1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Steglatro 5 mg film-coated tablets
Each tablet contains 5 mg ertugliflozin (as ertugliflozin L-pyroglutamic acid).

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

Steglatro 15 mg film-coated tablets
Each tablet contains 15 mg ertugliflozin (as ertugliflozin L-pyroglutamic acid).

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Steglatro 5 mg film-coated tablets
Pink, 6.4 x 6.6 mm, triangular-shaped, film-coated tablets debossed with “701” on one side and plain on the other side.

Steglatro 15 mg film-coated tablets
Red, 9.0 x 9.4 mm, triangular-shaped, film-coated tablets debossed with “702” on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Steglatro is indicated in adults aged 18 years and older with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control:

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

(For study results with respect to combinations and effects on glycaemic control see sections 4.4, 4.5, and 5.1.)

4.2 Posology and method of administration

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

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

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

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

Special populations

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

Initiation of this medicinal product is not recommended in patients with an estimated glomerular filtration rate (eGFR) less than 60 ml/min/1.73 m^2 or CrCl less than 60 ml/min (see section 4.4).

Steglatro should be discontinued when eGFR is persistently less than 45 ml/min/1.73 m^2 or CrCl is persistently less than 45 ml/min.

Steglatro should not be used in patients with severe renal impairment, with end-stage renal disease (ESRD), or receiving dialysis, as it is not expected to be effective in these patients.

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

Elderly (≥ 65 years old)
No dose adjustment of ertugliflozin is recommended based on age. Renal function and risk of volume depletion should be taken into account (see sections 4.4 and 4.8). There is limited experience with Steglatro in patients ≥ 75 years of age.

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

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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

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

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

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

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

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

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

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

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

The safety and efficacy of ertugliflozin in patients with type 1 diabetes have not been established and ertugliflozin should not be used for treatment of patients with type 1 diabetes. Limited data from

clinical trials suggest that DKA occurs with common frequency when patients with type 1 diabetes are treated with SGLT2 inhibitors.

Lower limb amputations
In an ongoing clinical study of ertugliflozin added to existing therapy in type 2 diabetes patients with a history of established cardiovascular disease, an approximately 1.2-1.6-fold increase in cases of lower limb amputation (primarily of the toe) has been observed in patients treated with ertugliflozin. An increase in cases of lower limb amputation (primarily of the toe) has also been observed in long-term clinical studies with another SGLT2 inhibitor. As an underlying mechanism has not been established, risk factors, apart from general risk factors, for amputation are unknown.

Before initiating ertugliflozin, consider factors in the patient history that may increase the risk for amputation. As precautionary measures, consideration should be given to carefully monitoring patients with a higher risk for amputation events and counselling patients about the importance of routine preventative foot care and maintaining adequate hydration. Consideration may also be given to stopping treatment with ertugliflozin in patients who develop events which may precede amputation such as lower-extremity skin ulcer, infection, osteomyelitis or gangrene.

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

Steglatro should not be initiated in patients with an eGFR below 60 ml/min/1.73 m^2 or CrCl below 60 ml/min. Steglatro should be discontinued when eGFR is persistently below 45 ml/min/1.73 m^2 or CrCl is persistently below 45 ml/min due to a reduction of efficacy.

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

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

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

Urinary tract infections
Urinary glucose excretion may be associated with an increased risk of urinary tract infections. The incidence of urinary tract infections was not notably different in the ertugliflozin 5 mg and 15 mg groups (4.0% and 4.1%) and the placebo group (3.9%). Most of the events were mild or moderate and no serious case was reported. 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, Steglatro should be discontinued and prompt treatment (including antibiotics and surgical debridement) should be instituted.

Elderly patients
Elderly patients may be at an increased risk of volume depletion. Patients 65 years and older treated with ertugliflozin had a higher incidence of adverse reactions related to volume depletion compared to younger patients. Ertugliflozin is expected to have diminished efficacy in elderly patients with renal impairment (see sections 4.2 and 4.8).

Cardiac failure
Experience in New York Heart Association (NYHA) class I-II is limited, and there is no experience in clinical studies with ertugliflozin in NYHA class III-IV.

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

Interference with 1,5-anhydroglucitol (1,5-AG) assay
Monitoring glycaemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycaemic control in patients taking SGLT2 inhibitors. Alternative methods should be used to monitor glycaemic control.

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

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

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

Diuretics
Ertugliflozin may add to the diuretic effect of diuretics and may increase the risk of dehydration and hypotension (see section 4.4).

Insulin and insulin secretagogues
Insulin and insulin secretagogues, such as sulphonylureas, cause hypoglycaemia. Ertugliflozin may increase the risk of hypoglycaemia when used in combination with insulin and/or an insulin secretagogue. Therefore, a lower dose of insulin or an insulin secretagogue may be required to reduce the risk of hypoglycaemia when used in combination with ertugliflozin (see sections 4.2, 4.4, and 4.8).

Pharmacokinetic interactions

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

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

Multiple-dose administration of 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.

4.6 Fertility, pregnancy and lactation

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

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

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

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

The most commonly reported adverse reactions across the clinical program were 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

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

* See Section 4.4.

† See subsections below for additional information.

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

§ Includes: thirst and polydipsia.

¶ Mean percent changes from baseline for ertugliflozin 5 mg and 15 mg versus placebo, respectively, were 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%.

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

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

0.5% for ertugliflozin 5 mg, ertugliflozin 15 mg, and the comparator group and for subjects with eGFR 45 to < 60 mL/min/1.73 m^2, the incidence was 6.4%, 3.7%, and 0% respectively.

Hypoglycaemia
In the pool of placebo-controlled studies, the incidence of documented hypoglycaemia was increased for ertugliflozin 5 mg and 15 mg (5.0% 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 patients with moderate renal impairment taking insulins, SU, 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
Across the clinical program, ketoacidosis was identified in 3 of 3,409 (0.1%) ertugliflozin-treated patients and 0.0% of comparator-treated patients (see section 4.4).

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

Renal-related adverse reactions (e.g., acute kidney injury, renal impairment, acute prerenal failure) may occur in patients treated with ertugliflozin, particularly in patients with moderate renal impairment where the incidence of renal-related adverse reactions was 2.5%, 1.3%, and 0.6% in patients treated with ertugliflozin 5 mg, ertugliflozin 15 mg, and placebo, respectively.

Genital mycotic infections
In the pool of three placebo-controlled clinical trials, female genital mycotic infections (e.g., genital candidiasis, genital infection fungal, vaginal infection, vulvitis, vulvovaginal candidiasis, vulvovaginal mycotic infection, vulvovaginitis) occurred in 9.1%, 12%, and 3.0% 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).

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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: /https://sideeffects.health.gov.il

4.9 Overdose

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

Pharmacodynamic effects

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

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

Ertugliflozin has been studied as monotherapy and in combination with metformin and/or a dipeptidyl peptidase 4 (DPP-4) inhibitor. Ertugliflozin has also been studied in combination with current diabetes treatments, including insulin and a sulphonylurea, in patients with type 2 diabetes with moderate renal impairment.

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

Table 2: Results at Week 26 from a placebo-controlled monotherapy study of Steglatro*

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

* N includes all randomised, treated patients who had at least one measurement of the outcome variable.
† Least squares means adjusted for treatment, 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).

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

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

	Steglatro 5 mg	Steglatro 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 treatment, time, prior antihyperglycaemic medication (metformin monotherapy or metformin + another AHA), baseline eGFR (continuous), menopausal status randomisation stratum (men, premenopausal women, women who are perimenopausal or < 3 years postmenopausal, women who are ≥ 3 years postmenopausal) 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 4).

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

	Steglatro 5 mg	**Steglatro 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 treatment, time, prior antihyperglycaemic medication (monotherapy or dual therapy), baseline eGFR (continuous) and the interaction of time by treatment. Time was treated as a categorical variable.
‡ Non-inferiority is declared when the upper bound of the two-sided 95% confidence interval (CI) for the mean difference is less than 0.3%.
§ p< 0.001 compared to glimepiride.

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

Table 5: Results at Week 26 from a factorial study with Steglatro and sitagliptin as add-on

combination therapy with metformin compared to individual components alone*

	Steglatro 5 mg	Steglatro 15 mg	Sitagliptin 100 mg	Steglatro 5 mg + Sitagliptin 100 mg	Steglatro 15 mg + Sitagliptin 100 mg
HbA1c (%)	**N = 250**	**N = 248**	**N = 247**	**N = 243**	**N = 244**
Baseline (mean)	8.6	8.6	8.5	8.6	8.6
Change from baseline (LS mean†)	-1.0	-1.1	-1.1	-1.5	-1.5
Difference from Sitagliptin				-0.4‡ (-0.6, -0.3)	-0.5‡ (-0.6, -0.3)
Difference from Steglatro 5 mg				-0.5‡ (-0.6, -0.3)	
Difference from Steglatro 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 treatment, time, baseline eGFR and the interaction of time by treatment.
‡ p< 0.001 compared to control group.
§ p< 0.001 compared to corresponding dose of ertugliflozin or sitagliptin (based on adjusted odds ratio comparisons from a logistic regression model using multiple imputation for missing data values).

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

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

	Steglatro 5 mg	Steglatro 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 randomized, treated patients who had at least one measurement of the outcome variable.
† Least squares means adjusted for treatment, time, prior antihyperglycaemic medication.
‡ p< 0.001 compared to placebo.

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

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

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

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

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

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

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

Efficacy in patients with baseline HbA1c ≥ 8%
In the monotherapy study conducted on a background of diet and exercise in patients with baseline HbA1c from 7-10.5%, the subgroup of patients in the study with a baseline HbA1c ≥ 8% had

placebo-corrected reductions in HbA1c of 1.11% and 1.52% with ertugliflozin 5 or 15 mg, respectively.

In the study of ertugliflozin added-on to metformin in patients with baseline HbA1c from 7.0-10.5%, 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 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% compared to 2.10%, 1.30%, and 1.82% for ertugliflozin 5 mg, ertugliflozin 15 mg and sitagliptin alone, respectively.

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

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

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

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

5.2 Pharmacokinetic properties

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

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

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

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

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

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

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

Elimination
The mean systemic plasma clearance following an intravenous 100 µg dose was 11 l/hr. The mean elimination half-life in type 2 diabetic patients with normal renal function was estimated to be 17 hours based on the population pharmacokinetic analysis. Following administration of an oral [^{14}C]-ertugliflozin solution to healthy subjects, approximately 41% and 50% of the drug-related radioactivity was eliminated in faeces and urine, respectively. Only 1.5% of the administered dose was excreted as unchanged ertugliflozin in urine and 34% as unchanged ertugliflozin in faeces, which is likely due to biliary excretion of glucuronide metabolites and subsequent hydrolysis to parent.

Special populations

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

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

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

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

Drug interactions

In vitro *assessment of ertugliflozin*
In *in vitro* studies, ertugliflozin and ertugliflozin glucuronides did not inhibit or inactivate CYPs 1A2, 2C9, 2C19, 2C8, 2B6, 2D6, or 3A4, and did not induce CYPs 1A2, 2B6, or 3A4. Ertugliflozin and

ertugliflozin glucuronides did not inhibit the activity of UGTs 1A6, 1A9 or 2B7 *in vitro*. Ertugliflozin was a weak inhibitor of UGTs 1A1 and 1A4 *in vitro* at higher concentrations that are not clinically relevant. Ertugliflozin glucuronides had no effect on these isoforms. Overall, ertugliflozin is unlikely to affect the pharmacokinetics of concurrently administered 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.

5.3 Preclinical safety data

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

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

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

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

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

In the pre- and postnatal development study, decreased postnatal growth and development were observed in rats administered ertugliflozin gestation day 6 through lactation day 21 at ≥ 100 mg/kg/day (estimated 239 times the human exposure at the maximum clinical dose of

15 mg/day, based on AUC). Sexual maturation was delayed in both sexes at 250 mg/kg/day (estimated 620 times the MRHD at 15 mg/day, based on AUC).

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Microcrystalline cellulose
Lactose monohydrate
Sodium starch glycolate (Type A)
Magnesium stearate

Film coating
HPMC – 2910/Hypromellose 6 cP
Titanium dioxide
Lactose monohydrate
Macrogol/PEG 3350
Triacetin

Iron oxide red

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging material.

6.4 Special precautions for storage

Store below 30° C . Store in the original package in order to protect from moisture

6.5 Nature and contents of container

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

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MANUFACTURER

Merck Sharp & Dohme Corp., New-Jersey, USA.

8. LICENSE HOLDER

Merck Sharp & Dohme (Israel-1996) Company Ltd., P.O.Box 7121, Petah-Tikva 49170.

9. REGISTRATION NUMBER

Steglatro 5 mg film-coated tablets
161-72-35636
Steglatro 15 mg film-coated tablets
161-73-35637

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