ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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

1. NAME OF THE MEDICINAL PRODUCT

Segluromet 2.5 mg/850 mg film-coated tablets
Segluromet 2.5 mg/1,000 mg film-coated tablets
Segluromet 7.5 mg/850 mg film-coated tablets
Segluromet 7.5 mg/1,000 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Segluromet 2.5 mg/850 mg film-coated tablets
Each tablet contains 2.5 mg ertugliflozin (as ertugliflozin L-pyroglutamic acid) and 850 mg of metformin hydrochloride.

Segluromet 2.5 mg/1,000 mg film-coated tablets
Each tablet contains 2.5 mg ertugliflozin (as ertugliflozin L-pyroglutamic acid) and 1,000 mg of metformin hydrochloride.

Segluromet 7.5 mg/850 mg film-coated tablets
Each tablet contains 7.5 mg ertugliflozin (as ertugliflozin L-pyroglutamic acid) and 850 mg metformin hydrochloride.

Segluromet 7.5 mg/1,000 mg film-coated tablets
Each tablet contains 7.5 mg ertugliflozin (as ertugliflozin L-pyroglutamic acid) and 1,000 mg metformin hydrochloride.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Segluromet 2.5 mg/850 mg film-coated tablets
Beige, 18 x 10 mm oval, film-coated tablet debossed with “2.5/850” on one side and plain on the other side.

Segluromet 2.5 mg/1,000 mg film-coated tablets
Pink, 19.1 x 10.6 mm oval, film-coated tablet debossed with “2.5/1000” on one side and plain on the other side.

Segluromet 7.5 mg/850 mg film-coated tablets
Dark brown, 18 x 10 mm oval, film-coated tablet debossed with “7.5/850” on one side and plain on the other side.

Segluromet 7.5 mg/1,000 mg film-coated tablets
Red, 19.1 x 10.6 mm oval, film-coated tablet debossed with “7.5/1000” on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Segluromet is indicated in adults for the treatment of type 2 diabetes mellitus as an adjunct to diet and exercise:

- in patients insufficiently controlled on their maximally tolerated dose of metformin alone
- in combination with other medicinal products for the treatment of diabetes in patients insufficiently controlled with metformin and these products
- in patients already being treated with the combination of ertugliflozin and metformin as separate tablets.

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

4.2 Posology and method of administration

Posology
The recommended dose is one tablet twice daily. The dosage should be individualised on the basis of the patient's current regimen, effectiveness, and tolerability using the recommended daily dose of 5 mg or 15 mg of ertugliflozin, while not exceeding the maximum recommended daily dose of metformin.

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

If a dose is missed, it should be taken as soon as the patient remembers. Patients should not take two doses of Segluromet at the same time.

Adults with normal renal function (glomerular filtration rate [GFR] ≥ 90 mL/min)

For patients insufficiently controlled on metformin (either alone or in combination with other medicinal products for the treatment of diabetes)
The recommended starting dose of Segluromet should provide ertugliflozin 2.5 mg twice daily (5 mg daily dose) and the dose of metformin similar to the dose already being taken. In patients tolerating a total daily dose of ertugliflozin 5 mg, the dose can be increased to a total daily dose of ertugliflozin 15 mg if additional glycaemic control is needed.

For patients switching from separate tablets of ertugliflozin and metformin
Patients switching from separate tablets of ertugliflozin (5 mg or 15 mg total daily dose) and metformin to Segluromet should receive the same daily dose of ertugliflozin and metformin already being taken or the nearest therapeutically appropriate dose of metformin.

When Segluromet 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).

Special populations

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

Initiation of this medicinal product is not recommended in patients with a GFR less than 45 mL/min (see section 4.4).

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 antihyperglycaemic agents should be considered (see section 4.4).

The maximum daily dose of metformin should preferably be divided into 2-3 daily doses. Factors that may increase the risk of lactic acidosis (see section 4.4) should be reviewed before considering initiation of metformin in patients with GFR < 60 mL/min.

If no adequate strength of Segluromet is available, individual monocomponents should be used instead of the fixed-dose combination.

GFR mL/min	**Metformin**	**Ertugliflozin**
60-89	*Maximum daily dose is 3,000 mg.* *Dose reduction may be considered in relation to declining renal function.*	*Maximum daily dose is 15 mg.* *Initiate with 5 mg.* *Up-titrate to 15 mg, as needed for glycaemic control.*
45-59	*Maximum daily dose is 2,000 mg.* *The starting dose is at most half of the maximum dose.*	*Maximum daily dose is 15 mg.* *Initiate with 5 mg.* *Up-titrate to 15 mg, as needed for glycaemic control.*
30-44	*Maximum daily dose is 1,000 mg.* *The starting dose is at most half of the maximum dose.*	*Initiation is not recommended.*
< 30	*Metformin is contraindicated.*	*Not recommended.*

Hepatic impairment
Segluromet is contraindicated in patients with hepatic impairment (see sections 4.3 and 4.4).

Elderly (≥ 65 years old)
Elderly patients are more likely to have decreased renal function. Because renal function abnormalities can occur after initiating ertugliflozin, and metformin is known to be substantially excreted by the kidneys, Segluromet should be used with caution in the elderly. Regular assessment of renal function is necessary to aid in prevention of metformin-associated lactic acidosis, particularly in elderly patients (see section 4.4). 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 Segluromet in children under 18 years of age have not been established. No data are available.

Method of administration
Segluromet should be taken orally twice daily with meals to reduce the gastrointestinal adverse reactions associated with metformin. 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 substances or to any of the excipients listed in section 6.1;
- any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis [DKA]);
- diabetic pre coma;
- severe renal failure (GFR less than 30 mL/min), end-stage renal disease (ESRD), or patients on dialysis (see section 4.4);
- acute condition with the potential to alter renal function, such as:
  - dehydration,
  - severe infection,
  - shock;
- acute or chronic disease that may cause tissue hypoxia, such as:
  - cardiac or respiratory failure,
  - recent myocardial infarction,
  - shock;
- hepatic impairment;
- acute alcohol intoxication, alcoholism.

4.4 Special warnings and precautions for use

General
Segluromet should not be used in patients with type 1 diabetes mellitus.

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

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

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

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

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

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).

Segluromet should not be initiated in patients with a GFR below 45 mL/min. Segluromet should be discontinued when GFR is persistently below 45 mL/min.

GFR should be assessed before treatment initiation and regularly thereafter (see section 4.2). More frequent renal function monitoring is recommended in patients with a GFR below 60 mL/min. Metformin is contraindicated in patients with GFR < 30 mL/min and should be temporarily discontinued in the presence of conditions that alter renal function (see section 4.3).

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

Hypotension/Volume depletion
Ertugliflozin causes an osmotic diuresis, which may lead to intravascular volume contraction. Therefore, symptomatic hypotension may occur after initiating Segluromet (see section 4.8), particularly in patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2 or a 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 Segluromet, 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 Segluromet 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 diabetic ketoacidosis must be considered in the event of non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue, or sleepiness. Patients should be assessed for ketoacidosis immediately if these symptoms occur, regardless of blood glucose level.

In patients where DKA is suspected or diagnosed, treatment with Segluromet 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 Segluromet may be restarted when the ketone values are normal and the patient's condition has stabilised.

Before initiating Segluromet, 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 Segluromet in patients with type 1 diabetes have not been established and Segluromet 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% (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.

Hypoglycaemia with concomitant use of 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 Segluromet (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 uro-genital infection or perineal abscess may precede necrotising fasciitis. If Fournier's gangrene is suspected, Segluromet 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. The risk of metformin-associated lactic acidosis increases with the patient's age because elderly patients have a greater likelihood of having hepatic, renal, or cardiac impairment than 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). Assess renal function more frequently in elderly patients.

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

Urine laboratory assessments
Due to the mechanism of action of ertugliflozin, patients taking Segluromet 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 medicines containing an SGLT2 inhibitor. Alternative methods should be used to monitor glycaemic control.

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

Pharmacokinetic drug interaction studies with Segluromet have not been performed; however, such studies have been conducted with ertugliflozin and metformin, the individual active substances of Segluromet.

Ertugliflozin

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 Segluromet (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 rifampin (a UGT and CYP inducer) decreases ertugliflozin AUC and 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 OATP inhibition by ertugliflozin. These increases are not considered to be clinically meaningful.

Metformin
Concomitant use not recommended.

Alcohol
Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in cases of fasting, malnutrition or hepatic impairment.

Iodinated contrast agents
Segluromet must be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable (see sections 4.2 and 4.4).

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

Organic cation transporters (OCT)
Metformin is a substrate of both transporters OCT1 and OCT2.

Coadministration of metformin with
- Inhibitors of OCT1 (such as verapamil) may reduce efficacy of metformin.
- Inducers of OCT1 (such as rifampicin) may increase gastrointestinal absorption and efficacy of metformin.
- Inhibitors of OCT2 (such as cimetidine, dolutegravir, ranolazine, trimethoprim, vandetanib, isavuconazole) may decrease the renal elimination of metformin and thus lead to an increase in metformin plasma concentration.
- Inhibitors of both OCT1 and OCT2 (such as crizotinib, olaparib) may alter efficacy and renal elimination of metformin.

Caution is therefore advised, especially in patients with renal impairment, when these drugs are coadministered with metformin, as metformin plasma concentration may increase. If needed, dose adjustment of metformin may be considered as OCT inhibitors/inducers may alter the efficacy of metformin.

Glucocorticoids (given by systemic and local routes), beta 2 agonists, and diuretics have intrinsic hyperglycaemic activity. The patient should be informed and more frequent blood glucose monitoring performed, especially at the beginning of treatment with such medicinal products. If necessary, the dose of the antihyperglycaemic medicinal product should be adjusted during therapy with the other medicinal product and on its discontinuation.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no data from the use of Segluromet in pregnant women.

A limited amount of data suggests the use of metformin in pregnant women is not associated with an increased risk of congenital malformations. Animal studies with metformin do not indicate harmful effects with respect to pregnancy, embryonic or foetal development, parturition or post-natal development (see section 5.3).

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, Segluromet 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. Metformin is present in human breast milk. Ertugliflozin and metformin are present in the milk of lactating rats. Ertugliflozin caused effects in the offspring of lactating rats.

Pharmacologically mediated effects were observed in juvenile rats treated with ertugliflozin (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. Segluromet should not be used during breast-feeding.

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

4.7 Effects on ability to drive and use machines

Segluromet has no or negligible influence on the ability to drive and use machines. Patients should be alerted to the risk of hypoglycaemia when Segluromet 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

Ertugliflozin and metformin
The safety of concomitantly administered ertugliflozin and metformin has been evaluated in 1,083 patients with type 2 diabetes mellitus treated for 26 weeks in a pool of two placebo-controlled trials: as ertugliflozin add on therapy to metformin and as ertugliflozin add-on therapy to sitagliptin and metformin (see section 5.1). The incidence and type of adverse reactions in these two trials were similar to the adverse reactions seen with ertugliflozin. There were no additional adverse reactions identified in the pooling of these two placebo-controlled trials that included metformin relative to the three placebo-controlled studies with ertugliflozin (see below).

Ertugliflozin
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
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 vulvovaginal mycotic infection, and other female genital mycotic infections. Serious diabetic ketoacidosis occurred rarely. See "Description of selected adverse reactions" for frequencies and see section 4.4.

Tabulated list of adverse reactions

Adverse reactions listed below are classified according to frequency and system organ class (SOC). Frequency categories are defined according to the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data).

Table 1: Adverse reactions from placebo- and active comparator-controlled clinical trials and post-marketing experience

System Organ Class Frequency	**Adverse Reaction**
Infections and infestations	
Very common	Vulvovaginal mycotic infection and other female genital mycotic infections*,†,1 Urinary tract infections†,1
Common	Balanitis candida and other male genital mycotic infections*,†,1
Not known	Necrotising fasciitis of the perineum (Fournier's gangrene)*
Metabolism and nutrition disorders	
Common	Hypoglycaemia*,†,1
Rare	Diabetic ketoacidosis*,†,1
Very rare	Lactic acidosis*,2, Vitamin B_{12} deficiency‡,2
Nervous system disorders	
Common	Taste disturbance2
Vascular disorders	
Common	Volume depletion*,†,1
Gastrointestinal disorders	
Very common	Gastrointestinal symptoms§,2
Hepatobiliary disorders	
Very rare	Liver function test abnormal2, Hepatitis2
Skin and subcutaneous tissue disorders	
Very rare	Erythema2, Pruritus2, Urticaria2
Renal and urinary disorders	
Common	Increased urination¶,1
Uncommon	Dysuria1, Blood creatinine increased/Glomerular filtration rate decreased†,1
Reproductive system and breast disorders	
Common	Vulvovaginal pruritus1
General disorders and administration site conditions	
Common	Thirst#,1
Investigations	
Common	Serum lipids changedÞ,1, Haemoglobin increasedß,1, BUN increasedà,1

1 Adverse reaction with ertugliflozin.

2 Adverse reaction with metformin.

* See section 4.4.
† See subsections below for additional information.
‡ Long-term treatment with metformin has been associated with a decrease in vitamin B_{12} absorption, which may very rarely result in clinically significant vitamin B_{12} deficiency (e.g., megaloblastic anaemia).
§ Gastrointestinal symptoms such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite occur most frequently during initiation of therapy and resolve spontaneously in most cases.
¶ Includes: pollakiuria, micturition urgency, polyuria, urine output increased, and nocturia.
# Includes: thirst and polydipsia.
Þ Mean percent changes from baseline for ertugliflozin 5 mg and 15 mg versus placebo, respectively, were LDL-C 5.8% and 8.4% versus 3.2%; total cholesterol 2.8% and 5.7% versus 1.1%; however, 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%.
ß 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%).
à The proportion of subjects having any occurrence of BUN values ≥ 50% increase and value >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%).

Description of selected adverse reactions

Volume depletion (ertugliflozin)
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 (ertugliflozin)
In the pool of placebo-controlled studies, the incidence of documented hypoglycaemia was increased for ertugliflozin 5 mg and 15 mg (5.0% 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 20.0%, 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 medication, 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 (ertugliflozin)
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 (ertugliflozin)
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. Up to Week 260, continued treatment with ertugliflozin was associated with a slower decline in eGFR compared to placebo.

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%, 10.0% 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 (ertugliflozin)
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 3.0% 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 (ertugliflozin)
In VERTIS CV, urinary tract infections occurred in 12.2%, 12.0% 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 4.0% 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

In the event of an overdose with Segluromet, 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.

Ertugliflozin
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. Removal of ertugliflozin by haemodialysis has not been studied.

Metformin
Overdose of metformin hydrochloride has occurred, including ingestion of amounts greater than 50 g. Hypoglycaemia was reported in approximately 10% of cases, but no causal association with metformin hydrochloride has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases (see section 4.4). Lactic acidosis is a medical emergency and must be treated in a hospital. Metformin is dialysable with a clearance of up to 170 mL/min under good haemodynamic conditions. Therefore, haemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdose is suspected.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, combinations of oral blood glucose lowering drugs, ATC code: A10BD23.

Mechanism of action
Segluromet combines two antihyperglycaemic agents with complementary mechanisms of action to improve glycaemic control in patients with type 2 diabetes: ertugliflozin, a SGLT2 inhibitor, and metformin hydrochloride, a member of the biguanide class.

Ertugliflozin
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.

Metformin
Metformin is an antihyperglycaemic agent which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and post-prandial plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral antihyperglycaemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilisation. Unlike sulphonylureas, metformin does not produce hypoglycaemia in either patients with type 2 diabetes or normal subjects, except in special circumstances (see section 4.5), and does not cause hyperinsulinaemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

Pharmacodynamic effects

Ertugliflozin

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.

Glycaemic control

The glycaemic efficacy and safety of ertugliflozin in combination with metformin have been studied in 4 multi-centre, randomised, double-blind, placebo- and active comparator-controlled, Phase 3 clinical studies involving 3,643 patients with type 2 diabetes. Across the four studies, the racial distribution ranged from 66.2% to 80.3% White, 10.6% to 20.3% Asian, 1.9% to 10.3% Black, and 4.5% to 7.4% other. Hispanic or Latino patients comprised 15.6% to 34.5% of the population. The mean age of the patients across these four studies ranged from 55.1 to 59.1 years (range 21 years to 86 years); 15.6% to 29.9% of patients were ≥65 years of age and 0.6% to 3.8% were ≥75 years of age.

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 2).

Table 2: 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 antihyperglycaemic medication, baseline eGFR menopausal status randomisation stratum 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).

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 3).

Table 3: 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	-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)
Difference from Ertugliflozin 5 mg				-0.5‡ (-0.6, -0.3)	
Difference from 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 4).

Table 4: 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 antihyperglycaemic medication, 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).

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 5).

Table 5: 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 antihyperglycaemic medication, 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.

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 (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 6).

Table 6: 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 7).

Table 7: 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).

Fasting plasma glucose
In three placebo-controlled studies, ertugliflozin resulted in statistically significant reductions in 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 on a background of metformin resulted in significantly greater reductions in FPG compared to sitagliptin or ertugliflozin alone. The combination of ertugliflozin 5 or 15 mg and sitagliptin resulted in incremental FPG reductions of 0.46 and 0.65 mmol/L compared to the ertugliflozin alone or 1.02 and 1.28 mmol/L compared to sitagliptin alone, respectively.

Efficacy in patients with baseline HbA1c ≥ 9%
In the study of ertugliflozin in combination with metformin in patients with baseline HbA1c from 7.0-10.5%, 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 mg and 15 mg, respectively.

In the study of patients inadequately controlled on metformin with baseline HbA1c from 7.5-11.0%, 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%, respectively, compared to 2.10%, 1.30%, and 1.82% for ertugliflozin 5 mg, ertugliflozin 15 mg, and sitagliptin alone, respectively.

Blood pressure
As add-on to metformin, ertugliflozin 5 mg and 15 mg resulted in statistically significant placebo-corrected reductions in SBP of 3.7 mmHg and 4.5 mmHg, respectively. As add-on to metformin and sitagliptin, ertugliflozin 5 mg and 15 mg resulted in statistically significant placebo-corrected reductions in SBP of 2.9 mmHg and 3.9 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 in combination with metformin, clinically meaningful reductions in HbA1c were observed in subgroups defined by age, sex, race, ethnicity, geographic region, baseline 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 medications including metformin (76%), insulin (47%), sulphonylureas (41%), DPP-4 inhibitors (11%) and 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 8). Results for the individual 5 mg and 15 mg doses were consistent with results for the combined dose groups.

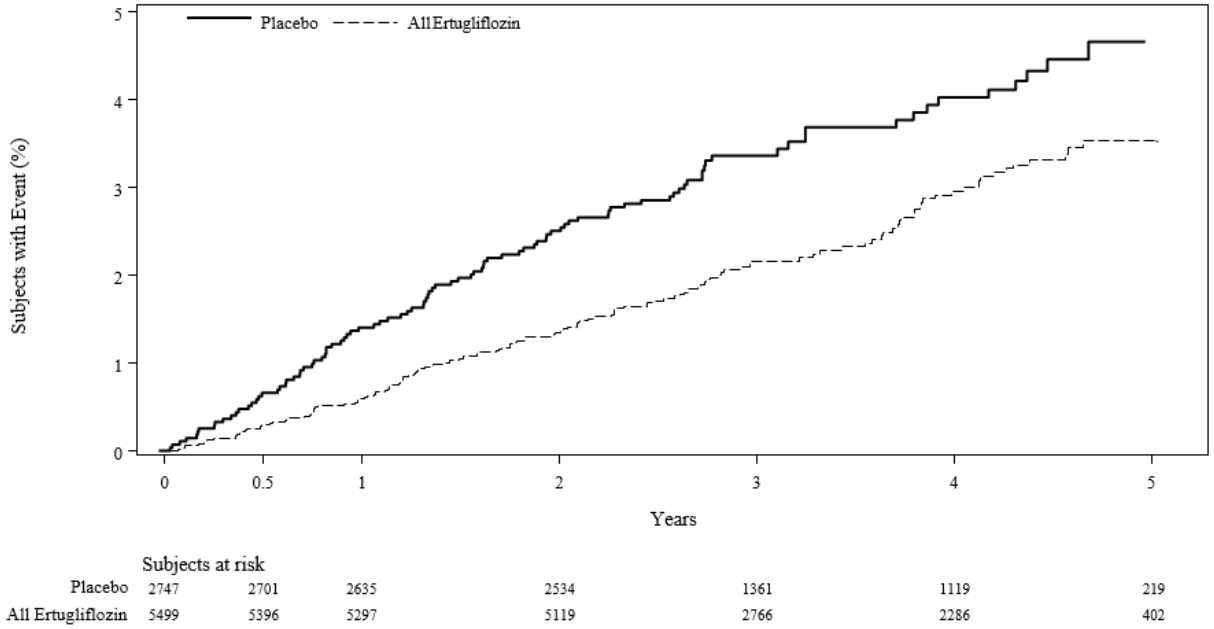
In patients treated with ertugliflozin, the rate of hospitalisation for heart failure was lower than in patients treated with placebo (see Table 8 and Figure 1).

Table 8: 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 waived the obligation to submit the results of studies with Segluromet in all subsets of the paediatric population in the treatment of type 2 diabetes (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Segluromet
Segluromet has been shown to be bioequivalent to coadministration of corresponding doses of ertugliflozin and metformin tablets.

Ertugliflozin
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 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.

The effects of a high-fat meal on the pharmacokinetics of ertugliflozin and metformin when administered as Segluromet tablets are comparable to those reported for the individual tablets. Food

had no meaningful effect on AUC_{inf} of ertugliflozin or metformin, but reduced mean ertugliflozin C_{max} by approximately 41% and metformin C_{max} by approximately 29% compared to the fasted condition.

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 drugs 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 medications that are substrates of these transporters.

Metformin

Absorption
The absolute bioavailability of a metformin hydrochloride 500-mg tablet given under fasting conditions is approximately 50-60%. Studies using single oral doses of metformin hydrochloride tablets 500 mg to 1,500 mg, and 850 mg to 2,550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination. At usual clinical doses and dosing schedules of metformin hydrochloride tablets, steady-state plasma concentrations of metformin are reached within 24-48 hours and are generally <1 µg/mL. During controlled clinical trials of metformin, maximum metformin plasma levels did not exceed 5 µg/mL, even at maximum doses.

Food decreases the extent of and slightly delays the absorption of metformin, as shown by approximately a 40% lower mean peak plasma concentration (C_{max}), a 25% lower area under the plasma concentration versus time curve (AUC), and a 35-minute prolongation of time to peak plasma concentration (T_{max}) following administration of a single 850-mg tablet of metformin with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

Distribution
The apparent volume of distribution (V/F) of metformin following single oral doses of metformin hydrochloride tablets 850 mg averaged 654 ± 358 l. Metformin is negligibly bound to plasma proteins. Metformin partitions into erythrocytes.

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

Elimination
Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours.

Special populations

Renal impairment
In patients with decreased renal function, the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased in proportion to the decrease in eGFR (see sections 4.3 and 4.4).

Hepatic impairment
No pharmacokinetic studies of metformin have been conducted in patients with hepatic insufficiency.

Effects of age, body weight, gender and race
Limited data from controlled pharmacokinetic studies of metformin in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and C_{max} is increased, compared to healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function.

Metformin pharmacokinetic parameters did not differ significantly between normal subjects and patients with type 2 diabetes when analysed according to gender. Similarly, in controlled clinical studies in patients with type 2 diabetes, the antihyperglycaemic effect of metformin was comparable in males and females.

No studies of metformin pharmacokinetic parameters according to race have been performed. In controlled clinical studies of metformin in patients with type 2 diabetes, the antihyperglycaemic effect was comparable in Whites (n=249), Blacks (n=51), and Hispanics (n=24).

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

Ertugliflozin
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

Ertugliflozin
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).

Metformin
Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1,500 mg/kg/day, respectively. These doses are both approximately four times the maximum recommended human daily dose of 2,000 mg based on body surface area comparisons. No evidence of carcinogenicity with

metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day.

Mutagenesis

Ertugliflozin
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.

Metformin
There was no evidence of a mutagenic potential of metformin in the following *in vitro* tests: Ames test (*S. typhimurium*), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the *in vivo* mouse micronucleus test were also negative.

Reproductive toxicology

Ertugliflozin
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 post-natal development study, decreased post-natal growth and development were observed in rats administered ertugliflozin gestation day 6 through lactation day 21 at ≥ 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 post-natal 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 MHRD of 15 mg/day based on AUC. The effects on kidney and bone did not fully reverse after the 1-month recovery period.

Metformin
Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately three times the maximum recommended human daily dose based on body surface area comparisons. Metformin did not adversely affect developmental outcomes when administered to rats and rabbits at doses up to 600 mg/kg/day. This represents an exposure of about 2 and 6 times the exposure at the maximum recommended human dose of 2,000 mg based on body surface area comparisons for rats and rabbits, respectively. Determination of foetal concentrations demonstrated a partial placental barrier to metformin.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Povidone K29-32 (E1201)
Microcrystalline cellulose (E460)
Crospovidone (E1202)
Sodium lauryl sulphate (E487)
Magnesium stearate (E470b)

Film coating
Segluromet 2.5 mg/850 mg film-coated tablets and Segluromet 7.5 mg/850 mg film-coated tablets
Hypromellose (E464)
Hydroxypropyl cellulose (E463)
Titanium dioxide (E171)
Iron oxide red (E172)
Iron oxide yellow (E172)
Iron oxide black (E172)
Carnauba wax (E903)

Segluromet 2.5 mg/1,000 mg film-coated tablets and Segluromet 7.5 mg/1,000 mg film-coated tablets
Hypromellose (E464)
Hydroxypropyl cellulose (E463)
Titanium dioxide (E171)
Iron oxide red (E172)
Carnauba wax (E903)

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, 56, 60, 168, and 180 film-coated tablets in non-perforated blisters and multipacks containing 196 (4 packs of 49) 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)

Segluromet 2.5 mg/850 mg film-coated tablets
EU/1/18/1265/001
EU/1/18/1265/002
EU/1/18/1265/003
EU/1/18/1265/004
EU/1/18/1265/005
EU/1/18/1265/006
EU/1/18/1265/007
EU/1/18/1265/029

Segluromet 2.5 mg/1,000 mg film-coated tablets
EU/1/18/1265/008
EU/1/18/1265/009
EU/1/18/1265/010
EU/1/18/1265/011
EU/1/18/1265/012
EU/1/18/1265/013
EU/1/18/1265/014
EU/1/18/1265/030

Segluromet 7.5 mg/850 mg film-coated tablets
EU/1/18/1265/015
EU/1/18/1265/016
EU/1/18/1265/017
EU/1/18/1265/018
EU/1/18/1265/019
EU/1/18/1265/020
EU/1/18/1265/021
EU/1/18/1265/031

Segluromet 7.5 mg/1,000 mg film-coated tablets
EU/1/18/1265/022
EU/1/18/1265/023
EU/1/18/1265/024
EU/1/18/1265/025
EU/1/18/1265/026
EU/1/18/1265/027
EU/1/18/1265/028
EU/1/18/1265/032

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 March 2018

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release
Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
Netherlands

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.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

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

OUTER CARTON FOR SEGLUROMET 2.5 mg/850 mg

1. NAME OF THE MEDICINAL PRODUCT

Segluromet 2.5 mg/850 mg film-coated tablets
ertugliflozin/metformin hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 2.5 mg of ertugliflozin (as ertugliflozin L-pyroglutamic acid) and 850 mg of metformin hydrochloride.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
28 film-coated tablets
30x1 film-coated tablets
56 film-coated tablets
60 film-coated tablets
168 film-coated tablets
180 film-coated tablets
Multipack: 196 (4 packs of 49) 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/1/18/1265/001 (14 film-coated tablets)
EU/1/18/1265/002 (28 film-coated tablets)
EU/1/18/1265/003 (30x1 film-coated tablets)
EU/1/18/1265/004 (56 film-coated tablets)
EU/1/18/1265/005 (60 film-coated tablets)
EU/1/18/1265/006 (168 film-coated tablets)
EU/1/18/1265/007 (180 film-coated tablets)
EU/1/18/1265/029 (196 (4 x 49) film-coated tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Segluromet 2.5 mg/850 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON WITHOUT BLUE BOX – MULTIPACKS - SEGLUROMET 2.5 mg/850 mg

1. NAME OF THE MEDICINAL PRODUCT

Segluromet 2.5 mg/850 mg film-coated tablets
ertugliflozin/metformin hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 2.5 mg of ertugliflozin (as ertugliflozin L-pyroglutamic acid) and 850 mg of metformin hydrochloride.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

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

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1265/029

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Segluromet 2.5 mg/850 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable.

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOR SEGLUROMET 2.5 mg/850 mg

1. NAME OF THE MEDICINAL PRODUCT

Segluromet 2.5 mg/850 mg tablets
ertugliflozin/metformin hydrochloride

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

OUTER CARTON FOR SEGLUROMET 2.5 mg/1000 mg

1. NAME OF THE MEDICINAL PRODUCT

Segluromet 2.5 mg/1000 mg film-coated tablets
ertugliflozin/metformin hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 2.5 mg of ertugliflozin (as ertugliflozin L-pyroglutamic acid) and 1000 mg of metformin hydrochloride.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
28 film-coated tablets
30x1 film-coated tablets
56 film-coated tablets
60 film-coated tablets
168 film-coated tablets
180 film-coated tablets
Multipack: 196 (4 packs of 49) 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/1/18/1265/008 (14 film-coated tablets)
EU/1/18/1265/009 (28 film-coated tablets)
EU/1/18/1265/010 (30x1 film-coated tablets)
EU/1/18/1265/011 (56 film-coated tablets)
EU/1/18/1265/012 (60 film-coated tablets)
EU/1/18/1265/013 (168 film-coated tablets)
EU/1/18/1265/014 (180 film-coated tablets)
EU/1/18/1265/030 (196 (4 x 49) film-coated tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Segluromet 2.5 mg/1000 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON WITHOUT BLUE BOX - MULTIPACKS - SEGLUROMET 2.5 mg/1000 mg

1. NAME OF THE MEDICINAL PRODUCT

Segluromet 2.5 mg/1000 mg film-coated tablets
ertugliflozin/metformin hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 2.5 mg of ertugliflozin (as ertugliflozin L-pyroglutamic acid) and 1000 mg of metformin hydrochloride.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

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

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1265/030

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Segluromet 2.5 mg/1000 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable.

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOR SEGLUROMET 2.5 mg/1000 mg

1. NAME OF THE MEDICINAL PRODUCT

Segluromet 2.5 mg/1000 mg tablets
ertugliflozin/metformin hydrochloride

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

OUTER CARTON FOR SEGLUROMET 7.5 mg/850 mg

1. NAME OF THE MEDICINAL PRODUCT

Segluromet 7.5 mg/850 mg film-coated tablets
ertugliflozin/metformin hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 7.5 mg of ertugliflozin (as ertugliflozin L-pyroglutamic acid) and 850 mg of metformin hydrochloride.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
28 film-coated tablets
30x1 film-coated tablets
56 film-coated tablets
60 film-coated tablets
168 film-coated tablets
180 film-coated tablets
Multipack: 196 (4 packs of 49) 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/1/18/1265/015 (14 film-coated tablets)
EU/1/18/1265/016 (28 film-coated tablets)
EU/1/18/1265/017 (30x1 film-coated tablets)
EU/1/18/1265/018 (56 film-coated tablets)
EU/1/18/1265/019 (60 film-coated tablets)
EU/1/18/1265/020 (168 film-coated tablets)
EU/1/18/1265/021 (180 film-coated tablets)
EU/1/18/1265/031 (196 (4 x 49) film-coated tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Segluromet 7.5 mg/850 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON WITHOUT BLUE BOX – MULTIPACKS - SEGLUROMET 7.5 mg/850 mg

1. NAME OF THE MEDICINAL PRODUCT

Segluromet 7.5 mg/850 mg film-coated tablets
ertugliflozin/metformin hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 7.5 mg of ertugliflozin (as ertugliflozin L-pyroglutamic acid) and 850 mg of metformin hydrochloride.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

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

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1265/031

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Segluromet 7.5 mg/850 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable.

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOR SEGLUROMET 7.5 mg/850 mg

1. NAME OF THE MEDICINAL PRODUCT

Segluromet 7.5 mg/850 mg tablets
ertugliflozin/metformin hydrochloride

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

OUTER CARTON FOR SEGLUROMET 7.5 mg/1000 mg

1. NAME OF THE MEDICINAL PRODUCT

Segluromet 7.5 mg/1000 mg film-coated tablets
ertugliflozin/metformin hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 7.5 mg of ertugliflozin (as ertugliflozin L-pyroglutamic acid) and 1000 mg of metformin hydrochloride.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
28 film-coated tablets
30x1 film-coated tablets
56 film-coated tablets
60 film-coated tablets
168 film-coated tablets
180 film-coated tablets
Multipack: 196 (4 packs of 49) 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/1/18/1265/022 (14 film-coated tablets)
EU/1/18/1265/023 (28 film-coated tablets)
EU/1/18/1265/024 (30x1 film-coated tablets)
EU/1/18/1265/025 (56 film-coated tablets)
EU/1/18/1265/026 (60 film-coated tablets)
EU/1/18/1265/027 (168 film-coated tablets)
EU/1/18/1265/028 (180 film-coated tablets)
EU/1/18/1265/032 (196 (4 x 49) film-coated tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Segluromet 7.5 mg/1000 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON WITHOUT BLUE BOX – MULTIPACKS - SEGLUROMET 7.5 mg/1000 mg

1. NAME OF THE MEDICINAL PRODUCT

Segluromet 7.5 mg/1000 mg film-coated tablets
ertugliflozin/metformin hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 7.5 mg of ertugliflozin (as ertugliflozin L-pyroglutamic acid) and 1000 mg of metformin hydrochloride.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

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

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1265/032

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Segluromet 7.5 mg/1000 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable.

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOR SEGLUROMET 7.5 mg/1000 mg

1. NAME OF THE MEDICINAL PRODUCT

Segluromet 7.5 mg/1000 mg tablets
ertugliflozin/metformin hydrochloride

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

Segluromet 2.5 mg/850 mg film-coated tablets
Segluromet 2.5 mg/1,000 mg film-coated tablets
Segluromet 7.5 mg/850 mg film-coated tablets
Segluromet 7.5 mg/1,000 mg film-coated tablets
ertugliflozin/metformin hydrochloride

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

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

What is in this leaflet

1. What Segluromet is and what it is used for

What Segluromet is
Segluromet contains two active substances, ertugliflozin and metformin.
- Ertugliflozin belongs to a group of medicines called sodium glucose co-transporter-2 (SGLT2) inhibitors.
- Metformin belongs to a group of medicines called biguanides.

What Segluromet is used for
- Segluromet lowers blood sugar levels in adult patients (aged 18 years and older) with type 2 diabetes. It can also help prevent heart failure.
- Segluromet can be used instead of taking both ertugliflozin and metformin as separate tablets.
- Segluromet 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 Segluromet.

How Segluromet works
- Ertugliflozin works by blocking the SGLT2 protein in your kidneys. This causes blood sugar to be removed in your urine.
- Metformin works by inhibiting sugar (glucose) production in the liver.

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. Your body can also make too much sugar. When this happens, sugar (glucose) builds up in the blood. 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 Segluromet

Do not take Segluromet

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

Do not take Segluromet if any of the above apply to you. If you are not sure, talk to your doctor before taking Segluromet.

Warnings and precautions

Talk to your doctor, pharmacist, or nurse before and while taking Segluromet, if you:

- have kidney problems.
- have or have had yeast infections of the vagina or penis.
- have type 1 diabetes. Segluromet should not be used to treat this condition.
- 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] 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.

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

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

Stop taking Segluromet and contact a doctor or the nearest hospital immediately if you experience some of the symptoms of lactic acidosis, as this condition may lead to coma.
Symptoms of lactic acidosis include:
- vomiting
- stomach ache (abdominal pain)
- muscle cramps
- a general feeling of not being well with severe tiredness
- difficulty in breathing
- reduced body temperature and heartbeat

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

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

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

Urine glucose
Because of how Segluromet 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 Segluromet
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

You may need more frequent blood glucose and kidney function tests, or your doctor may need to adjust the dose of Segluromet. 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 you are taking medicines used to treat pain and inflammation (NSAID and COX-2-inhibitors, such as ibuprofen and celecoxib).
- if you are taking certain medicines for the treatment of high blood pressure (ACE inhibitors and angiotensin II receptor antagonists).

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

If you need to have an injection of a contrast medium that contains iodine into your bloodstream, for example, in the context of an X-ray or scan, you must stop taking Segluromet before or at the time of

the injection. Your doctor will decide when you must stop and when to restart your treatment with Segluromet.

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

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant, or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

It is not known if Segluromet 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. You should not use Segluromet if you are pregnant.

It is not known if Segluromet passes into breast milk. Talk with your doctor about the best way to feed your baby if you take this medicine. You should not use Segluromet if you are breast-feeding.

Driving and using machines
This medicine has no or negligible influence on the ability to drive and use machines. 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 Segluromet.

Segluromet 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 Segluromet

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 recommended dose of Segluromet is one tablet twice a day.
- The dose of Segluromet that you take will depend on your condition and the amount of ertugliflozin and metformin needed to control your blood sugar.
- 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 in swallowing the tablet can be broken or crushed.
- Take one tablet twice daily. Try to take it at the same time each day; this will help you remember to take it.
- It is best to take your tablet with a meal. This will lower your chance of having an upset stomach.
- You need to keep following your food and exercise plan while taking Segluromet.

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

If you forget to take Segluromet
If you forget a dose, take it as soon as you remember. However, if it is nearly time for your next dose, skip the missed dose and go back to your regular schedule.

Do not take a double dose (two doses at the same time) to make up for a forgotten dose.

If you stop taking Segluromet
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:

Lactic acidosis (very rare, may affect up to 1 in 10,000 people)
Segluromet may cause a very rare, but very serious side effect called lactic acidosis (see section "Warnings and precautions"). If this happens, you must stop taking Segluromet and contact a doctor or the nearest hospital immediately, as lactic acidosis may lead to coma.

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 Segluromet.

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 include:

Very common
- vaginal yeast infection (thrush)
- feeling sick (nausea)
- vomiting
- diarrhoea
- stomach ache
- loss of appetite

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
- change in taste
- 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 LDL - 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’)

Very rare
- decreased vitamin B_{12} levels. This may cause anaemia (low levels of red blood cells).
- liver function test disorders
- hepatitis (a liver problem)
- hives
- redness of the skin
- itching

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

5. How to store Segluromet

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 Segluromet contains

- The active substances are ertugliflozin and metformin.
  - Each Segluromet 2.5 mg/850 mg film-coated tablet contains 2.5 mg ertugliflozin (as ertugliflozin L-pyroglutamic acid) and 850 mg of metformin hydrochloride.
  - Each Segluromet 2.5 mg/1,000 mg film-coated tablet contains 2.5 mg ertugliflozin (as ertugliflozin L-pyroglutamic acid) and 1,000 mg of metformin hydrochloride.
  - Each Segluromet 7.5 mg/850 mg film-coated tablet contains 7.5 mg ertugliflozin (as ertugliflozin L-pyroglutamic acid) and 850 mg of metformin hydrochloride.
  - Each Segluromet 7.5 mg/1,000 mg film-coated tablet contains 7.5 mg ertugliflozin (as ertugliflozin L-pyroglutamic acid) and 1,000 mg of metformin hydrochloride.
- The other ingredients are:
  - Tablet core: povidone (K29-32) (E1201), microcrystalline cellulose (E460), crospovidone (E1202), sodium lauryl sulphate (E487), magnesium stearate (E470b).
- Film coating:
  - Segluromet 2.5 mg/850 mg tablets and Segluromet 7.5 mg/850 mg tablets: hypromellose (E464), hydroxypropyl cellulose (E463), titanium dioxide (E171), iron oxide red (E172), iron oxide yellow (E172), iron oxide black (E172), carnauba wax (E903).
  - Segluromet 2.5 mg/1,000 mg tablets and Segluromet 7.5 mg/1,000 mg tablets: hypromellose (E464), hydroxypropyl cellulose (E463), titanium dioxide (E171), iron oxide red (E172), carnauba wax (E903).

What Segluromet looks like and contents of the pack
- Segluromet 2.5 mg/850 mg film-coated tablets (tablets) are beige, 18 x 10 mm oval, film-coated tablets debossed with “2.5/850” on one side and plain on the other side.
- Segluromet 2.5 mg/1,000 mg film-coated tablets (tablets) are pink, 19.1 x 10.6 mm oval, film-coated tablets debossed with “2.5/1000” on one side and plain on the other side.
- Segluromet 7.5 mg/850 mg film-coated tablets (tablets) are dark brown, 18 x 10 mm oval, film-coated tablets debossed with “7.5/850” on one side and plain on the other side.
- Segluromet 7.5 mg/1,000 mg film-coated tablets (tablets) are red, 19.1 x 10.6 mm oval, film-coated tablets debossed with “7.5/1000” on one side and plain on the other side.

Segluromet is available in Alu/PVC/PA/Alu blisters. The pack sizes are 14, 28, 56, 60, 168, and 180 film-coated tablets in non-perforated blisters, multipack containing 196 (4 packs of 49) 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 and Manufacturer
Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

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

België/Belgique/Belgien
MSD Belgium
Tél/Tel: +32(0)27766211
dpoc_belux@merck.com

Lietuva
UAB Merck Sharp & Dohme
Tel: + 370 5 2780247
msd_lietuva@merck.com

България
Мерк Шарп и Доум България ЕООД
Тел.: + 359 2 819 3737
info-msdbg@merck.com

Luxembourg/Luxemburg
MSD Belgium
Tél/Tel: +32(0)27766211
dpoc_belux@merck.com

Česká republika
Merck Sharp & Dohme s.r.o.
Tel.: +420 233 010 111
dpoc_czechslovak@merck.com

Magyarország
MSD Pharma Hungary Kft.
Tel.: + 36 1 888-5300
hungary_msd@merck.com

Danmark
MSD Danmark ApS
Tlf: +45 4482 4000
dkmail@merck.com

Malta
Merck Sharp & Dohme Cyprus Limited
Tel: 8007 4433 (+356 99917558)
malta_info@merck.com

Deutschland
MSD Sharp & Dohme GmbH
Tel: 0800 673 673 673 (+49 (0) 89 4561 0)
e-mail@msd.de

Nederland
Merck Sharp & Dohme B.V.
Tel: 0800 9999000 (+31 23 5153153)
medicalinfo.nl@merck.com

Eesti
Merck Sharp & Dohme OÜ
Tel: + 372 6144 200
msdeesti@merck.com

Norge
MSD (Norge) AS
Tlf: + 47 32 20 73 00
msdnorge@msd.no

Ελλάδα
MSD A.Φ.B.E.E.
Τηλ: + 30 210 98 97 300
dpoc_greece@merck.com

Österreich
Merck Sharp & Dohme Ges.m.b.H.
Tel: +43 (0) 1 26 044
msd-medizin@merck.com

España
Merck Sharp & Dohme de España, S.A.
Tel: +34 91 321 06 00
msd_info@merck.com

Polska
MSD Polska Sp. z o.o.
Tel.: +48 22 549 51 00
msdpolska@merck.com

France
MSD France
Tél: + 33 (0) 1 80 46 40 40

Hrvatska
Merck Sharp & Dohme d.o.o.
Tel: + 385 1 6611 333
croatia_info@merck.com

Ireland
Merck Sharp & Dohme Ireland (Human Health) Limited
Tel: +353 (0)1 2998700
medinfo_ireland@merck.com

Ísland
Vistor hf.
Sími: + 354 535 7000

Italia
MSD Italia S.r.l.
Tel: +39 06 361911
medicalinformation.it@merck.com

Κύπρος
Merck Sharp & Dohme Cyprus Limited
Τηλ: 800 00 673
+357 22866700
cyprus_info@merck**.**com

Latvija
SIA Merck Sharp & Dohme Latvija
Tel: + 371 67 364224
msd_lv@merck.com

Portugal
Merck Sharp & Dohme, Lda
Tel: + 351 21 4465700
inform_pt@merck.com

România
Merck Sharp & Dohme Romania S.R.L.

Tel: +40 21 529 29 00

msdromania@merck.com

Slovenija
Merck Sharp & Dohme, inovativna zdravila d.o.o.
Tel: + 386 1 5204201
msd_slovenia@merck.com

Slovenská republika
Merck Sharp & Dohme, s.r.o.
Tel: + 421 (2) 58282010
dpoc_czechslovak@merck.com

Suomi/Finland
MSD Finland Oy
Puh/Tel: + 358 (0)9 804650
info@msd.fi

Sverige
Merck Sharp & Dohme (Sweden) AB
Tfn: + 46 (0)77 570 04 88
medicinskinfo@merck.com

United Kingdom (Northern Ireland)
Merck Sharp & Dohme Ireland (Human Health) Limited
Tel: +353 (0)1 2998700
medinfoNI@msd.com

This leaflet was last revised in {**MM/YYYY**}

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