatal day (PND) 21 to PND 90, a period of renal development corresponding to the late second and third trimesters of human pregnancy, increased kidney weights, dilatation of the renal pelvis and tubules, and renal tubular mineralisation were seen at an exposure 13 times the maximum clinical dose of 15 mg/day, based on AUC. Effects on bone (shorter femur length, increased trabecular bone in the femur) as well as effects of delayed puberty were observed at an exposure 817 times the MRHD of 15 mg/day based on AUC. The effects on kidney and bone did not fully reverse after the 1-month recovery period.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Microcrystalline cellulose (E460)
Lactose monohydrate
Sodium starch glycolate (Type A)
Magnesium stearate (E470b)

Film coating

Hypromellose 2910/6 (E464)
Lactose monohydrate
Macrogol 3350 (E1521)
Triacetin (E1518)
Titanium dioxide (E171)
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 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/PVC/PA/Alu blisters**.**
Packs of 14, 28, 30, 84, 90 and 98 film-coated tablets in non-perforated blisters.
Packs of 30x1 film-coated tablets in perforated unit dose blisters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

Steglatro 5 mg film-coated tablets

EU/1/18/1267/001
EU/1/18/1267/002
EU/1/18/1267/003
EU/1/18/1267/004
EU/1/18/1267/005
EU/1/18/1267/006
EU/1/18/1267/013

Steglatro 15 mg film-coated tablets

EU/1/18/1267/007
EU/1/18/1267/008
EU/1/18/1267/009
EU/1/18/1267/010
EU/1/18/1267/011
EU/1/18/1267/012
EU/1/18/1267/014

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 March 2018
Date of latest renewal: 15 November 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://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
Organon Heist bv
Industriepark 30
2220 Heist-op-den-Berg
Belgium

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
Netherlands

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 (PSURs)**

The requirements for submission of PSURs 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 marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

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

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR STEGLATRO 5 mg

1. NAME OF THE MEDICINAL PRODUCT

Steglatro 5 mg film-coated tablets
ertugliflozin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains ertugliflozin L-pyroglutamic acid, equivalent to 5 mg ertugliflozin.

3. LIST OF EXCIPIENTS

Contains lactose. See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

film-coated tablet

14 film-coated tablets
28 film-coated tablets
30 film-coated tablets
30x1 film-coated tablets
84 film-coated tablets
90 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

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1267/001 (14 film-coated tablets)
EU/1/18/1267/002 (28 film-coated tablets)
EU/1/18/1267/003 (30 film-coated tablets)
EU/1/18/1267/004 (30x1 film-coated tablets)
EU/1/18/1267/005 (84 film-coated tablets)
EU/1/18/1267/006 (90 film-coated tablets)
EU/1/18/1267/013 (98 film-coated tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Steglatro 5 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

BLISTER FOR STEGLATRO 5 mg

1. NAME OF THE MEDICINAL PRODUCT

Steglatro 5 mg tablets
ertugliflozin

2. NAME OF THE MARKETING AUTHORISATION HOLDER

MSD

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR STEGLATRO 15 mg

1. NAME OF THE MEDICINAL PRODUCT

Steglatro 15 mg film-coated tablets
ertugliflozin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains ertugliflozin L-pyroglutamic acid, equivalent to 15 mg ertugliflozin.

3. LIST OF EXCIPIENTS

Contains lactose. See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

film-coated tablet

14 film-coated tablets
28 film-coated tablets
30 film-coated tablets
30x1 film-coated tablets
84 film-coated tablets
90 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

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1267/007 (14 film-coated tablets)
EU/1/18/1267/008 (28 film-coated tablets)
EU/1/18/1267/009 (30 film-coated tablets)
EU/1/18/1267/010 (30x1 film-coated tablets)
EU/1/18/1267/011 (84 film-coated tablets)
EU/1/18/1267/012 (90 film-coated tablets)
EU/1/18/1267/014 (98 film-coated tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Steglatro 15 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

BLISTER FOR STEGLATRO 15 mg

1. NAME OF THE MEDICINAL PRODUCT

Steglatro 15 mg tablets
ertugliflozin

2. NAME OF THE MARKETING AUTHORISATION HOLDER

MSD

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Steglatro 5 mg film-coated tablets
Steglatro 15 mg film-coated tablets
ertugliflozin

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 or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Steglatro is and what it is used for

What Steglatro is
Steglatro contains the active substance ertugliflozin.

Steglatro is a member of a group of medicines called sodium glucose co-transporter-2 (SGLT2) inhibitors.

What Steglatro is used for
- Steglatro lowers blood sugar levels in adult patients (aged 18 years and older) with type 2 diabetes.
- It can also help prevent heart failure in patients with type 2 diabetes.
- Steglatro can be used alone or with some other medicines that lower blood sugar.
- You need to keep following your food and exercise plan while taking Steglatro.

How Steglatro works
Ertugliflozin works by blocking the SGLT2 protein in your kidneys. This causes blood sugar to be removed in your urine.

What is type 2 diabetes?
Type 2 diabetes is a condition in which your body does not make enough insulin or the insulin that your body produces does not work as well as it should. This leads to a high level of sugar in your blood. When this happens, this can lead to serious medical problems like heart disease, kidney disease, blindness and poor circulation.

2. What you need to know before you take Steglatro

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

Warnings and precautions
Talk to your doctor, pharmacist, or nurse before and while taking Steglatro if you:

- have kidney problems. Your doctor may do blood tests to check how well your kidneys are working.
- have or have had urinary tract infections.
- have or have had yeast infections of the vagina or penis.
- have type 1 diabetes. Steglatro should not be used to treat this condition as it may increase the risk of diabetic ketoacidosis in these patients.
- take other diabetes medicines; you are more likely to get low blood sugar with certain medicines.
- might be at risk of dehydration (for example, if you are taking medicines that increase urine production [diuretics] or lower blood pressure or if you are over 65 years old). Ask about ways to prevent dehydration.
- 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.

It is important to check your feet regularly and adhere to any other advice regarding foot care given by your healthcare professional.

Talk to your doctor immediately if you develop a combination of symptoms of pain, tenderness, redness, or swelling of the genitals or the area between the genitals and the anus with fever or feeling generally unwell. These symptoms could be a sign of a rare but serious or even life-threatening infection, called necrotising fasciitis of the perineum or Fournier's gangrene which destroys the tissue under the skin. Fournier's gangrene has to be treated immediately.

When this medicine is used in combination with insulin or medicines that increase insulin release from the pancreas, low blood sugar (hypoglycaemia) can occur. Your doctor may reduce the dose of your insulin or other medicine.

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

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

Children and adolescents
Children and adolescents below 18 years should not take this medicine. It is not known if this medicine is safe and effective when used in children and adolescents under 18 years of age.

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

In particular, tell your doctor:

- if you are taking medicines which increase urine production (diuretics).
- if you are taking other medicines that lower the sugar in your blood, such as insulin or medicines that increase insulin release from the pancreas.

If any of the above apply to you (or you are not sure), tell your doctor.

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.

It is not known if Steglatro can harm your unborn baby. If you are pregnant, talk with your doctor about the best way to control your blood sugar while you are pregnant. Do not use Steglatro if you are pregnant.

It is not known if Steglatro passes into breast milk. Talk with your doctor about the best way to feed your baby if you take Steglatro. Do not use Steglatro if you are breast-feeding.

Driving and using machines
This medicine has no or negligible influence on the ability to drive and use machines. However, taking this medicine in combination with insulin or medicines that increase insulin release from the pancreas can cause blood sugar levels to drop too low (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 while taking Steglatro.

Steglatro contains lactose
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

Steglatro contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

3. How to take Steglatro

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

How much to take
- The starting dose of Steglatro is one 5 mg tablet each day. Your doctor will decide whether to increase your dose to 15 mg.
- Your doctor will prescribe the right dose for you. Do not change your dose unless your doctor has told you to.

Taking this medicine
- Swallow the tablet; if you have difficulties with swallowing, the tablet can be broken or crushed.
- Take one tablet every morning. Try to take it at the same time; this will help you remember to take it.
- You can take your tablet with or without food.
- You need to keep following your food and exercise plan while taking Steglatro.

If you take more Steglatro than you should
If you take too much Steglatro, talk to a doctor or pharmacist straight away.

If you forget to take Steglatro
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 Steglatro 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 (two doses on the same day) to make up for a forgotten dose.

If you stop taking Steglatro
Do not stop taking this medicine without talking to your doctor. Your blood sugar levels may increase if you stop the 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.

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

Diabetic ketoacidosis (rare, may affect up to 1 in 1 000 people)
These are the signs of diabetic ketoacidosis (see also section "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 Steglatro.

Necrotising fasciitis of the perineum or Fournier's gangrene (not known, cannot be estimated from the available data)
A serious soft tissue infection of the genitals or the area between the genitals and the anus (see section "Warnings and precautions" for symptoms).

If you notice any of the side effects above, contact a doctor or the nearest hospital straight away.

Contact your doctor as soon as possible if you notice the following side effects:

Urinary tract infection (very common, may affect more than 1 in 10 people)
The signs of urinary tract infection are:
- burning sensation when passing urine
- urine that appears cloudy
- pain in the pelvis or mid-back (when kidneys are infected)

Although uncommon, if you have fever or see blood in your urine, tell your doctor immediately.

Dehydration (losing too much water from your body; common, may affect up to 1 in 10 people)
Symptoms of dehydration include:
- dry mouth
- feeling dizzy, light-headed, or weak, especially when you stand up
- fainting

You may be more likely to get dehydrated if you:
- have kidney problems
- take medicines that increase your urine production (diuretics) or lower blood pressure

- are 65 years or older

Low blood sugar (hypoglycaemia; common)
Your doctor will tell you how to treat low blood sugar and what to do if you have any of the symptoms or signs below. The doctor may lower the dose of your insulin or other diabetes medicine.

Signs and symptoms of low blood sugar may include:
- headache
- drowsiness
- irritability
- hunger
- dizziness
- confusion
- sweating
- feeling jittery
- weakness
- fast heartbeat

If you notice any of the side effects above, contact your doctor as soon as possible.

Other side effects when taking Steglatro:
Very common
- vaginal yeast infection (thrush)

Common
- yeast infections of the penis
- changes in urination, including urgent need to urinate more often, in larger amounts, or at night
- thirst
- vaginal itching
- blood tests may show changes in the amount of urea in your blood
- blood tests may show changes in the amount of total and "bad" cholesterol (called low density lipoprotein (LDL)-cholesterol - a type of fat in your blood)
- blood tests may show changes in the amount of red blood cells in your blood (called haemoglobin)

Uncommon (may affect up to 1 in 100 people)
- blood tests may show changes related to kidney function (such as 'creatinine')

Not known
- rash

Reporting of side effects
If you get any side effects, talk to your doctor or, 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 Steglatro

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 and the 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 use this medicine if the packaging is damaged or shows signs of tampering.

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

6. Contents of the pack and other information

What Steglatro contains

- The active substance is ertugliflozin.
  - Each Steglatro 5 mg film-coated tablet contains ertugliflozin L-pyroglutamic acid, equivalent to 5 mg ertugliflozin.
  - Each Steglatro 15 mg film-coated tablet contains ertugliflozin L-pyroglutamic acid, equivalent to 15 mg ertugliflozin.
- The other ingredients are:
  - Tablet core: microcrystalline cellulose (E460), lactose monohydrate (see section 2), sodium starch glycolate (Type A), magnesium stearate (E470b).
  - Film coating: hypromellose 2910/6 (E464), lactose monohydrate (see section 2), macrogol 3350 (E1521), triacetin (E1518), titanium dioxide (E171), iron oxide red (E172).

What Steglatro looks like and contents of the pack

- Steglatro 5 mg film-coated tablets (tablets) are pink, 6.4 x 6.6 mm, triangular-shaped, with "701" on one side and plain on the other side.
- Steglatro 15 mg film-coated tablets (tablets) are red, 9.0 x 9.4 mm, triangular-shaped, with "702" on one side and plain on the other side.

Steglatro is available in Alu/PVC/PA/Alu blisters. The pack sizes are 14, 28, 30, 84, 90 and 98 film-coated tablets in non-perforated blisters and 30x1 film-coated tablets in perforated unit dose blisters.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Merck Sharp & Dohme B.V.
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The Netherlands

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Industriepark 30
2220 Heist-op-den-Berg
Belgium

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
Netherlands

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

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This leaflet was last revised in

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