PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

ℙ STEGLATRO™

ertugliflozin tablets
5 mg and 15 mg ertugliflozin, tablets, oral

ATC Code: A10BK04

Sodium-glucose co-transporter 2 (SGLT2) inhibitors

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Monotherapy: STEGLATRO™ (ertugliflozin tablets) is indicated for use as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus for whom metformin is inappropriate due to contraindications or intolerance.

Add-on combination: STEGLATRO™ (ertugliflozin tablets) is indicated in adult patients with type 2 diabetes mellitus to improve glycemic control in combination with:

- metformin,
- metformin and sitagliptin

when the therapy listed above, along with diet and exercise, does not provide adequate glycemic control (see CLINICAL TRIALS).

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (≥65 years of age): STEGLATRO™ should be used with caution in geriatric patients. Evidence from clinical studies suggests that use in the geriatric population is associated with an increase in risk of adverse reactions related to volume depletion in this population (see DOSAGE AND ADMINISTRATION, WARNINGS AND PRECAUTIONS, Special Populations, and ACTION AND CLINICAL PHARMACOLOGY).

2 CONTRAINDICATIONS

STEGLATRO™ is contraindicated in:

- Patients with a history of a serious hypersensitivity reaction to STEGLATRO™ or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING section.
- Renally impaired patients with an estimated glomerular filtration rate (eGFR) less than 45 mL/min/1.73 m^2, severe renal impairment, end-stage renal disease or patients on dialysis.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Diabetic Ketoacidosis

- Clinical trial and post-market cases of diabetic ketoacidosis (DKA), a serious life-threatening condition requiring urgent hospitalization, have been reported in patients with type 2 diabetes mellitus (T2DM) treated with sodium-glucose co-transporter 2 (SGLT2) inhibitors and cases have been reported in clinical trials with STEGLATRO™ (see ADVERSE REACTIONS). Fatal cases of ketoacidosis have been reported in patients taking SGLT2 inhibitors. A number of these cases have been atypical with blood glucose values below 13.9 mmol/L (250 mg/dL).

- Patients should be assessed for diabetic ketoacidosis immediately if non-specific symptoms such as difficulty breathing, nausea, vomiting, abdominal pain, confusion, anorexia, excessive thirst and unusual fatigue or sleepiness occur, regardless of blood glucose level, and STEGLATRO™ should be **discontinued immediately**.

- STEGLATRO™ should not be used for the treatment of DKA or in patients with a history of DKA.

- STEGLATRO™ is not indicated, and should not be used, in patients with type 1 diabetes.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Diuretics: STEGLATRO™ should be used with caution in patients taking diuretics, particularly loop diuretics, due to the increased risk of adverse events of volume depletion during co-administration (see WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS, and DRUG INTERACTIONS).

4.2 Recommended Dose and Dosage Adjustment

The recommended starting dose of STEGLATRO™ is 5 mg once daily, taken in the morning, with or without food. In patients tolerating STEGLATRO™ 5 mg once daily, the dose may be increased to a maximum recommended dose of 15 mg once daily if additional glycemic control is needed.

In patients with evidence of volume depletion, correct this condition prior to initiation of STEGLATRO™ (see WARNINGS AND PRECAUTIONS).

Pediatrics (<18 years of age): Safety and effectiveness of STEGLATRO™ in pediatric and adolescent patients have not been established; therefore, Health Canada has not authorized an indication for pediatric use (see INDICATIONS).

Geriatrics (≥65 years of age): No dosage adjustment of STEGLATRO™ is required based on age; however elderly patients may have reduced renal function and be at greater risk for adverse reactions related to volume depletion (see WARNINGS AND PRECAUTIONS, Special Population).

Renal Impairment: The efficacy of STEGLATRO™ declines with decreasing renal function (see CLINICAL TRIALS, Study in Special Population – Use in Patients with Type 2 Diabetes and Renal Impairment). Renal function must be assessed prior to initiation of STEGLATRO™ therapy and periodically thereafter, with more intensive monitoring of glycemic and renal biomarkers, and signs and symptoms of renal dysfunction in patients whose eGFR decreases <60 mL/min/1.73 m^2 (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, Renal Function).

STEGLATRO™ is contraindicated in renally impaired patients with an eGFR less than 45 mL/min/1.73 m^2, severe renal impairment, end-stage renal disease or patients on dialysis (see CONTRAINDICATIONS).

STEGLATRO™ should not be initiated in patients with an eGFR <60 mL/min/1.73 m^2. Use of STEGLATRO™ is not recommended in patients with an eGFR persistently between 45 to <60 mL/min/1.73 m^2. STEGLATRO™ should be discontinued if eGFR falls below 45 mL/min/1.73 m^2 (see WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS and ACTION AND CLINICAL PHARMACOLOGY).

No dosage adjustment for STEGLATRO™ is indicated in patients with mild renal impairment (eGFR ≥60 mL/min/1.73 m^2).

Hepatic impairment: No dosage adjustment of STEGLATRO™ 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 this patient population.

4.3 Administration

STEGLATRO™ should be taken in the morning, with or without food.

4.4 Reconstitution

Not applicable.

4.5 Missed Dose

If a dose of STEGLATRO™ is missed, it should be taken as soon as the patient remembers. A double dose of STEGLATRO™ should not be taken on the same day.

5 OVERDOSAGE

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 hemodialysis has not been studied.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form/Strength/Composition	Non-medicinal Ingredients
Oral	Tablets 5 mg* 15 mg*	Hypromellose, iron oxide red, lactose monohydrate, macrogol, magnesium stearate, microcrystalline cellulose, sodium starch glycolate, titanium dioxide and triacetin

*Ertugliflozin (as ertugliflozin L-pyroglutamic acid)

STEGLATRO™ (ertugliflozin tablets) is available in the strengths listed below:

- STEGLATRO™ tablets, 5 mg, are pink, triangular-shaped, film-coated tablets debossed with "701" on one side and plain on the other side. They are supplied in bottles of 30 tablets.

- STEGLATRO™ tablets, 15 mg, are red, triangular-shaped, film-coated tablets debossed with "702" on one side and plain on the other side. They are supplied in bottles of 30 tablets.

7 WARNINGS AND PRECAUTIONS

Please see the Serious Warnings and Precautions Box at the beginning of Part I: Health Professional Information.

General

STEGLATRO™ is not indicated for use in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

Cardiovascular

Patients at Risk for Volume Depletion, Hypotension and/or Electrolyte Imbalances: STEGLATRO™ is not recommended for use in patients who are volume-depleted. Due to its mechanism of action, STEGLATRO™ causes diuresis that can result in intravascular volume contraction. Therefore, symptomatic hypotension, including postural dizziness can occur after initiating STEGLATRO™ (see ADVERSE REACTIONS).

Caution should be exercised in patients for whom an ertugliflozin-induced decrease in blood pressure could pose a risk. This includes patients who have known cardiovascular disease, patients on anti-hypertensive therapy or on diuretics, who are elderly (≥65 years), patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2), patients with low systolic blood pressure, or patients with intercurrent conditions that may lead to volume depletion (such as gastrointestinal illness).

Before initiating STEGLATRO™, careful monitoring of volume status is recommended (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, and ADVERSE REACTIONS).

Temporary interruption of treatment with STEGLATRO™ is recommended for patients who develop volume depletion until the fluid loss is corrected.

Endocrine and Metabolism

Diabetic Ketoacidosis: STEGLATRO™ is not indicated, and should not be used, in patients with type 1 diabetes mellitus. The diagnosis of T2DM should therefore be confirmed before initiating STEGLATRO™.

Clinical trial and post-market cases of DKA, a serious life-threatening condition requiring urgent hospitalization, have been reported in patients with T2DM treated with SGLT2 inhibitors and cases have been reported in clinical trials with ertugliflozin (see ADVERSE REACTIONS). Fatal cases of ketoacidosis have been reported in patients taking SGLT2 inhibitors. In a number of reported cases, the presentation of the condition was atypical with only moderately increased blood glucose values, below 13.9 mmol/L (250 mg/dL).

DKA must be considered in the event of non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness. **If these symptoms occur, regardless of blood glucose level, patients should discontinue STEGLATRO™ treatment and be assessed for diabetic ketoacidosis immediately.**

Consider interrupting treatment with STEGLATRO™ in T2DM patients who are hospitalized for major surgical procedures, serious infections or acute serious medical illnesses.

SGLT2 inhibitors have been shown to increase blood ketones in clinical trial subjects. Conditions that can precipitate DKA while taking STEGLATRO™ include a very low carbohydrate diet (as the combination may further increase ketone body production),

dehydration, high alcohol consumption, and a low beta-cell function reserve. STEGLATRO™ should be used with caution in these patients and these patients should be monitored closely.

Hypoglycemia: STEGLATRO™ is not indicated in combination with insulin or insulin secretagogues, such as sulfonylurea (see INDICATIONS). The use of SGLT2 inhibitors in combination with these drugs has been shown to increase the risk of hypoglycemia.

Increases in Low-Density Lipoprotein Cholesterol (LDL-C): Dose-related increases in LDL-C are seen with STEGLATRO™ treatment (see ADVERSE REACTIONS). LDL-C levels should be monitored in patients treated with STEGLATRO™ and treated as appropriate (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

Genitourinary

Genital Mycotic Infections: STEGLATRO™ increases the risk of genital mycotic infections. Patients who have a history of genital mycotic infections or who are uncircumcised are more likely to develop genital mycotic infections (see ADVERSE REACTIONS). Monitor and treat as appropriate.

Urinary tract infections (including urosepsis and pyelonephritis): Cases of pyelonephritis have been reported in STEGLATRO™-treated patients in clinical trials (see ADVERSE REACTIONS). There have also been post-marketing reports of serious urinary tract infections including urosepsis and pyelonephritis, some of them requiring hospitalization, in patients receiving SGLT2 inhibitors. Treatment with SGLT2 inhibitors increases the risk of urinary tract infections. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated.

Hematologic

Elevated Hemoglobin: Mean hemoglobin increased in patients administered STEGLATRO™, as did the frequency of patients with abnormally elevated values for hemoglobin (see ADVERSE REACTIONS). STEGLATRO™ should be used with caution in patients with elevated hemoglobin.

Hepatic/Biliary/Pancreatic

Hepatic Impairment: STEGLATRO™ has not been studied in patients with severe hepatic impairment and is therefore not recommended for use in this patient population (see DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY).

Lower Limb Amputation

An increased risk for lower limb amputation (primarily of the toe) has been observed in clinical studies with another SGLT2 inhibitor. A numerical imbalance in non-traumatic lower limb amputations is reported in trials with STEGLATRO™ (see ADVERSE REACTIONS). Based on the current data and the presence of confounding factors, a causal association between ertugliflozin and lower limb amputation remains uncertain. It is anticipated that completion of the ongoing long-term clinical study will further inform on this risk with STEGLATRO™.

Before initiating STEGLATRO™, consider factors in the patient history that may predispose them to the need for amputations, such as a history of prior amputation, peripheral vascular disease, neuropathy and diabetic foot ulcers. Counsel patients about the importance of routine preventative foot care and adequate hydration. Monitor patients receiving STEGLATRO™ for signs and symptoms of infection (including osteomyelitis), new pain or tenderness, sores or ulcers involving the lower limbs, and discontinue STEGLATRO™ if these complications occur.

Monitoring and Laboratory Tests

Blood Glucose and HbA1c: Response to STEGLATRO™ treatment should be monitored by periodic measurements of blood glucose and HbA1c levels.

LDL-cholesterol: LDL-C levels should be measured at baseline and at regular intervals during treatment with STEGLATRO™ due to dose-dependent increases in LDL-C seen with STEGLATRO™ therapy (see ADVERSE REACTIONS).

Renal Function: Renal function must be assessed prior to initiation of STEGLATRO™ and periodically thereafter, with more frequent monitoring in patients whose eGFR decreases to <60 mL/min/1.73 m^2. STEGLATRO™ is contraindicated in patients with renal impairment with an eGFR less than 45 mL/min/1.73 m^2 (see CONTRAINDICATIONS). STEGLATRO™ must be discontinued if eGFR falls below 45 mL/min/1.73 m^2 (see DOSAGE AND ADMINISTRATION).

Monitoring of renal function is recommended prior to and following initiation of any concomitant drug which might have an impact on renal function.

Reduced Intravascular Volume: STEGLATRO™ is not recommended for use in patients who are volume depleted (see DOSAGE AND ADMINISTRATION). Before initiating STEGLATRO™, assess volume status, particularly in patients at risk, such as patients with known cardiovascular disease, patients on anti-hypertensive therapy or on diuretics, elderly patients (≥65 years), patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2), or patients with low systolic blood pressure (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION). In patients with volume depletion, the condition should be corrected prior to initiation of STEGLATRO™ (see DOSAGE AND ADMINISTRATION).

Volume status should also be assessed in cases of intercurrent conditions that may lead to fluid loss (such as a gastrointestinal illness) for patients already taking STEGLATRO™. In these

patients, careful monitoring of volume status (e.g., physical examination, blood pressure measurements, laboratory tests, including hematocrit, serum electrolytes and renal function tests) is recommended. Temporary interruption of treatment with STEGLATRO™ should be considered until fluid loss is corrected.

Renal

STEGLATRO™ may cause intravascular volume contraction and increases serum creatinine and decreases eGFR. Renal-related adverse reactions can occur after initiating STEGLATRO™ and the risk is increased in patients with moderate renal impairment (eGFR 30 to less than 60 mL/min/1.73 m^2) (see ADVERSE REACTIONS).

The glucose-lowering benefit of STEGLATRO™, which decreases with declining renal function, was not demonstrated to be statistically significant in subjects with eGFR less than 60 mL/min/1.73 m^2, and adverse reactions are more frequent (see ADVERSE REACTIONS and CLINICAL TRIALS, Study in Special Population – Use in Patients with Type 2 Diabetes and Renal Impairment).

Renal function must be assessed prior to initiation of STEGLATRO™ and periodically thereafter (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

STEGLATRO™ is contraindicated in patients with an eGFR less than 45 mL/min/1.73 m^2, severe renal impairment or on dialysis (see CONTRAINDICATIONS).

STEGLATRO™ should not be initiated in patients with an eGFR <60 mL/min/1.73 m^2 and must be discontinued if eGFR falls below 45 mL/min/1.73 m^2 (see DOSAGE AND ADMINISTRATION).

In patients whose eGFR decreases to <60 mL/min/1.73 m^2, close monitoring of renal function is recommended (see DOSAGE AND ADMINISTRATION and WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

Cases of acute kidney injury have been observed with STEGLATRO™ in clinical trials (see ADVERSE REACTIONS). There have also been post-marketing reports of acute kidney injury some requiring hospitalization and dialysis in patients receiving SGLT2 inhibitors. Patients with moderate renal impairment are more susceptible to these changes (see ADVERSE REACTIONS). Before initiating STEGLATRO™, consider factors that may predispose patients to acute kidney injury including hypovolemia, chronic renal insufficiency, congestive heart failure and concomitant medications (diuretics, ACE inhibitors, ARBs, NSAIDs). Consider temporarily discontinuing STEGLATRO™ in any setting of reduced oral intake (such as acute illness or fasting) or fluid losses (such as gastrointestinal illness or excessive heat exposure); monitor patients for signs and symptoms of acute kidney injury. If acute kidney injury occurs, discontinue STEGLATRO™ promptly and institute treatment

7.1 Special Populations

7.1.1 Pregnant Women

STEGLATRO™ should not be used during pregnancy. There are very limited data for the use of ertugliflozin in pregnant women in clinical studies, including no adequate and well-controlled studies in this population. When pregnancy is detected, STEGLATRO™ should be discontinued. Based on results from animal studies, ertugliflozin may affect renal development and maturation (see TOXICOLOGY).

7.1.2 Breast-feeding

STEGLATRO™ should not be used in nursing women. There is no information regarding the presence of ertugliflozin in human milk, the effects on the breastfed infant, or the effects on milk production. Ertugliflozin is present in the milk of lactating rats. Since human kidney maturation occurs *in utero* and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney if STEGLATRO™ is used during breastfeeding.

7.1.3 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

A total of 876 (25.7%) patients of 65 years and older, and 152 (4.5%) patients of 75 years and older were exposed to ertugliflozin across the clinical program (see CLINICAL TRIALS). An increased risk of adverse reactions related to volume depletion was seen with STEGLATRO™ in patients ≥65 years of age (see ADVERSE REACTIONS). Therapeutic experience in patients aged ≥75 years is limited. STEGLATRO™ is expected to have diminished antihyperglycemic efficacy in elderly patients who have impaired renal function (see INDICATIONS, DOSAGE AND ADMINISTRATION, WARNINGS AND PRECAUTIONS, and ACTION AND CLINICAL PHARMACOLOGY).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

A total of 3409 subjects with type 2 diabetes mellitus were exposed to STEGLATRO™ in seven Phase 3 clinical trials to evaluate the safety of STEGLATRO™ alone or in combination with other antidiabetic agents.

The primary assessment of safety and tolerability was conducted in a pooled analysis of three Phase 3 placebo-controlled clinical trials where 1544 subjects were randomized and received at least 1 dose of study medication.

In this data pool, the most frequently reported (≥10%) adverse reaction was female genital mycotic infections. The most common (>1%) adverse reactions were male genital mycotic infections and increased urination. The incidences of serious adverse events and adverse events resulting in discontinuation from study medication were similar across groups.

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

In a pooled dataset of the three 26-week placebo-controlled clinical trials, STEGLATRO™ was used as monotherapy in one trial and as add-on therapy in two trials. These data reflect exposure of 1029 patients to STEGLATRO™. Patients received STEGLATRO™ 5 mg (N=519), STEGLATRO™ 15 mg (N=510), or placebo (N=515) once daily. Across the treatment arms, the mean age of patients was 57.3 years, 2.1% were 75 years or older and 52.6% of the population was male. The population in these studies was 73.4% White, 6.6% Black or African American, 15.1% Asian; 18.7% were of Hispanic or Latino ethnicity. At baseline, the population had diabetes for an average of 7.5 years and had a mean HbA1c of 8.1%, and 19.4% had established microvascular complications of diabetes. Baseline estimated renal function was normal or mildly impaired in 97% of patients and moderately impaired in 3% of patients (overall mean eGFR 88.9 mL/min/1.73 m^2).

Table 2 summarizes adverse events regardless of causality, excluding hypoglycemia, that occurred in ≥2% of patients receiving STEGLATRO™ and more commonly than in patients given placebo.

Table 2 – Adverse Events Reported in ≥2% of Patients with Type 2 Diabetes Mellitus Treated with STEGLATRO™* and More Frequently than in Patients Treated with Placebo

System Organ Class Preferred Term	Number (%) of Patients		
	STEGLATRO™ 5 mg N = 519	STEGLATRO™ 15 mg N = 510	Placebo N = 515
Infections and Infestations			
Female genital mycotic infections†	9.1%	12.2%	3.0%
Male genital mycotic infections‡	3.7%	4.2%	0.4%
Urinary tract infections§	4.0%	4.1%	3.9%
Nasopharyngitis	2.5%	2.0%	2.3%
Nervous system disorders			
Headache	3.5%	2.9%	2.3%
Musculoskeletal and connective tissue disorders			
Back pain	1.7%	2.5%	2.3%
Renal and urinary disorders			
Increased urination¶	2.7%	2.4%	1.0%
Investigations			
Weight decreased	1.2%	2.4%	1.0%

* The three placebo controlled studies included one monotherapy trial and two add-on combination trials with metformin or with metformin and sitagliptin.

† Includes: genital candidiasis, genital infection fungal, vaginal infection, vulvitis, vulvovaginal candidiasis, vulvovaginal mycotic infection, and vulvovaginitis. Percentages calculated with the number of female patients in each group as denominator: placebo (N=235), STEGLATRO™ 5 mg (N=252), STEGLATRO™ 15 mg (N=245).

‡ Includes: balanitis candida, balanoposthitis, genital infection, and genital infection fungal. Percentages calculated with the number of male patients in each group as denominator: placebo (N=280), STEGLATRO™ 5 mg (N=267), STEGLATRO™ 15 mg (N=265).

§ Includes: cystitis, dysuria, streptococcal urinary tract infection, urethritis, urinary tract infection.

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

Description of selected adverse reactions

Diabetic Ketoacidosis

Cases of diabetic ketoacidosis, a serious life-threatening condition requiring urgent hospitalization, have been reported in 3 of 3409 (0.1%) of STEGLATRO™-treated patients with T2DM and 0% of comparator-treated patients across the clinical program. STEGLATRO™ is not indicated, and should not be used, in patients with type 1 diabetes. Fatal cases of ketoacidosis have been reported in patients taking SGLT2 inhibitors. In some cases, the presentation of the condition was atypical, with blood glucose levels only moderately elevated (<13.9 mmol/L (250 mg/dL) (see WARNINGS AND PRECAUTIONS).

Genital Mycotic Infections
In the pool of three placebo-controlled clinical trials, the incidence of female genital mycotic infections (e.g., genital candidiasis, genital infection fungal, vaginal infection, vulvitis, vulvovaginal candidiasis, vulvovaginal mycotic infection, vulvovaginitis) occurred in 9.1%, 12.2%, and 3.0% of females treated with STEGLATRO™ 5 mg, STEGLATRO™ 15 mg, and placebo, respectively. In females, discontinuation due to genital mycotic infections occurred in 0.6% and 0% of patients treated with STEGLATRO™ and placebo, respectively.

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 STEGLATRO™ 5 mg, STEGLATRO™ 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 STEGLATRO™ and placebo, respectively. Across the clinical program, phimosis was reported at an incidence of 0.5% in ertugliflozin treated patients, 50% of these male ertugliflozin-treated patients required circumcision.

Hypoglycemia
The incidence of hypoglycemia depended on the type of background therapy used in each study and is shown in Table 3.

Table 3 – Incidence of Overall* and Severe† Hypoglycemia in Placebo-Controlled Clinical Studies

Monotherapy (26 weeks)			
	STEGLATRO™ 5 mg (N =156)	**STEGLATRO™ 15 mg (N = 152)**	**Placebo (N = 153)**
Overall [N (%)]	4 (2.6)	4 (2.6)	1 (0.7)
Severe [N (%)]	0 (00)	2 (1.3)	0 (0.0)
In Combination with Metformin (26 weeks)			
	STEGLATRO™ 5 mg (N = 207)	**STEGLATRO™ 15 mg (N = 205)**	**Placebo (N = 209)**
Overall [N (%)]	15 (7.2)	16 (7.8)	9 (4.3)
Severe [N (%)]	1 (0.5)	0 (0.0)	1 (0.5)
In Combination with Metformin and Sitagliptin (26 weeks)			
	STEGLATRO™ 5 mg (N = 156)	**STEGLATRO™ 15 mg (N = 153)**	**Placebo (N = 153)**
Overall [N (%)]	7 (4.5)	3 (2.0)	5 (3.3)
Severe [N (%)]	1 (0.6)	0 (0.0)	1 (0.7)
Patients with Moderate Renal Impairment (26 weeks)			
	STEGLATRO™ 5 mg (N = 148)	**STEGLATRO™ 15 mg (N = 143)**	**Placebo (N = 133)**
Overall [N (%)]	53 (35.8)	39 (27.3)	48 (36.1)
Severe [N (%)]	5 (3.4)	3 (2.1)	3 (2.3)

* Overall hypoglycemic events: plasma or capillary glucose of less than or equal to 3.89 mmol/L.
† Severe hypoglycemic events: required assistance, lost consciousness, or experienced a seizure regardless of blood glucose.

In a 52-week study comparing the efficacy and safety of ertugliflozin 5 mg or 15 mg versus glimepiride in patients with inadequate glycemic control on metformin alone, treatment with ertugliflozin resulted in a lower proportion of patients with hypoglycemic events compared to glimepiride (5.6% for ertugliflozin 5 mg, 8.2% for ertugliflozin 15 mg, 27.2% for glimepiride). Ertugliflozin treatment also resulted in a lower proportion of severe hypoglycemic events

compared to glimepiride (0.2% for ertugliflozin 5 mg, 0.2% for ertugliflozin 15 mg, 2.3% for glimepiride).

Impairment of Renal Function
Use of STEGLATRO™ was associated with increases in serum creatinine and decreases in eGFR; patients with moderate renal impairment at baseline (eGFR 30 to <60 mL/min/1.73m^2) displayed larger mean changes (see ADVERSE REACTIONS, Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data).

Renal-related adverse reactions (e.g., acute kidney injury, renal impairment, acute prerenal failure) may occur in patients treated with STEGLATRO™. A higher incidence of renal-related adverse reactions was seen in a study of patients with moderate renal impairment; events were reported by 2.5%, 1.3%, and 0.6% of patients treated with STEGLATRO™ 5 mg, STEGLATRO™ 15 mg, and placebo, respectively.

Lower Limb Amputation
Across seven Phase 3 clinical trials in which STEGLATRO™ was studied as monotherapy and in combination with other antihyperglycemic agents, non-traumatic lower limb amputations occurred in 1 (0.1%) patient in the comparator group, 3 (0.2%) patients in the STEGLATRO™ 5 mg group, and 8 (0.5%) patients in the STEGLATRO™ 15 mg group. A causal association between STEGLATRO™ and lower limb amputation remains uncertain (see WARNINGS AND PRECAUTIONS).

Volume Depletion
STEGLATRO™ causes an osmotic diuresis, which may lead to intravascular volume contraction and adverse reactions related to volume depletion, particularly in patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2), elderly patients (≥65 years) or patients on diuretics (see WARNINGS AND PRECAUTIONS). In the pool of three placebo-controlled clinical trials, adverse reactions related to volume depletion (e.g., dehydration, dizziness postural, presyncope, syncope, hypotension, and orthostatic hypotension) were reported by 0.8%, 1.0%, and 1.7% of patients treated with STEGLATRO™ 5 mg, STEGLATRO™ 15 mg, and placebo, respectively. A higher incidence was seen in a study of patients with moderate renal impairment (eGFR <60 mL/min/1.73 m^2); events were reported by 4.4%, 1.9%, and 0% of patients treated with STEGLATRO™ 5 mg, STEGLATRO™ 15 mg, and placebo, respectively. The incidence of volume depletion was increased in patients ≥65 years of age across the clinical trial program, with adverse events reported for 2.2%, 2.6%, and 1.1% of patients treated with STEGLATRO™ 5 mg, 15 mg, and placebo/comparator, respectively.

8.3 Less Common Clinical Trial Adverse Reactions (<2%)[1]

General disorders and administration site conditions: thirst[2]

Reproductive system and breast disorders: pruritus genital, vulvovaginal pruritus.

1 Based on medical assessment (including biological plausibility/mechanism of action/dose response) of adverse events reported in <2% of subjects in the 3-study placebo-controlled pool.
2 Includes thirst and polydipsia

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Increases in Hemoglobin
In the pool of three placebo-controlled trials, hemoglobin increases with STEGLATRO™ were observed. Mean changes (percent changes) from baseline in hemoglobin were 3.5%, 3.5% and -1.4% for STEGLATRO™ 5 mg, STEGLATRO™ 15 mg, and placebo, respectively. Elevations of hemoglobin above the upper limit of normal occurred more frequently in patients receiving ertugliflozin than in those receiving placebo (1.5%, 0.7% and 0.0% for STEGLATRO™ 5 mg, 15 mg, and placebo, respectively).

Increases in Lipids
In the pool of three placebo-controlled trials, dose-related increases in LDL-C and total cholesterol were observed in patients treated with STEGLATRO™. Mean percent changes from baseline in LDL-C relative to placebo were 2.6% and 5.4% with STEGLATRO™ 5 mg and STEGLATRO™ 15 mg, respectively. Increases in total cholesterol of 1.5% and 4.0% were seen, relative to placebo, for STEGLATRO™ 5 mg and STEGLATRO™ 15 mg, respectively. Small non-dose dependent increases were also seen in HDL-C and small decreases were seen in triglyceride levels for both ertugliflozin groups relative to the placebo group.

Increases in Serum Creatinine, Decreases in eGFR and Increases in Blood Urea Nitrogen (BUN)
In the pool of three placebo-controlled clinical trials, mean changes from baseline for creatinine (µmol/L) at 6 weeks were 2.41 and 2.76 for ertugliflozin 5 mg and 15 mg, respectively, compared to 0.24 for placebo. At 26 weeks, mean changes from baseline for creatinine were -0.08 and 0.80 for ertugliflozin 5 mg and 15 mg, respectively, compared to -0.57 for placebo.

At 6 weeks, mean changes from baseline for eGFR (mL/min/1.73 m^2) were -2.7 and -3.1 for ertugliflozin 5 mg and 15 mg, respectively, compared to -0.3 for placebo. Mean changes from baseline for eGFR at 26 weeks were 0.5 and -0.6 for ertugliflozin 5 mg and 15 mg, respectively, compared to 0.7 for placebo.

Patients with moderate renal impairment at baseline had larger mean changes in both serum creatinine and eGFR. At 6 weeks, mean changes from baseline for creatinine (µmol/L) were 9.4 and 10.2 for ertugliflozin 5 mg and 15 mg, respectively, compared to -1.4 for placebo. At 26 weeks, mean changes from baseline for creatinine were 7.2 and 9.0 for ertugliflozin 5 mg and 15 mg, respectively, compared to 1.8 for placebo.

At 6 weeks, mean changes from baseline for eGFR (mL/min/1.73 m^2) were -3.2 and -4.1 for ertugliflozin 5 mg and 15 mg, respectively, compared to 0.6 for placebo. Mean changes from baseline for eGFR at 26 weeks were -2.7 and -2.6 for ertugliflozin 5 mg and 15 mg, respectively, compared to 0.0 for placebo.

These changes were observed to reverse after treatment discontinuation.

In the pool of three placebo controlled trials, mean percent increases from baseline in BUN were 13.2% and 17.0% for ertugliflozin 5 mg and ertugliflozin 15 mg, respectively, compared to 5.9% for placebo. The proportion of subjects having any occurrence of BUN values ≥50% increase and value >ULN was numerically higher in the ertugliflozin groups (8.8%) relative to the placebo group (5.1%).

Increases in Serum Phosphate
In the pool of three placebo-controlled trials, percent changes from baseline in serum phosphate were 6.8%, 8.5%, and 1.9% with STEGLATRO™ 5 mg, STEGLATRO™ 15 mg, and placebo. Elevations of serum phosphate above the upper limit of normal and greater than 0.5 mg/dL occurred more frequently in patients receiving ertugliflozin than in those receiving placebo (5.1%, 5.3% and 1.6% for STEGLATRO™ 5 mg, 15 mg, and placebo, respectively). In a clinical trial of patients with moderate renal impairment, percent changes from baseline at Week 26 in serum phosphate were 9.7% with STEGLATRO™ 5 mg, 7.8% with STEGLATRO™ 15 mg, and 0.8% with placebo.

8.5 Clinical Trial Adverse Reactions (Pediatrics)

Not applicable.

8.6 Post-Market Adverse Reactions

Not applicable.

9 DRUG INTERACTIONS

9.1 Overview

***In Vitro* Assessment of Drug Interactions**
In *in vitro* studies, ertugliflozin and ertugliflozin glucuronides did not inhibit CYP450 isoenzymes (CYPs) 1A2, 2C9, 2C19, 2C8, 2B6, 2D6, or 3A4, and did not induce CYPs 1A2, 2B6, or 3A4. Ertugliflozin was not a time-dependent inhibitor of CYP3A *in vitro*. Ertugliflozin did not inhibit UGT1A6, 1A9, or 2B7 *in vitro* and was a weak inhibitor (IC50 >39 μM) of UGT1A1 and 1A4. Ertugliflozin glucuronides did not inhibit UGT1A1, 1A4, 1A6, 1A9, or 2B7 *in vitro*. Overall, ertugliflozin is unlikely to affect the pharmacokinetics of drugs eliminated by these enzymes. Ertugliflozin is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) transporters and is not a substrate of organic anion transporters (OAT1, OAT3), organic cation transporters (OCT1, OCT2), or organic anion transporting polypeptides (OATP1B1, OATP1B3). 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. Overall, ertugliflozin is unlikely to affect the pharmacokinetics of concurrently administered medications that are substrates of these transporters.

9.2 Drug-Drug Interactions

No clinically significant pharmacokinetic interaction was seen when STEGLATRO™ was co-administered with metformin (OCT2), sitagliptin (OAT3), glimepiride (CYP2C9), or simvastatin (CYP3A4, OATP1B1, OATP1B3 substrate).

Pharmacokinetic interactions

Effects of other co-administered drugs on ertugliflozin

The effects of co-administered drugs on the pharmacokinetics of ertugliflozin have been assessed in drug-drug interaction studies. Ertugliflozin pharmacokinetics were similar with and without co-administration of metformin, glimepiride, sitagliptin, and simvastatin in healthy subjects (see Table 4).

Co-administration of ertugliflozin with multiple doses of 600 mg once daily rifampin (an inducer of UGT and CYP enzymes) resulted in approximately 39% and 15% mean reductions in ertugliflozin AUC and C_{max}, respectively, relative to ertugliflozin administered alone. These changes in exposure are not considered clinically relevant.

Table 4 – Effects of Other Drugs on the Pharmacokinetics of Ertugliflozin

Co-administered drug	Dose of co-administered drug	Dose of STEGLATRO™	Geometric mean ratio (ratio with/without co-administered drug); No effect=100%		Clinical comment
			AUC (90% CI)	C_{max} (90% CI)	
Metformin	1000 mg, single dose	15 mg, single dose	100.34% (97.43%, 103.34%)	97.14% (88.77%, 106.30%)	No dosage adjustment needed
Sitagliptin	100 mg, single dose	15 mg, single dose	102.27% (99.72%, 104.89%)	98.18% (91.20%, 105.70%)	No dosage adjustment needed
Glimepiride	1 mg, single dose	15 mg, single dose	102.11% (97.19%, 107.27%)	98.20% (92.17%, 104.63%)	No dosage adjustment needed
Simvastatin	40 mg, single dose	15 mg, single dose	102.40% (99.57%, 105.31%)	105.16% (98.26%, 112.54%)	No dosage adjustment needed
Rifampin	600 mg q.d. x 10 days	15 mg, single dose (dosed on Day 8)	61.16% (57.22%, 65.37%)	84.62% (74.17%, 96.53%)	No dosage adjustment needed

Effects of ertugliflozin on other co-administered drugs

The effects of ertugliflozin on the pharmacokinetics of co-administered drugs have been assessed in drug-drug interaction studies. Ertugliflozin had no clinically relevant effect on the pharmacokinetics of metformin, glimepiride, sitagliptin, and simvastatin when co-administered in healthy subjects (see Table 5).

Physiologically-based PK (PBPK) modeling suggests that co-administration of mefenamic acid (UGT inhibitor) may increase the AUC and C_{max} of ertugliflozin by 1.51- and 1.19-fold, respectively. These predicted changes in exposure of ertugliflozin are not expected to be clinically relevant.

Table 5 – Effects of Ertugliflozin on the Pharmacokinetics of Other Drugs

Co-administered drug	Dose of co-administered drug	Dose of STEGLATRO™	Geometric mean ratio (ratio with/without co-administered drug); No effect=100%		Clinical comment
			AUC (90% CI)	C_{max} (90% CI)	
Metformin	1000 mg, single dose	15 mg, single dose	100.94% (90.62%, 112.44%)	94.00% (82.94%, 106.55%)	No dosage adjustment needed
Sitagliptin	100 mg, single dose	15 mg, single dose	101.67% (98.40%, 105.04%)	101.68% (91.65%, 112.80%)	No dosage adjustment needed
Glimepiride	1 mg, single dose	15 mg, single dose	109.80% (98.14%, 122.86%)	97.39% (71.07%, 133.46%)	No dosage adjustment needed
Simvastatin	40 mg, single dose	15 mg, single dose	123.83% (90.92%, 168.66%)	119.05% (97.22%, 145.77%)	No dosage adjustment needed
			Simvastatin acid: 130.46% (108.32%, 157.13%)	Simvastatin acid: 115.66% (95.74%, 139.71%)	

Pharmacodynamic interactions
Diuretics: STEGLATRO™ may add to the diuretic effect of diuretics and may increase the risk of dehydration and hypotension. Caution is recommended when STEGLATRO™ is co-administered with diuretics, particularly loop diuretics (see DOSAGE AND ADMINISTRATION and WARNINGS AND PRECAUTIONS).

9.3 Drug-Food Interactions

Administration of STEGLATRO™ 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, STEGLATRO™ was administered without regard to meals (see DOSAGE AND ADMINISTRATION).

9.4 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.5 Drug-Laboratory Test Interactions

Positive Urine Glucose Test
Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors as SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. Use alternative methods to monitor glycemic control.

Interference with 1,5-anhydroglucitol (1,5-AG) Assay
Monitoring glycemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

9.6 Drug-Lifestyle Interactions

Effects of Smoking, Alcohol, and Diet
The effects of smoking, diet, and alcohol use on the pharmacokinetics of STEGLATRO™ have not been specifically studied.

Effects on Ability to Drive and Use Machines
No formal studies have been conducted with STEGLATRO™ on the effects on the ability to drive and use machines. However, patients should be alerted to the elevated risk of adverse reactions related to reduced intravascular volume, such as postural dizziness (see DOSAGE AND ADMINISRATION, WARNINGS AND PRECAUTIONS, and ADVERSE REACTIONS).

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

SGLT2 is the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. Ertugliflozin is an 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.

10.2 Pharmacodynamics

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 T2DM following single- and multiple-dose administration of ertugliflozin. Dose-response modeling indicates that ertugliflozin 5 mg and 15 mg result in near maximal urinary glucose excretion (UGE). Enhanced UGE is maintained after multiple-dose administration. UGE with ertugliflozin also results in increases in urinary volume.

Cardiac Electrophysiology
In a randomized, placebo- and positive-controlled, crossover study in 42 healthy subjects, there was no evidence of a treatment-related effect on the QTcF interval, the QRS duration, the PR interval, or ventricular heart rate with a single supratherapeutic oral dose of ertugliflozin 100 mg (6.7 times the maximum recommended dose).

10.3 Pharmacokinetics

The pharmacokinetics of ertugliflozin are similar in healthy subjects and patients with T2DM. Based on the population PK analysis, a T2DM patient had ~9% lower CL/F relative to a healthy subject, which is not considered clinically meaningful. The steady state mean plasma AUC and C_{max} were 398 ng·hr/mL and 81.3 ng/mL, respectively, with 5 mg ertugliflozin once daily treatment, and 1193 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.

Table 6 – Summary of STEGLATRO™ Pharmacokinetic Parameters in Healthy Subjects at Steady State

Ertugliflozin Dose	C_{max}[1]	AUC_{τ}[1]	T_{max}[1]
5 mg, multiple dose	81.3 ng/mL	398 ng·hr/mL	1 hour
15 mg, multiple dose	268 ng/mL	1193 ng·hr/mL	

[1] Steady state with once daily dosing of STEGLATRO™, healthy subjects

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%.

Distribution:
The mean steady state volume of distribution of ertugliflozin following an intravenous dose is 85.5 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.

Metabolism:
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 11.2 L/hr. The mean elimination half-life in T2DM patients with normal renal function was estimated to be 16.6 hours based on the population pharmacokinetic analysis. Following administration of an oral [^{14}C]-ertugliflozin solution to healthy subjects, approximately 40.9% and 50.2% of the drug-related radioactivity was eliminated in feces and urine, respectively. Only 1.5% of the administered dose was excreted as unchanged ertugliflozin in urine and 33.8% as unchanged ertugliflozin in feces, which is likely due to biliary excretion of glucuronide metabolites and subsequent hydrolysis to parent.

Special Populations and Conditions

Pediatrics: No studies with STEGLATRO™ have been performed in pediatric patients.

Geriatrics: Based on a population pharmacokinetic analysis, age does not have a clinically meaningful effect on the pharmacokinetics of ertugliflozin. Relative to the ≥45 and <55 ages for the ertugliflozin 5 and 15 mg once-daily doses, median AUCτ changed by <14% across all other ages (<45 and >55 years). However, across clinical studies, patients 65 years and older had a higher incidence of adverse reactions related to volume depletion compared to younger patients treated with STEGLATRO™ (see DOSAGE AND ADMINISTRATION, WARNINGS AND PRECAUTIONS, and ADVERSE REACTIONS).

Sex: Based on a population pharmacokinetic analysis, gender does not have a clinically meaningful effect on the pharmacokinetics of ertugliflozin. The geometric mean exposure in females was 4% higher compared to males and is not considered clinically meaningful.

Ethnic origin: Based on a population pharmacokinetic analysis, race does not have a clinically meaningful effect on the pharmacokinetics of ertugliflozin. The geometric mean exposure in African American patients was comparable to Caucasian patients. The geometric mean exposure in Asian patients was 7% lower compared to Caucasian patients when matched with covariates such as baseline body weight, baseline eGFR and is not considered clinically meaningful.

Hepatic Insufficiency: 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.

Renal Insufficiency: In a Phase 1 clinical pharmacology study in patients with T2DM and mild, moderate, or severe renal impairment (as determined by eGFR), following a single-dose administration of 15 mg STEGLATRO™, the mean increases in AUC of ertugliflozin were 1.6-, 1.7- and 1.6-fold for mild, moderate and severe renally impaired patients respectively, compared to subjects with normal renal function. The C_{max} increased by 1.4-fold in mild and moderate renally impaired subjects and decreased by 0.1-fold in severe renally impaired subjects. These increases in ertugliflozin AUC and changes in C_{max} are not considered clinically relevant. The 24-hour urinary glucose excretion declined with increasing severity of renal impairment (see WARNINGS AND PRECAUTIONS). The plasma protein binding of ertugliflozin was unaffected in patients with renal impairment.

Obesity: Based on a population pharmacokinetic analysis body weight does not have a clinically meaningful effect on the pharmacokinetics of ertugliflozin. Relative to the approximate median weight (85 kg), body weight over a range of 59.5 kg to 123 kg (representing 5th and 95th percentiles of the observed weights), was estimated to be associated with ≤31% change in AUC_{tau}, which is not considered clinically relevant.

Genetic Polymorphism: Based on the results of a pooled analysis of AUC values from 20 Phase 1 studies evaluating the impact of UGT1A9 genotype on the pharmacokinetics of STEGLATRO™, the effect of the UGT1A9 allelic variants on ertugliflozin AUC was within ±10% of the wild type and is not considered clinically meaningful.

11 STORAGE, STABILITY AND DISPOSAL

Store at 15°C to 30°C. Protect from moisture.

12 SPECIAL HANDLING INSTRUCTIONS

Not applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

STEGLATRO™ contains ertugliflozin (in the form of ertugliflozin co-crystallized with L-pyroglutamic acid)

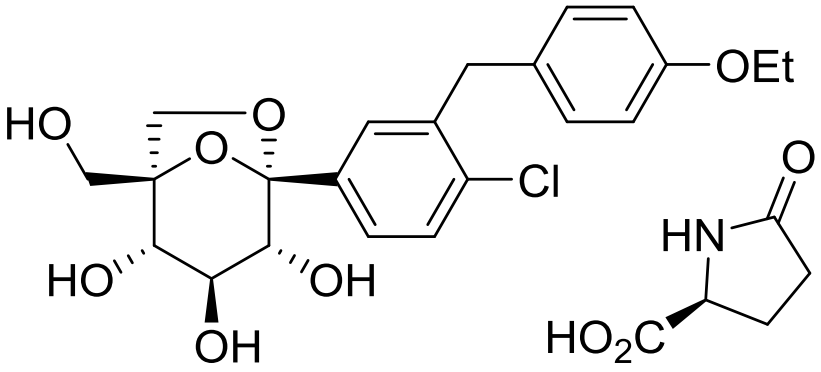
Proper/common name: Ertugliflozin L-pyroglutamic acid

Chemical name: (1*S*,2*S*,3*S*,4*R*,5*S*)-5-(4-chloro-3-(4-ethoxybenzyl)phenyl)-1-(hydroxymethyl)-6,8-dioxabicyclo[3.2.1]octane-2,3,4-triol, compound with (2*S*)-5-oxopyrrolidine-2-carboxylic acid

Molecular formula: $C_{22}H_{25}ClO_7$ (Ertugliflozin) / $C_{22}H_{25}ClO_7$ with $C_5H_7NO_3$ (Ertugliflozin L-PGA)

Molecular mass: 436.88 Daltons (Ertugliflozin) / 566.00 Daltons (Ertugliflozin L-PGA)

Structural formula:



Physicochemical properties: Ertugliflozin is co-crystallized with L-pyroglutamic acid (L-PGA) to form a crystalline, white to off-white powder. Due to rapid dissociation of ertugliflozin L-PGA in aqueous media, the thermodynamic aqueous solubility of ertugliflozin L-PGA cannot be determined. However, using ertugliflozin L-PGA as a source of ertugliflozin, the solubility of ertugliflozin in unbuffered water at pH 5.5, simulated gastric fluid without enzyme at pH 1.2 and phosphate buffered saline at pH 6.5 was found to be 0.76, 0.74 and 0.64 mg/mL respectively.

14 CLINICAL TRIALS

STEGLATRO™ (ertugliflozin tablets) has been studied as monotherapy and in combination with other antidiabetic medications, including metformin and metformin with sitagliptin (a dipeptidyl peptidase-4 inhibitor), in patients with type 2 diabetes mellitus (T2DM). STEGLATRO™ has also been studied in patients with T2DM with moderate renal impairment.

Treatment with STEGLATRO™ as monotherapy and in combination with metformin or metformin with sitagliptin produced clinically and statistically significant improvements in HbA1c compared to placebo after 26 weeks of treatment. In a 52-week study, reductions of HbA1c were sustained. In patients with T2DM treated with STEGLATRO™, the reduction in HbA1c was generally similar across subgroups defined by age, sex, race, geographic region, baseline body mass index, and duration of disease.

In patients with T2DM and moderate renal impairment, treatment with STEGLATRO™ did not result in a reduction in HbA1c compared to placebo.

14.1 Trial Design and Study Demographics

Table 7 – Summary of Patient Demographics for Clinical Trials in Specific Indication

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age years (Range)	Gender (%M/F)
Monotherapy					
P003/1022	Randomised, double-blind, placebo-controlled, multicentre	Ertugliflozin 5 mg or 15 mg vs. placebo Tablets, orally, once daily Main treatment period: 26 weeks	Ertugliflozin 5 mg: 156 Ertugliflozin 15 mg: 152 Placebo: 153	56.4 (23-87)	56.6/43.4
Add-on Therapy with Metformin					
P007/1017	Randomised, double-blind, placebo-controlled, multicentre	Ertugliflozin 5 mg or 15 mg vs. placebo Tablets, orally, once daily Main treatment period: 26 weeks	Ertugliflozin 5 mg: 207 Ertugliflozin 15 mg: 205 Placebo: 209	56.6 (24-79)	46.4/53.6
P002/1013	Randomised, double-blind, active-controlled, multicentre	Ertugliflozin 5 mg or 15 mg or Glimepiride titrated up to a maximum dose of 6 or 8 mg/day Tablets, orally, once daily Main treatment period: 52 weeks	Ertugliflozin 5 mg: 448 Ertugliflozin 15 mg: 441 Glimepiride: 437	58.2 (22-86)	48.5/51.5

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age years (Range)	Gender (%M/F)
Add-on Therapy with Metformin and Sitagliptin					
P006/1015	Randomised, double-blind, placebo-controlled, multicentre	Ertugliflozin 5 mg or 15 mg vs. placebo Tablets, orally, once daily Main treatment period: 26 weeks	Ertugliflozin 5 mg: 156 Ertugliflozin 15 mg: 154 Placebo: 153	59.1 (34-84)	56.9/43.1
Study in Special Population					
P001/1016	Randomised, double-blind, placebo-controlled, multicentre study in moderate renal impairment patients	Ertugliflozin 5 mg or 15 mg vs. placebo Tablets, orally, once daily Main treatment period: 26 weeks	Ertugliflozin 5 mg: 158 Ertugliflozin 15 mg: 156 Placebo: 154	67.3 (35-87)	49.5/50.5

14.2 Study Results

Monotherapy

A total of 461 treatment-naïve patients with type 2 diabetes mellitus and inadequately controlled (HbA1c between 7% and 10.5%) on diet and exercise was evaluated for efficacy in a 26-week clinical trial of STEGLATRO™ monotherapy.

In Study P003/1022, patients were randomized (1:1:1) to receive STEGLATRO™ 5 mg, STEGLATRO™ 15 mg or placebo administered once daily. Of the randomized and treated patients, 22.8% were aged ≥65 to <75 years, and 3.3% were aged ≥75 years. Mean baseline body mass (BMI) was 33.0 kg/m^2, 83.7% of patients were Caucasian/White, with lesser representation of Asian (8.5%), Black (6.3%), and other races (1.5%). In the study, mean duration of diabetes at screening was 5.0 years.

For the primary endpoint, treatment of STEGLATRO™ provided statistically significant improvements in HbA1c after 26 weeks of treatment compared to placebo (see Table 8).

Table 8 – Results at Week 26 (cLDA)* from a Placebo-Controlled Monotherapy Study of STEGLATRO™ in Patients with Type 2 Diabetes Mellitus

Efficacy Parameter	STEGLATRO™ 5 mg	STEGLATRO™ 15 mg	Placebo
N (FAS)	156	151	153
HbA1c (%)			
Baseline (mean)	8.2	8.4	8.1
Change from baseline (LS mean†)	-0.79	-0.96	0.20
Difference from placebo (LS mean†, 95% CI)	-0.99‡ (-1.22, -0.76)	-1.16‡ (-1.39, -0.93)	
Patients (%) with HbA1c <7%	28.2§	35.8§	13.1
N (FAS)	155	152	153
FPG (mmol/mL)			
Baseline (mean)	10.0	9.9	10.0
Change from baseline (LS mean†)	-1.88	-2.41	0.03
Difference from placebo (LS mean†, 95% CI)	-1.92‡ (-2.37, -1.46)	-2.44‡ (-2.90, -1.98)	
N (FAS)	156	152	153
Body Weight (kg)			
Baseline (mean)	94.0	90.6	94.2
Change from baseline (LS mean†)	-3.18	-3.58	-1.42
Difference from placebo (LS mean†, 95% CI)	-1.76‡ (-2.57, -0.95)	-2.16‡ (-2.98, -1.34)	

* cLDA = constrained longitudinal data analysis; FAS = full analysis set; N = includes all randomized, treated patients who had at least one measurement of the outcome variable.

† Least squares means adjusted for treatment, time, prior antihyperglycemic 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).

Add-on Combination Therapy with Metformin

A total of 621 patients with type 2 diabetes mellitus inadequately controlled (HbA1c between 7% and 10.5%) on metformin monotherapy (≥1500 mg/day for ≥8 weeks) was evaluated for efficacy of STEGLATRO™ in combination with metformin.

In Study P007/1017, patients were randomized (1:1:1) to receive STEGLATRO™ 5 mg, STEGLATRO™ 15 mg or placebo administered once daily in addition to continuation of background metformin therapy. Of the randomized and treated patients, 15.0% were aged ≥65 to <75 years, and 0.6% were aged ≥75 years. Mean BMI was 30.9 kg/m^2, 66.2% of patients were Caucasian/White, with lesser representation of Asian (16.1%), Black (10.3%), and other races (7.4%). In the study, mean duration of diabetes at screening was 8.0 years.

For the primary endpoint, treatment of STEGLATRO™ provided statistically significant improvements in HbA1c after 26 weeks of treatment compared to placebo (see Table 9).

Table 9 – Results at Week 26 (cLDA)* from a Placebo-Controlled Study of STEGLATRO™ in Add-on Combination with Metformin

Efficacy Parameter	STEGLATRO™ 5 mg	STEGLATRO™ 15 mg	Placebo + Metformin
N (FAS)	207	205	209
HbA1c (%)			
Baseline (mean)	8.1	8.1	8.2
Change from baseline (LS mean†)	-0.73	-0.91	-0.03
Difference from placebo (LS mean†, 95% CI)	-0.70‡ (-0.87, -0.53)	-0.88‡ (-1.05, -0.71)	
Patients (%) with HbA1c <7%	35.3§	40.0§	15.8
N (FAS)	207	205	209
FPG (mmol/L)			
Baseline (mean)	9.3	9.3	9.4
Change from baseline (LS mean†)	-1.53	-2.17	-0.05
Difference from placebo (LS mean†, 95% CI)	-1.48‡ (-1.83, -1.14)	-2.12‡ (-2.47, -1.78)	
N (FAS)	207	205	209
Body Weight (kg)			
Baseline (mean)	84.9	85.3	84.5
Change from baseline (LS mean†)	-3.01	-2.93	-1.33
Difference from placebo (LS mean†, 95% CI)	-1.67‡ (-2.24, -1.11)	-1.60‡ (-2.16, -1.03)	

* cLDA = constrained longitudinal data analysis; FAS = full analysis set; N = includes all randomized, treated patients who had at least one measurement of the outcome variable.

† Least squares means adjusted for treatment, time, prior antihyperglycemic medication (metformin monotherapy or metformin + another AHA), baseline eGFR (continuous), menopausal status randomization 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).

Statistically significant ($p<0.001$) reductions in systolic blood pressure were observed with STEGLATRO™ 5 mg and 15 mg, -3.3 mmHg and -3.8 mmHg, respectively, relative to placebo.

Add-on Combination Therapy with Metformin –
Active-Controlled Study of STEGLATRO™ versus Glimepiride

A total of 1326 patients with type 2 diabetes mellitus inadequately controlled (HbA1c between 7% and 9%) on metformin monotherapy was evaluated for efficacy of STEGLATRO™ in combination with metformin.

In Study P002/1013, these patients, who were receiving metformin monotherapy (≥1500 mg/day for ≥8 weeks), were randomized (1:1:1) to receive STEGLATRO™ 5 mg, STEGLATRO™ 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 or a maximum tolerated dose or down-titrated to avoid or manage hypoglycemia. The mean daily dose of glimepiride was 3 mg. Of randomized and treated patients 21.6% were aged ≥65 to <75 years, and 3.8% were aged ≥75 years. Mean BMI was 31.4 kg/m^2, 72.9% of patients were Caucasian/White, with lesser representation of Asian (18.0%), Black (4.6%), and other races (4.5%). In the study, mean duration of diabetes at screening was 7.5 years.

For the primary endpoint, only treatment with STEGLATRO™ at 15 mg daily was non-inferior to glimepiride after 52 weeks of treatment (see Table 10).

Table 10 – Results at Week 52 (cLDA)* from an Active-Controlled Study Comparing STEGLATRO™ to Glimepiride as Add-on Therapy to Metformin

Efficacy Parameter	STEGLATRO™ 5 mg	STEGLATRO™ 15 mg	Glimepiride + Metformin
N (FAS)	448	440	437
HbA1c (%)			
Baseline (mean)	7.8	7.8	7.8
Change from baseline (LS mean†)	-0.56	-0.64	-0.74
Difference from glimepiride (LS mean†, 95% CI)	0.18 (0.06, 0.30)	0.10‡ (-0.02, 0.22)	
Patients (%) with HbA1c <7%**	34.4	38.0	43.5
N (FAS)	448	440	437
Body Weight (kg)			
Baseline (mean)	87.9	85.6	86.8
Change from baseline (LS mean†)	-2.96	-3.38	0.91
Difference from glimepiride (LS mean†, 95% CI)	-3.87 (-4.36, -3.38)	-4.29§ (-4.77, -3.80)	

* cLDA = constrained longitudinal data analysis; FAS = full analysis set; N = includes all randomized, treated patients who had at least one measurement of the outcome variable.

** Statistical tests for this endpoint were not included in the multiplicity scheme.

† Least squares means adjusted for treatment, time, prior antihyperglycemic 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.

Add-on Combination Therapy with Metformin and Sitagliptin

A total of 463 patients with type 2 diabetes mellitus inadequately controlled (HbA1c between 7% and 10.5%) on metformin (≥1500 mg/day for ≥8 weeks) and sitagliptin 100 mg once daily was evaluated for efficacy of STEGLATRO™ in combination with metformin and sitagliptin.

In Study P006/1015, patients were randomized (1:1:1) to receive STEGLATRO™ 5 mg, STEGLATRO™ 15 mg, or placebo administered once daily in addition to continuation of background metformin and sitagliptin therapy. Of randomized and treated patients, 27.1% were aged ≥65 to <75 years, and 2.8% were aged ≥75 years. Mean BMI was 30.8 kg/m^2, 72.9% of patients were Caucasian/White, with lesser representation of Asian (20.3%), Black (1.9%), and other races (4.8%). In the study, mean duration of diabetes at screening was 9.5 years.

For the primary endpoint, treatment of STEGLATRO™ provided statistically significant improvements in HbA1c after 26 weeks of treatment compared to placebo (see Table 11).

Table 11 – Results of a 26-Week (cLDA)* Placebo-Controlled Study of STEGLATRO™ in Add-on Combination Therapy to Metformin and Sitagliptin

Efficacy Parameter	STEGLATRO™ 5 mg	STEGLATRO™ 15 mg	Placebo + Metformin/ Sitagliptin
N (FAS)	156	153	153
HbA1c (%)			
Baseline (mean)	8.1	8.0	8.0
Change from baseline (LS mean†)	-0.78	-0.86	-0.09
Difference from placebo (LS mean†, 95% CI)	-0.69‡ (-0.87, -0.50)	-0.76‡ (-0.95, -0.58)	
Patients (%) with HbA1c <7%	32.1§	39.9§	17.0
N (FAS)	156	153	156
FPG (mmol/mL)			
Baseline (mean)	9.3	9.5	9.4
Change from baseline (LS mean†)	-1.49	-1.83	-0.10
Difference from placebo (LS mean†, 95% CI)	-1.40‡ (-1.82, -0.97)	-1.74‡ (-2.16, -1.31)	
N (FAS)	156	153	156
Body Weight (kg)			
Baseline (mean)	87.6	86.6	86.5
Change from baseline (LS mean†)	-3.35	-3.04	-1.32
Difference from placebo (LS mean†, 95% CI)	-2.03‡ (-2.65, -1.40)	-1.72‡ (-2.35, -1.09)	

* cLDA = constrained longitudinal data analysis; FAS = full analysis set; N = includes all randomized, treated patients who had at least one measurement of the outcome variable.

† Least squares means adjusted for treatment, time, prior antihyperglycemic medication.

‡ $p<0.001$ 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).

Statistically significant ($p<0.001$) reductions in systolic blood pressure were observed with STEGLATRO™ 5 mg and 15 mg, -3.7 mmHg and -4.3 mmHg, respectively, relative to placebo.

Study in Special Population

Use in Patients with Type 2 Diabetes Mellitus and Moderate Renal Impairment

The efficacy of STEGLATRO™ was 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).

In Study P001/1016, 202 patients exposed to STEGLATRO™ (5 mg or 15 mg) had an eGFR between 45 and less than 60 mL/min/1.73 m^2 and 111 patients exposed to STEGLATRO™ (5 mg or 15 mg) had an eGFR between 30 and less than 45 mL/min/1.73 m^2.

STEGLATRO™ did not show efficacy in this study. In patients with moderate renal impairment, the HbA1c reductions from baseline to Week 26 were not significantly different between placebo and STEGLATRO™ 5 mg or 15 mg.

15 MICROBIOLOGY

Not applicable.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

Acute Toxicity
Single doses of ertugliflozin were well tolerated in male and female Beagle dogs at 5 or 50 mg/kg (approximately 180 times human exposure at the maximum recommended human dose (MRHD) of 15 mg/day based on AUC comparisons). However, the dose of 500 mg/kg resulted in emesis.

Chronic 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 47 times the human exposure (AUC) at the 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, diarrhea, 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), renal tubular mineralization (rats) and increased trabecular bone (rats). Most of these changes resolved or showed signs of on-going recovery following the 8-week non-dosing recovery period; however, incidences of tubular mineralization remained high in males at the end of the recovery period. There were no adverse toxicity findings in dogs at 379 times the human 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 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 may be related to carbohydrate malabsorption leading to altered calcium homeostasis, which has been associated with pheochromocytoma development in rats and has unclear relevancy to human risk. The no-observed-effect level (NOEL) for neoplasia was 5 mg/kg/day (approximately 16 times human 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 and Developmental Toxicology

Reproduction

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 exposure at the MRHD of 15 mg/day based on AUC comparisons).

Development

In embryo-fetal development studies, ertugliflozin (50, 100 and 250 mg/kg/day) was administered orally to rats on gestation days 6 to 17 and to rabbits on gestation days 7 to 19. 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 fetal viability, lower maternal body weight, a higher incidence of a visceral malformation (membranous ventricular septal defect) and skeletal variations were observed at maternal exposure that was 510 times the human exposure at the 15 mg/day maximum clinical dose. 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).

When ertugliflozin was orally administered to juvenile rats from PND 21 to PND 90, increased kidney weight, renal tubule and renal pelvis dilatation, and renal mineralization occurred at doses greater than or equal to 5 mg/kg (13-fold the human exposure at the maximum clinical dose of 15 mg/day, based on AUC). These effects did not fully reverse within the 1 month recovery period. Following the 4-week non-dosing recovery period, there was no recovery of kidney mineralization. These effects occurred with drug exposure during periods in rats that correspond to the late second and third trimester of human renal development. Similar effects were seen in adult mice and rats.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

Steglatro™

ertugliflozin tablets

Read this carefully before you start taking Steglatro™ and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about Steglatro™.

Serious Warnings and Precautions

Diabetic ketoacidosis (DKA) can happen while you are taking Steglatro™. It is a serious and life-threatening condition. Some cases of **DKA** can lead to death. It needs urgent hospital care. **DKA** can happen to diabetic patients with normal or high blood sugar levels. In **DKA** your body produces high levels of blood acids called ketones. It occurs when your body cannot produce enough insulin.

Seek medical help and **stop taking Steglatro™ right away** if you have any of the **DKA** symptoms. Do this even if your blood sugar levels are normal. The symptoms of **DKA** are: difficult breathing, nausea, vomiting, stomach pain, and loss of appetite. Confusion, thirst, unusual fatigue, sleepiness or tiredness, along with a sweet or metallic taste in the mouth or sweet smelling breath can be noticed. You may have a different odour to your urine or sweat.

Do not use Steglatro™ if you have type 1 diabetes. It is a disease where your body does not produce any insulin.

Do not use Steglatro™ if you have a history of **DKA**.

What is Steglatro™ used for?
Steglatro™ is used along with diet and exercise to improve blood sugar levels in adults with type 2 diabetes.

Steglatro™ can be used:
- alone, if you cannot take metformin, or
- with metformin, or
- with metformin and sitagliptin.

How does Steglatro™ work?
Steglatro™ helps remove sugar from the body through the urine. This reduces the amount of sugar in the blood.

What are the ingredients in Steglatro™?

- Medicinal ingredients: ertugliflozin (in the form of ertugliflozin co-crystallized with L-pyroglutamic acid).
- Non-medicinal ingredients: hypromellose, iron oxide red, lactose monohydrate, macrogol, magnesium stearate, microcrystalline cellulose, sodium starch glycolate, titanium dioxide and triacetin.

Steglatro™ comes in the following dosage forms:

- Tablets: 5 mg and 15 mg ertugliflozin.

Do not use Steglatro™ if you:

- Are allergic to any of its ingredients.
- Have severe or end-stage kidney disease or are on dialysis. If you have moderate kidney problems, talk to your health care professional before you take Steglatro™.
- Have severe liver disease.
- Are experiencing a loss of fluids from the body for any reason. This could be due to excess heat exposure, vomiting, diarrhea or dehydration. It can be due to reduced drinking with illness or fasting.
- Are pregnant or planning to become pregnant. It is not known if Steglatro™ may 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.
- Are breast-feeding or plan to breast-feed. It is not known if Steglatro™ passes into breast milk. Talk with your doctor if you would like to breast-feed.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Steglatro™. Talk about any health conditions or problems you may have, including if you:

- are older than 65 years of age;
- have any kidney problems;
- have liver problems;
- have heart failure or heart disease;
- have low blood pressure;
- are taking high blood pressure medicine;
- are taking a diuretic medicine also known as water pills. They are used to remove excess water from the body;
- have intolerance to some milk sugars. Steglatro™ tablets contain lactose;
- often get urinary tract infections;
- have an increased chance of developing **DKA**, if you:
    - are dehydrated or suffer from excessive vomiting, diarrhea, or sweating;
    - are on a very low carbohydrate diet;
    - drink a lot of alcohol;
    - have/have had problems with your pancreas. This includes pancreatitis or surgery on your pancreas;

    - are hospitalized for major surgery, serious infection, or sudden serious medical illness;
    - have a history of **DKA**;
- are at increased risk for a possible **Lower Limb Amputation**, if you:
    - have a history of amputation;
    - have had blocked or narrowed blood vessels, usually in your leg;
    - have damage to the nerves (neuropathy) in your leg. This feels like tingling or numb hands and feet;
    - have had diabetic foot ulcers or sores;
    - have a lower limb infection;
    - are dehydrated. Staying well hydrated and doing regular foot care may help you avoid amputations. Ask your doctor for advice on these topics.

Other warnings you should know about:

- Steglatro™ is not recommended for use in patients under 18 years of age.
- Steglatro™ may cause higher levels of bad cholesterol, called LDL (a type of fat in your blood).
- Steglatro™ increases the chance of getting a yeast infection of the penis or vagina. This is more likely in people who have had yeast infections in the past. It is also more common in uncircumcised men. In rare instances, phimosis (when the foreskin of the penis cannot be pulled back past the glans) was reported and sometimes circumcision was performed.
- Steglatro™ may cause abnormal kidney function.

Driving and using machines: Steglatro™ may cause you to feel dizzy, weak or lightheaded. Do not drive or use machines until you know how the medicine affects you.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements, or alternative medicines.

If you start any new medicine, tell your healthcare professional.

The following may interact with Steglatro™:

- diuretics, known as water pills. They are used to remove excess water from the body.
- medicines to lower your blood pressure.

Tell your healthcare professional if you take drugs to lower your blood sugar. Examples are glyburide, gliclazide, glimepiride (sulfonylureas) or insulin. If you take Steglatro™ with any of these drugs it can increase the risk of low blood sugar. This is called **hypoglycemia**. Steglatro™ is not approved for use with these drugs.

How to take Steglatro™:

Follow the directions given to you by your doctor.

- once a day in the morning;
- by mouth;
- with or without food.

Usual Adult Dose: 1 tablet a day.
The usual starting dose is one 5 mg tablet each day. Your doctor may increase your dose to one 15 mg tablet to further control your blood sugar level.

Overdose:

If you think you have taken too much Steglatro™, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

- If you miss a dose, take it as soon as you remember. If you do not remember until it is time for your next dose, skip the missed dose and go back to your regular schedule.
- Do not take 2 doses of Steglatro™ on the same day.

What are possible side effects from using Steglatro™?
These are not all the possible side effects you may have when taking Steglatro™. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- Unusual thirst
- Vaginal itching
- You feel generally well and have changes in your urination. These include the need to urinate more often, in larger amounts, or at night
- Headache

Steglatro™ will cause your urine to test positive for sugar (glucose). You should use a different way to monitor your diabetes.

Steglatro™ can cause abnormal blood test results. Your doctor may do blood tests before you start Steglatro™ and while you take it. They may check your blood sugar, blood fat levels, liver function, amount of red blood cells in your blood and how well your kidneys are working. Your doctor will decide when to perform blood tests and will interpret the results.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Genital infections –Vaginal yeast infection: severe itching, burning, soreness, irritation and a whitish-grey cottage cheese-like discharge.	X		
COMMON			
Volume depletion (dehydration, loss of fluids from your body): dry or sticky mouth, headache, dizziness, urinating less often than normal, thirst.		X	
Low blood sugar (hypoglycemia): shaking, sweating, rapid heartbeat, change in vision, hunger, headache and change in mood.		X	
Genital infections – Yeast infection of the penis: red, swollen, itchy head of the penis; thick, lumpy discharge under foreskin with an unpleasant odour; difficulty retracting foreskin, pain when passing urine or during sex.	X		
UNCOMMON			
Urinary tract infection: burning sensation when passing urine, pain in the pelvis or mid-back pain, increased need to urinate.		X	
Acute kidney infection: painful, urgent or frequent urination, lower back (flank) pain, fever or chills, cloudy or foul smelling urine, blood in your urine.			X
Kidney problems: you feel unwell and you have any change in the amount, frequency or colour (pale or dark) of your urine		X	
Low blood pressure: dizziness, fainting, lightheadedness which may occur when you go from lying to sitting to standing up and when you start on Steglatro™.		X	
Possible need for lower limb amputation: on the feet, toes or legs, new pain or tenderness in a specific bone with redness; non-healing sores or ulcers; brownish/black cold skin.		X	
RARE			
Diabetic ketoacidosis (DKA): difficulty breathing, nausea, vomiting, stomach pain, loss of appetite, confusion, thirst, unusual fatigue, sleepiness or tiredness, a sweet or metallic taste in the mouth, sweet smelling breath, or different odour to urine or sweat.			X

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Store at 15°C to 30°C. Protect from moisture.

Keep out of reach and sight of children.

If you want more information about Steglatro™:
- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website or the Merck Canada website www.merck.ca or by calling Merck Canada at 1-800-567-2594.

To report an adverse event related to Steglatro™, please contact 1-800-567-2594.

This leaflet was prepared by Merck Canada Inc.

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