HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use STEGLATRO safely and effectively. See full prescribing information for STEGLATRO.

STEGLATRO® (ertugliflozin) tablets, for oral use
Initial U.S. Approval: 2017

----------RECENT MAJOR CHANGES ----------

Dosage and Administration (2.3)	12/2024
Warnings and Precautions (5.2, 5.5)	12/2024

----------INDICATIONS AND USAGE----------

STEGLATRO is a sodium glucose co-transporter 2 (SGLT2) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. (1)

Limitations of Use:
Not recommended for use to improve glycemic control in patients with type 1 diabetes mellitus. (1)

---------- DOSAGE AND ADMINISTRATION ----------

- Assess renal function before initiating and as clinically indicated. (2.1)
- Correct volume depletion before initiating STEGLATRO. (2.1)
- Recommended starting dosage is 5 mg orally once daily, taken in the morning, with or without food. (2.2)
- Increase dosage to 15 mg orally once daily in those tolerating STEGLATRO and needing additional glycemic control. (2.2)
- Use is not recommended in patients with an estimated glomerular filtration rate (eGFR) less than 45 mL/min/1.73 m^2. (2.2)
- Withhold STEGLATRO for at least 4 days, if possible, prior to surgery or procedures associated with prolonged fasting. (2.3)

---------- DOSAGE FORMS AND STRENGTHS ----------

Tablets: 5 mg and 15 mg (3)

----------CONTRAINDICATIONS----------

- Hypersensitivity to ertugliflozin or any of the excipients in STEGLATRO. (4)

---------- WARNINGS AND PRECAUTIONS----------

- *Diabetic Ketoacidosis in Patients with Type 1 Diabetes Mellitus and Other Ketoacidosis:* Consider ketone monitoring in patients at risk for ketoacidosis, as indicated. Assess for ketoacidosis regardless of presenting blood glucose levels and discontinue STEGLATRO if ketoacidosis is suspected. Monitor patients for resolution of ketoacidosis before restarting. (5.1)
- *Lower Limb Amputation:* Monitor patients for infections or ulcers of lower limbs, and discontinue if these occur. (5.2)
- *Volume Depletion:* May result in acute kidney injury. Before initiating, assess and correct volume status in patients with renal impairment or low systolic blood pressure, elderly patients, or patients on diuretics. Monitor for signs and symptoms during therapy. (5.3)
- *Urosepsis and Pyelonephritis:* Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated. (5.4)
- *Hypoglycemia:* Consider a lower dose of insulin or insulin secretagogue to reduce risk of hypoglycemia when used in combination. (5.5)
- *Necrotizing Fasciitis of the Perineum (Fournier's Gangrene):* Serious, life-threatening cases have occurred in both females and males. Assess patients presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise. If suspected, institute prompt treatment. (5.6)
- *Genital Mycotic Infections:* Monitor and treat if indicated. (5.7)

---------- ADVERSE REACTIONS ----------

Most common adverse reactions (incidence ≥ 5%) were female genital mycotic infections. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme LLC at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS----------

See full prescribing information for information on drug interactions and interference of STEGLATRO with laboratory tests. (7)

---------- USE IN SPECIFIC POPULATIONS ----------

- *Pregnancy:* Advise females of the potential risk to a fetus especially during the second and third trimesters. (8.1)
- *Lactation:* Breastfeeding not recommended. (8.2)
- *Geriatrics:* Higher incidence of adverse reactions related to reduced intravascular volume. (8.5)
- *Renal Impairment:* Higher incidence of adverse reactions related to reduced intravascular volume and renal function. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

STEGLATRO® is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Limitations of Use

- Not recommended for use to improve glycemic control in patients with type 1 diabetes mellitus *[see Warnings and Precautions (5.1)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Prior to Initiation of STEGLATRO

- Assess renal function before initiating STEGLATRO and as clinically indicated *[see Warnings and Precautions (5.3)]*.
- Assess volume status. In patients with volume depletion, correct this condition before initiating STEGLATRO *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.5, 8.6)].*

2.2 Recommended Dosage

- The recommended starting dosage of STEGLATRO is 5 mg orally once daily, taken in the morning, with or without food.
- For additional glycemic control, the dosage may be increased to 15 mg orally once daily in patients tolerating STEGLATRO.
- Use of STEGLATRO is not recommended in patients with an estimated glomerular filtration rate (eGFR) less than 45 mL/min/1.73 m^2.

2.3 Temporary Interruption for Surgery

Withhold STEGLATRO for at least 4 days, if possible, prior to surgery or procedures associated with prolonged fasting. Resume STEGLATRO when the patient is clinically stable and has resumed oral intake *[see Warnings and Precautions (5.1) and Clinical Pharmacology (12.2)]*.

3 DOSAGE FORMS AND STRENGTHS

- Tablets: 5 mg, pink, triangular-shaped debossed with “701” on one side and plain on the other side.
- Tablets: 15 mg, red, triangular-shaped debossed with “702” on one side and plain on the other side.

4 CONTRAINDICATIONS

STEGLATRO is contraindicated in patients with hypersensitivity to ertugliflozin or any excipient in STEGLATRO. Reactions such as angioedema have occurred *[see Adverse Reactions (6.2)].*

5 WARNINGS AND PRECAUTIONS

5.1 Diabetic Ketoacidosis in Patients with Type 1 Diabetes Mellitus and Other Ketoacidosis

In patients with type 1 diabetes mellitus, STEGLATRO significantly increases the risk of diabetic ketoacidosis, a life-threatening event, beyond the background rate. In placebo-controlled trials of patients with type 1 diabetes mellitus, the risk of ketoacidosis was markedly increased in patients who received sodium glucose transporter 2 (SGLT2) inhibitors compared to patients who received placebo; this risk may be greater with higher doses. STEGLATRO is not indicated for glycemic control in patients with type 1 diabetes mellitus.

Type 2 diabetes mellitus and pancreatic disorders (e.g., history of pancreatitis or pancreatic surgery) are also risk factors for ketoacidosis. There have been postmarketing reports of fatal events of ketoacidosis in patients with type 2 diabetes mellitus using SGLT2 inhibitors.

Precipitating conditions for diabetic ketoacidosis or other ketoacidosis include under-insulinization due to insulin dose reduction or missed insulin doses, acute febrile illness, reduced caloric intake, ketogenic diet, surgery, volume depletion, and alcohol abuse.

Signs and symptoms are consistent with dehydration and severe metabolic acidosis and include nausea, vomiting, abdominal pain, generalized malaise, and shortness of breath. Blood glucose levels at presentation may be below those typically expected for diabetic ketoacidosis (e.g., less than 250 mg/dL). Ketoacidosis and glucosuria may persist longer than typically expected. Urinary glucose excretion persists for 4 days after discontinuing STEGLATRO *[see Clinical Pharmacology (12.2)];* however, there have been postmarketing reports of ketoacidosis and/or glucosuria lasting greater than 6 days and some up to 2 weeks after discontinuation of SGLT2 inhibitors.

Consider ketone monitoring in patients at risk for ketoacidosis if indicated by the clinical situation. Assess for ketoacidosis regardless of presenting blood glucose levels in patients who present with signs and symptoms consistent with severe metabolic acidosis. If ketoacidosis is suspected, discontinue STEGLATRO, promptly evaluate, and treat ketoacidosis, if confirmed. Monitor patients for resolution of ketoacidosis before restarting STEGLATRO.

Withhold STEGLATRO, if possible, in temporary clinical situations that could predispose patients to ketoacidosis. Resume STEGLATRO when the patient is clinically stable and has resumed oral intake *[see Dosage and Administration (2.3)].*

Educate all patients on the signs and symptoms of ketoacidosis and instruct patients to discontinue STEGLATRO and seek medical attention immediately if signs and symptoms occur.

5.2 Lower Limb Amputation

In a long-term cardiovascular outcomes study *[see Clinical Studies (14.2)]*, in patients with type 2 diabetes mellitus and established cardiovascular disease, the occurrence of non-traumatic lower limb amputations was reported with event rates of 4.7, 5.7, and 6.0 events per 1,000 patient-years in the placebo, STEGLATRO 5 mg, and STEGLATRO 15 mg treatment arms, respectively.

Amputation of the toe and foot were most frequent (81 out of 109 patients with lower limb amputations). Some patients had multiple amputations, some involving both lower limbs.

Lower limb infections, gangrene, and diabetic foot ulcers were the most common precipitating medical events leading to the need for an amputation. Patients with amputations were more likely to be male, have higher A1C (%) at baseline, have a history of peripheral arterial disease, amputation or peripheral revascularization procedure, diabetic foot, and to have been taking diuretics or insulin.

Across seven STEGLATRO clinical trials, non-traumatic lower limb amputations were reported 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.

Counsel patients about the importance of routine preventative foot care. 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.

5.3 Volume Depletion

STEGLATRO can cause intravascular volume contraction which may sometimes manifest as symptomatic hypotension or acute transient changes in creatinine *[see Adverse Reactions (6.1)]*. There have been postmarketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients with type 2 diabetes mellitus receiving SGLT2 inhibitors, including STEGLATRO. Patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2) *[see Use in Specific Populations (8.6)]*, elderly patients, patients with low systolic blood pressure, or patients on loop diuretics may be at increased risk for volume depletion or hypotension. Before initiating STEGLATRO in patients with one or more of these characteristics, assess volume status and renal function. In patients with volume depletion, correct this condition before initiating STEGLATRO. Monitor for signs and symptoms of volume depletion, and renal function after initiating therapy.

5.4 Urosepsis and Pyelonephritis

There have been postmarketing reports of serious urinary tract infections, including urosepsis and pyelonephritis, requiring hospitalization in patients receiving SGLT2 inhibitors. Treatment with SGLT2 inhibitors increases the risk for urinary tract infections. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated *[see Adverse Reactions (6.1)]*.

5.5 Hypoglycemia with Concomitant Use with Insulin or Insulin Secretagogues

Insulin and insulin secretagogues (e.g., sulfonylurea) are known to cause hypoglycemia. STEGLATRO may increase the risk of hypoglycemia when used in combination with insulin or an insulin secretagogue *[see Adverse Reactions (6.1)]*. The risk of hypoglycemia may be lowered by a reduction in the dose of insulin or sulfonylurea (or other concomitantly administered insulin secretagogues). Inform patients using these medications concomitantly of this risk and educate them on the signs and symptoms of hypoglycemia.

5.6 Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)

Reports of necrotizing fasciitis of the perineum (Fournier's Gangrene), a rare but serious and life-threatening necrotizing infection requiring urgent surgical intervention, have been identified in postmarketing surveillance in patients with diabetes mellitus receiving SGLT2 inhibitors, including STEGLATRO. Cases have been reported in females and males. Serious outcomes have included hospitalization, multiple surgeries, and death.

Patients treated with STEGLATRO presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise, should be assessed for necrotizing fasciitis. If suspected, start treatment immediately with broad-spectrum antibiotics and, if necessary, surgical debridement. Discontinue STEGLATRO, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.

5.7 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 (6.1)]*. Monitor and treat appropriately.

6 ADVERSE REACTIONS

The following important adverse reactions are described elsewhere in the labeling:

- Diabetic Ketoacidosis in Patients with Type 1 Diabetes and Other Ketoacidosis *[see Warnings and Precautions (5.1)]*
- Lower Limb Amputation *[see Warnings and Precautions (5.2)]*
- Volume Depletion *[see Warnings and Precautions (5.3)]*
- Urosepsis and Pyelonephritis *[see Warnings and Precautions (5.4)]*
- Hypoglycemia with Concomitant Use with Insulin or Insulin Secretagogues *[see Warnings and Precautions (5.5)]*
- Necrotizing Fasciitis of the Perineum (Fournier's Gangrene) *[see Warnings and Precautions (5.6)]*
- Genital Mycotic Infections *[see Warnings and Precautions (5.7)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Pool of Placebo-Controlled Trials Evaluating STEGLATRO 5 and 15 mg

The data in Table 1 are derived from a pool of three 26-week, placebo-controlled trials. STEGLATRO was used as monotherapy in one trial and as add-on therapy in two trials *[see Clinical Studies (14)]*. These data reflect exposure of 1,029 patients to STEGLATRO with a mean exposure duration of approximately 25 weeks. Patients received STEGLATRO 5 mg (N=519), STEGLATRO 15 mg (N=510), or placebo (N=515) once daily. The mean age of the population was 57 years and 2% were older than 75 years of age. Fifty-three percent (53%) of the population was male and 73% were White, 15% were Asian, and 7% were Black or African American. At baseline the population had diabetes for an average of 7.5 years, had a mean HbA1c of 8.1%, and 19.4% had established microvascular complications of diabetes. Baseline renal

function (mean eGFR 88.9 mL/min/1.73 m^2) was normal or mildly impaired in 97% of patients and moderately impaired in 3% of patients.

Table 1 shows common adverse reactions associated with the use of STEGLATRO. These adverse reactions were not present at baseline, occurred more commonly on STEGLATRO than on placebo, and occurred in at least 2% of patients treated with either STEGLATRO 5 mg or STEGLATRO 15 mg.

Table 1: Adverse Reactions Reported in ≥2% of Patients with Type 2 Diabetes Mellitus Treated with STEGLATRO* and Greater than Placebo in Pooled Placebo-Controlled Clinical Studies of STEGLATRO Monotherapy or Combination Therapy

	Number (%) of Patients		
	Placebo N = 515	**STEGLATRO 5 mg N = 519**	**STEGLATRO 15 mg N = 510**
Female genital mycotic infections†	3.0%	9.1%	12.2%
Male genital mycotic infections‡	0.4%	3.7%	4.2%
Urinary tract infections§	3.9%	4.0%	4.1%
Headache	2.3%	3.5%	2.9%
Vaginal pruritus¶	0.4%	2.8%	2.4%
Increased urination#	1.0%	2.7%	2.4%
Nasopharyngitis	2.3%	2.5%	2.0%
Back pain	2.3%	1.7%	2.5%
Weight decreased	1.0%	1.2%	2.4%
Thirstᵖ	0.6%	2.7%	1.4%

* The three placebo-controlled studies included one monotherapy trial and two add-on combination trials with metformin HCl or with metformin HCl 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: vulvovaginal pruritus and pruritus genital. Percentages calculated with the number of female patients in each group as denominator: placebo (N=235), ertugliflozin 5 mg (N=252), ertugliflozin 15 mg (N=245).

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

ᵖ Includes: thirst, dry mouth, polydipsia, and dry throat.

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). In patients with moderate renal impairment, adverse reactions related to volume depletion (e.g., dehydration, dizziness postural, presyncope, syncope, hypotension, and orthostatic hypotension) were reported in 0%, 4.4%, and 1.9% of patients treated with placebo, STEGLATRO 5 mg, and STEGLATRO 15 mg, respectively. STEGLATRO may also increase the risk of hypotension in other patients at risk for volume contraction *[see Use in Specific Populations (8.5, 8.6)]*.

Hypoglycemia

The incidence of hypoglycemia by study is shown in Table 2.

Table 2: Incidence of Overall* and Severe† Hypoglycemia in Placebo-Controlled Clinical Studies in Patients with Type 2 Diabetes Mellitus

Monotherapy (26 weeks)	**Placebo (N = 153)**	**STEGLATRO 5 mg (N =156)**	**STEGLATRO 15 mg (N = 152)**
Overall [N (%)]	1 (0.7)	4 (2.6)	4 (2.6)
Severe [N (%)]	0 (0.0)	0 (0.0)	2 (1.3)
Add-on Combination Therapy with Metformin HCl (26 weeks)	**Placebo (N = 209)**	**STEGLATRO 5 mg (N = 207)**	**STEGLATRO 15 mg (N = 205)**
Overall [N (%)]	9 (4.3)	15 (7.2)	16 (7.8)
Severe [N (%)]	1 (0.5)	1 (0.5)	0 (0.0)
Add-on Combination Therapy with Metformin HCl and Sitagliptin (26 weeks)	**Placebo (N = 153)**	**STEGLATRO 5 mg (N = 156)**	**STEGLATRO 15 mg (N = 153)**
Overall [N (%)]	5 (3.3)	7 (4.5)	3 (2.0)
Severe [N (%)]	1 (0.7)	1 (0.6)	0 (0.0)
In Combination with Insulin and/or an Insulin Secretagogue in Patients with Moderate Renal Impairment (26 weeks)	**Placebo (N = 133)**	**STEGLATRO 5 mg (N = 148)**	**STEGLATRO 15 mg (N = 143)**
Overall [N (%)]	48 (36.1)	53 (35.8)	39 (27.3)
Severe [N (%)]	3 (2.3)	5 (3.4)	3 (2.1)
Add-on Combination with Insulin with or without Metformin HCl (18 weeks)	**Placebo (N = 347)**	**STEGLATRO 5 mg (N = 348)**	**STEGLATRO 15 mg (N = 370)**
Overall [N (%)]	130 (37.5)	137 (39.4)	144 (38.9)
Severe [N (%)]	12 (3.5)	13 (3.7)	19 (5.1)
Add-on Combination with a Sulfonylurea (18 weeks)	**Placebo (N =48)**	**STEGLATRO 5 mg (N =55)**	**STEGLATRO 15 mg (N =54)**
Overall [N (%)]	2 (4.2)	4 (7.3)	5 (9.3)
Severe [N (%)]	0 (0.0)	0 (0.0)	0 (0.0)
Add-on Combination with Metformin HCl and a Sulfonylurea (18 weeks)	**Placebo (N = 117)**	**STEGLATRO 5 mg (N = 100)**	**STEGLATRO 15 mg (N = 113)**
Overall [N (%)]	17 (14.5)	20 (20.0)	30 (26.5)
Severe [N (%)]	1 (0.9)	2 (2.0)	2 (1.8)

* Overall hypoglycemic events: plasma or capillary glucose of less than or equal to 70 mg/dL.
† Severe hypoglycemic events: required assistance, lost consciousness, or experienced a seizure regardless of blood glucose.

Lower Limb Amputation

In a long-term cardiovascular outcomes study *[see Clinical Studies (14.2)]*, in patients with type 2 diabetes mellitus and established cardiovascular disease, the occurrence of non-traumatic lower limb amputations was reported with event rates of 4.7, 5.7, and 6.0 events per 1,000 patient-years in the placebo, STEGLATRO 5 mg, and STEGLATRO 15 mg treatment arms, respectively.

Across seven STEGLATRO clinical trials, non-traumatic lower limb amputations were reported 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.

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 3%, 9.1%, and 12.2% of females treated with placebo, STEGLATRO 5 mg, and STEGLATRO 15 mg, respectively (see Table 1). In females, discontinuation due to genital mycotic infections occurred in 0% and 0.6% of patients treated with placebo and STEGLATRO, respectively.

In the same pool, male genital mycotic infections (e.g., balanitis candida, balanoposthitis, genital infection, genital infection fungal) occurred in 0.4%, 3.7%, and 4.2% of males treated with placebo, STEGLATRO 5 mg, and STEGLATRO 15 mg, respectively (see Table 1). Male genital mycotic infections occurred more commonly in uncircumcised males. In males, discontinuations due to genital mycotic infections occurred in 0% and 0.2% of patients treated with placebo and STEGLATRO, respectively. Phimosis was reported in 8 of 1729 (0.5%) male ertugliflozin-treated patients, of which four required circumcision.

Urinary Tract Infections

In VERTIS CV, urinary tract infections (e.g., urinary tract infection, cystitis, dysuria) occurred in 10.2%, 12.2% and 12.0% of patients treated with placebo, STEGLATRO 5 mg and STEGLATRO 15 mg, respectively. The incidences of serious urinary tract infections were 0.8%, 0.9% and 0.4% with placebo, STEGLATRO 5 mg and STEGLATRO 15 mg, respectively.

Laboratory Tests

Changes in Serum Creatinine and eGFR

Initiation of STEGLATRO causes an increase in serum creatinine and decrease in eGFR within weeks of starting therapy and then these changes stabilize. In a study of patients with moderate renal impairment, larger mean changes were observed. In a long-term cardiovascular outcomes trial, an initial increase in serum creatinine and a decrease in eGFR within weeks of starting therapy was observed (at Week 6 eGFR changes of -2.7, -3.8 and -0.4 mL/min/1.73 m^2 in the STEGLATRO 5 mg, STEGLATRO 15 mg and placebo arms, respectively). The initial decline was followed by a recovery toward baseline to Week 52 (eGFR change from baseline of - 0.4, - 1.1 and - 0.2 mL/min/1.73 m^2 in STEGLATRO 5 mg, STEGLATRO 15 mg, and placebo arms, respectively). Acute hemodynamic changes may play a role in the early renal function changes observed with STEGLATRO since they are reversed after treatment discontinuation.

Increases in Low-Density Lipoprotein Cholesterol (LDL-C)

In the pool of three placebo-controlled trials, dose-related increases in LDL-C were observed in patients treated with STEGLATRO. Mean percent changes from baseline to Week 26 in LDL-C relative to placebo were 2.6% and 5.4% with STEGLATRO 5 mg and STEGLATRO 15 mg, respectively. The range of mean baseline LDL-C was 96.6 to 97.7 mg/dL across treatment groups.

Increases in Hemoglobin

In the pool of three placebo-controlled trials, mean changes (percent changes) from baseline to Week 26 in hemoglobin were -0.21 g/dL (-1.4%) with placebo, 0.46 g/dL (3.5%) with STEGLATRO 5 mg, and 0.48 g/dL (3.5%) with STEGLATRO 15 mg. The range of mean baseline hemoglobin was 13.90 to 14.00 g/dL across treatment groups. At the end of treatment, 0.0%, 0.2%, and 0.4% of patients treated with placebo, STEGLATRO 5 mg, and STEGLATRO 15 mg, respectively, had a hemoglobin increase greater than 2 g/dL and above the upper limit of normal.

Increases in Serum Phosphate

In the pool of three placebo-controlled trials, mean changes (percent changes) from baseline in serum phosphate were 0.04 mg/dL (1.9%) with placebo, 0.21 mg/dL (6.8%) with STEGLATRO 5 mg, and 0.26 mg/dL (8.5%) with STEGLATRO 15 mg. The range of mean baseline serum phosphate was 3.53 to 3.54 mg/dL across treatment groups. In a clinical trial of patients with moderate renal impairment, mean changes (percent changes) from baseline at Week 26 in serum phosphate were -0.01 mg/dL (0.8%) with placebo, 0.29 mg/dL (9.7%) with STEGLATRO 5 mg, and 0.24 mg/dL (7.8%) with STEGLATRO 15 mg.

6.2 Postmarketing Experience

Additional adverse reactions have been identified during postapproval use of STEGLATRO. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- *Infections:* necrotizing fasciitis of the perineum (Fournier's Gangrene)
- *Skin and Subcutaneous Tissue Disorders:* angioedema, rash

7 DRUG INTERACTIONS

Table 3: Clinically Significant Drug Interactions with STEGLATRO

Insulin or Insulin Secretagogues	
Clinical Impact:	The risk of hypoglycemia is increased when STEGLATRO is used in combination with insulin or an insulin secretagogue.
Intervention:	A lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with STEGLATRO.
Lithium	
Clinical Impact:	Concomitant use of an SGLT2 inhibitor with lithium may decrease serum lithium concentrations.
Intervention:	Monitor serum lithium concentration more frequently during STEGLATRO initiation and dosage changes.
Positive Urine Glucose Test	
Clinical Impact:	SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests.
Intervention:	Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.
Interference with 1,5-anhydroglucitol (1,5-AG) Assay	
Clinical Impact:	Measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors.
Intervention:	Monitoring glycemic control with 1,5-AG assay is not recommended. Use alternative methods to monitor glycemic control.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on animal data showing adverse renal effects, STEGLATRO is not recommended during the second and third trimesters of pregnancy.

The limited available data with STEGLATRO in pregnant women are not sufficient to determine a drug-associated risk of adverse developmental outcomes. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy *(see Clinical Considerations)*.

In animal studies, adverse renal changes were observed in rats when ertugliflozin was administered during a period of renal development corresponding to the late second and third trimesters of human pregnancy. Doses approximately 13 times the maximum clinical dose caused renal pelvic and tubule dilatations and renal mineralization that were not fully reversible. There was no evidence of fetal harm in rats or rabbits at exposures of ertugliflozin approximately 300 times higher than the maximal clinical dose of 15 mg/day when administered during organogenesis *(see Data)*.

The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with a HbA1c >7 and has been reported to be as high as 20-25% in women with HbA1c >10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Data

Animal Data

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 human exposures, based on AUC). These effects occurred with drug exposure during periods of renal development in rats that correspond to the late second and third trimester of human renal development, and did not fully reverse within a 1-month recovery period.

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 approximately 300 times the human exposure at the maximum clinical dose of 15 mg/day, based on AUC. A maternally toxic dose (250 mg/kg/day) in rats (707 times the clinical dose), was associated with reduced fetal viability, and a higher incidence of a visceral malformation (membranous ventricular septal defect). In the pre- and post-natal development study in pregnant rats, ertugliflozin was administered to the dams from gestation day 6 through lactation day 21 (weaning). Decreased post-natal growth (weight gain) was observed at maternal doses ≥100 mg/kg/day (greater than or equal to 331 times the human exposure at the maximum clinical dose of 15 mg/day, based on AUC).

8.2 Lactation

Risk Summary

There is no information regarding the presence of STEGLATRO in human milk, the effects on the breastfed infant, or the effects on milk production. Ertugliflozin is present in the milk of lactating rats *(see Data)*. 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. Because of the potential for serious adverse reactions in a breastfed infant, advise women that the use of STEGLATRO is not recommended while breastfeeding.

Data

The lacteal excretion of radiolabeled ertugliflozin in lactating rats was evaluated 10 to 12 days after parturition. Ertugliflozin derived radioactivity exposure in milk and plasma were similar, with a milk/plasma ratio of 1.07, based on AUC. Juvenile rats directly exposed to STEGLATRO during a developmental period corresponding to human kidney maturation were associated with a risk to the developing kidney (persistent increased organ weight, renal mineralization, and renal pelvic and tubular dilatations).

8.4 Pediatric Use

Safety and effectiveness of STEGLATRO in pediatric patients under 18 years of age have not been established.

8.5 Geriatric Use

No dosage adjustment of STEGLATRO is recommended based on age. In STEGLATRO clinical trials, a total of 876 (25.7%) patients treated with STEGLATRO were 65 years and older, and 152 (4.5%) patients treated with STEGLATRO were 75 years and older. Patients 65 years and older had a higher incidence of adverse reactions related to volume depletion compared to younger patients; events were reported in 1.1%, 2.2%, and 2.6% of patients treated with comparator, STEGLATRO 5 mg, and STEGLATRO 15 mg, respectively *[see Warnings and Precautions (5.3) and Adverse Reactions (6.1)]*.

In VERTIS CV, a total of 2780 (50.5%) patients treated with STEGLATRO were 65 years and older, and 595 (10.8%) patients treated with STEGLATRO were 75 years and older. Safety and efficacy were generally similar for patients age 65 years and older compared to patients younger than 65.

8.6 Renal Impairment

A 26-week placebo-controlled study of 313 patients with Stage 3 Chronic Kidney Disease (eGFR ≥30 to less than 60 mL/min/1.73 m^2) treated with STEGLATRO did not demonstrate improvement in glycemic control.

In the VERTIS CV study, there were 1370 patients (25%) with an eGFR ≥90 mL/min/1.73 m^2, 2929 patients (53%) with an eGFR of ≥60 to less than 90 mL/min/1.73 m^2, 879 patients (16%) with an eGFR of ≥45 to less than 60 mL/min/1.73 m^2, and 299 patients (5%) with eGFR of 30 to <45 mL/min/1.73 m^2 treated with STEGLATRO. Similar effects on glycemic control at Week 18 were observed in patients treated with STEGLATRO in each eGFR subgroup and also in the overall patient population.

No dosage adjustment is needed in patients with eGFR ≥45 mL/min/1.73 m^2.

8.7 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 *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

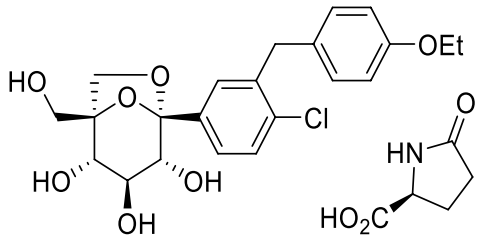
In the event of an overdose with STEGLATRO, contact the Poison Help line (1-800-222-1222) or a medical toxicologist for additional overdosage management recommendations. Employ the usual supportive measures as dictated by the patient's clinical status. Removal of ertugliflozin by hemodialysis has not been studied.

11 DESCRIPTION

STEGLATRO (ertugliflozin) tablets for oral use contain ertugliflozin L-pyroglutamic acid, a SGLT2 inhibitor.

The chemical name of ertugliflozin L-pyroglutamic acid is (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. The molecular formula is $C_{27}H_{32}ClNO_{10}$ and the molecular weight is 566.00.

The chemical structure is:



Ertugliflozin L-pyroglutamic acid is a white to off-white powder that is soluble in ethyl alcohol and acetone, slightly soluble in ethyl acetate and acetonitrile and very slightly soluble in water.

STEGLATRO is supplied as film-coated tablets, containing 6.48 or 19.43 mg of ertugliflozin L-pyroglutamic acid, which is equivalent to 5 and 15 mg of ertugliflozin.

Inactive ingredients are microcrystalline cellulose, lactose monohydrate, sodium starch glycolate, and magnesium stearate.

The film coating contains: hypromellose, lactose monohydrate, macrogol, triacetin, titanium dioxide and iron oxide red.

12 CLINICAL PHARMACOLOGY

12.1 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.

12.2 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 type 2 diabetes mellitus 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

The effect of STEGLATRO on QTc interval was evaluated in a Phase 1 randomized, placebo- and positive-controlled 3-period crossover study in 42 healthy subjects. At 6.7 times the therapeutic exposures with maximum recommended dose, STEGLATRO does not prolong QTc to any clinically relevant extent.

12.3 Pharmacokinetics

The pharmacokinetics of ertugliflozin are similar in healthy subjects and patients with type 2 diabetes mellitus. 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 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 (0.1 times the lowest recommended dose) to 300 mg (20 times the highest recommended dose) and following multiple doses from 1 mg (0.2 times the lowest recommended dose) to 100 mg (6.7 times the highest recommended dose). The absolute oral bioavailability of ertugliflozin following administration of a 15 mg dose is approximately 100%.

Effect of Food

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.

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.

Elimination

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%).

Excretion

The mean systemic plasma clearance following an intravenous 100 µg dose was 11.2 L/hr. The mean elimination half-life in type 2 diabetic 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.

Specific Populations

Patients with Renal Impairment

In a clinical pharmacology study in patients with type 2 diabetes mellitus 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, respectively, for mild, moderate and severe renally impaired patients, compared to subjects with normal renal function. These increases in ertugliflozin AUC are not considered clinically meaningful. The 24-hour urinary glucose excretion declined with increasing severity of renal impairment *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.6)]*. The plasma protein binding of ertugliflozin was unaffected in patients with renal impairment.

Patients with 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 *[see Use in Specific Populations (8.7)].*

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 Interaction Studies

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 (IC_{50} >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.

In Vivo Assessment of Drug Interactions

No dose adjustment of STEGLATRO is recommended when coadministered with commonly prescribed medicinal products. Ertugliflozin pharmacokinetics were similar with and without coadministration of metformin, glimepiride, sitagliptin, and simvastatin in healthy subjects (see Figure 1). Coadministration 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. Ertugliflozin had no clinically relevant effect on the pharmacokinetics of metformin, glimepiride, sitagliptin, and simvastatin when coadministered in healthy subjects (see Figure 2). Physiologically-based PK (PBPK) modeling suggests that coadministration 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 are not considered clinically relevant.

Figure 1: Effects of Other Drugs on the Pharmacokinetics of Ertugliflozin

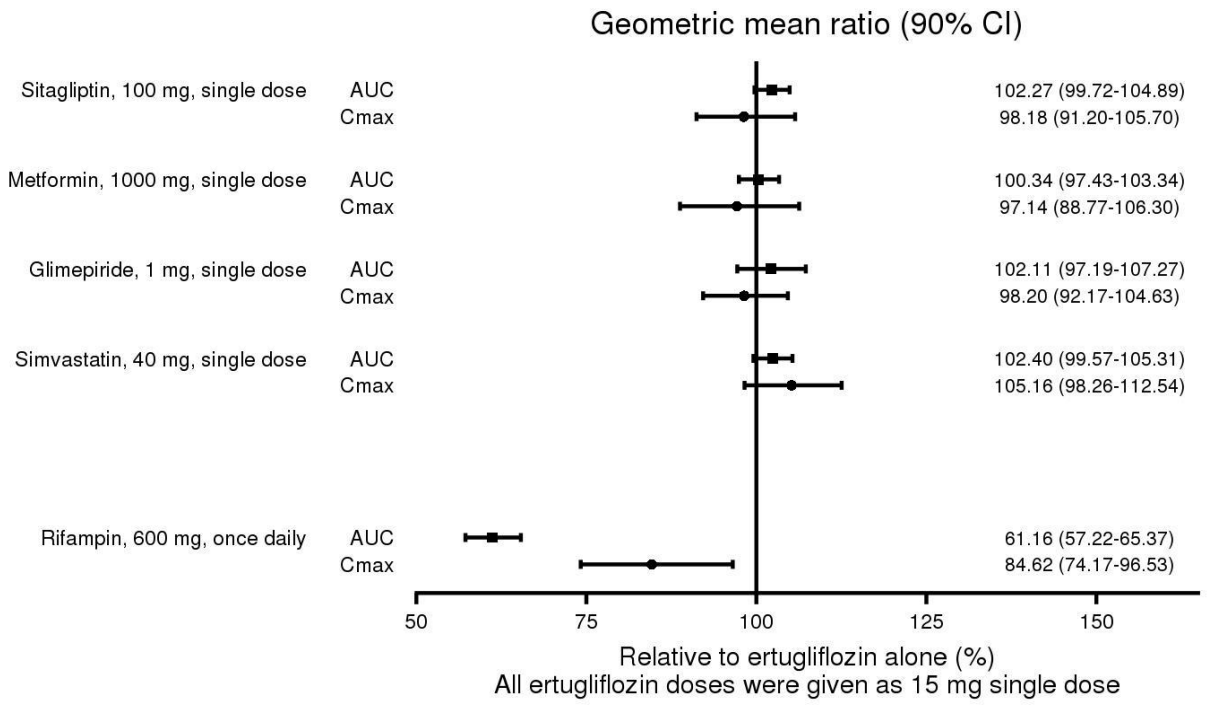
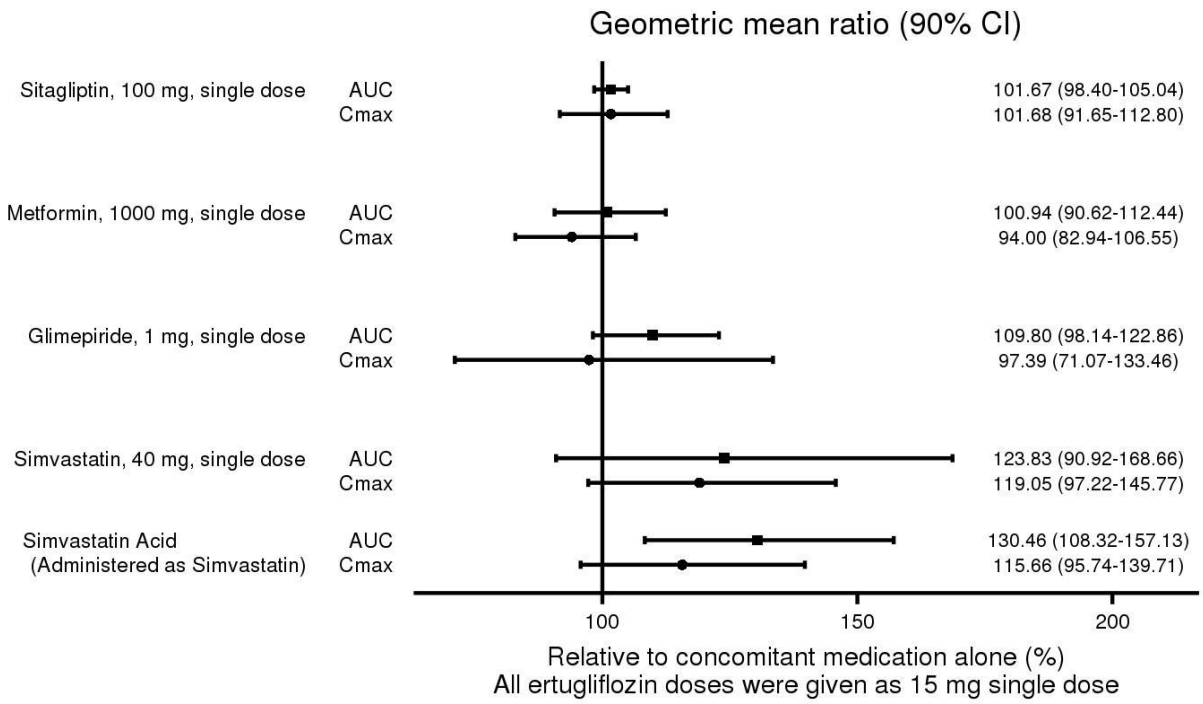


Figure 2: Effects of Ertugliflozin on the Pharmacokinetics of Other Drugs



13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity was evaluated in CD-1 mice and Sprague-Dawley rats. In the mouse study, ertugliflozin was administered by oral gavage at doses of 5, 15, and 40 mg/kg/day for up to 97 weeks in males and 102 weeks in females. There were no ertugliflozin-related neoplastic findings at doses up to 40 mg/kg/day (approximately 50 times human exposure at the maximum recommended human dose [MRHD] of 15 mg/day based on AUC). In the rat study, ertugliflozin was administered by oral gavage at doses of 1.5, 5, and 15 mg/kg/day for up to 92 weeks in females and 104 weeks in males. Ertugliflozin-related neoplastic findings included an increased incidence of adrenal medullary pheochromocytoma (PCC) in male rats at 15 mg/kg/day. Although the molecular mechanism remains unknown, this finding may be related to carbohydrate malabsorption leading to altered calcium homeostasis, which has been associated with PCC 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, based on AUC).

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.

Impairment of Fertility

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 480 and 570 times male and female human exposures, respectively, at the MRHD of 15 mg/day based on AUC comparison).

14 CLINICAL STUDIES

14.1 Glycemic Control Trials in Patients with Type 2 Diabetes Mellitus

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

In patients with type 2 diabetes mellitus treatment with STEGLATRO reduced hemoglobin A1c (HbA1c) compared to placebo. Reduction in HbA1c was generally similar across subgroups defined by age, sex, race, geographic region, baseline body mass index (BMI), and duration of type 2 diabetes mellitus.

Monotherapy

A total of 461 patients with type 2 diabetes mellitus inadequately controlled (HbA1c between 7% and 10.5%) on diet and exercise participated in a randomized, double-blind, multi-center, 26-week, placebo-controlled study (NCT01958671) to evaluate the efficacy and safety of STEGLATRO monotherapy. These patients, who were either treatment naïve or not receiving any background antihyperglycemic treatment ≥8 weeks, entered a 2-week, single-blind, placebo run-in period and were randomized to placebo, STEGLATRO 5 mg, or STEGLATRO 15 mg, administered once daily.

At Week 26, treatment with STEGLATRO at 5 mg or 15 mg orally once daily provided statistically significant reductions in HbA1c compared to placebo. STEGLATRO also resulted in a greater proportion of patients achieving an HbA1c <7% compared with placebo (see Table 4 and Figure 3).

Table 4: Results at Week 26 from a Placebo-Controlled Monotherapy Study of STEGLATRO in Patients with Type 2 Diabetes Mellitus*

	Placebo	STEGLATRO 5 mg	STEGLATRO 15 mg
HbA1c (%)	**N = 153**	**N = 155**	**N = 151**
Baseline (mean)	8.1	8.2	8.4
Change from baseline (LS mean†)	-0.2	-0.7	-0.8
Difference from placebo (LS mean†, 95% CI)		-0.6‡ (-0.8, -0.4)	-0.7‡ (-0.9, -0.4)
Patients [N (%)] with HbA1c <7%	26 (16.9)	47 (30.1)	59 (38.8)
FPG (mg/dL)	**N = 150**	**N = 151**	**N = 149**
Baseline (mean)	180.2	180.9	179.1
Change from baseline (LS mean†)	-11.6	-31.0	-36.4
Difference from placebo (LS mean†, 95% CI)		-19.4‡ (-27.6, -11.2)	-24.8‡ (-33.2, -16.4)

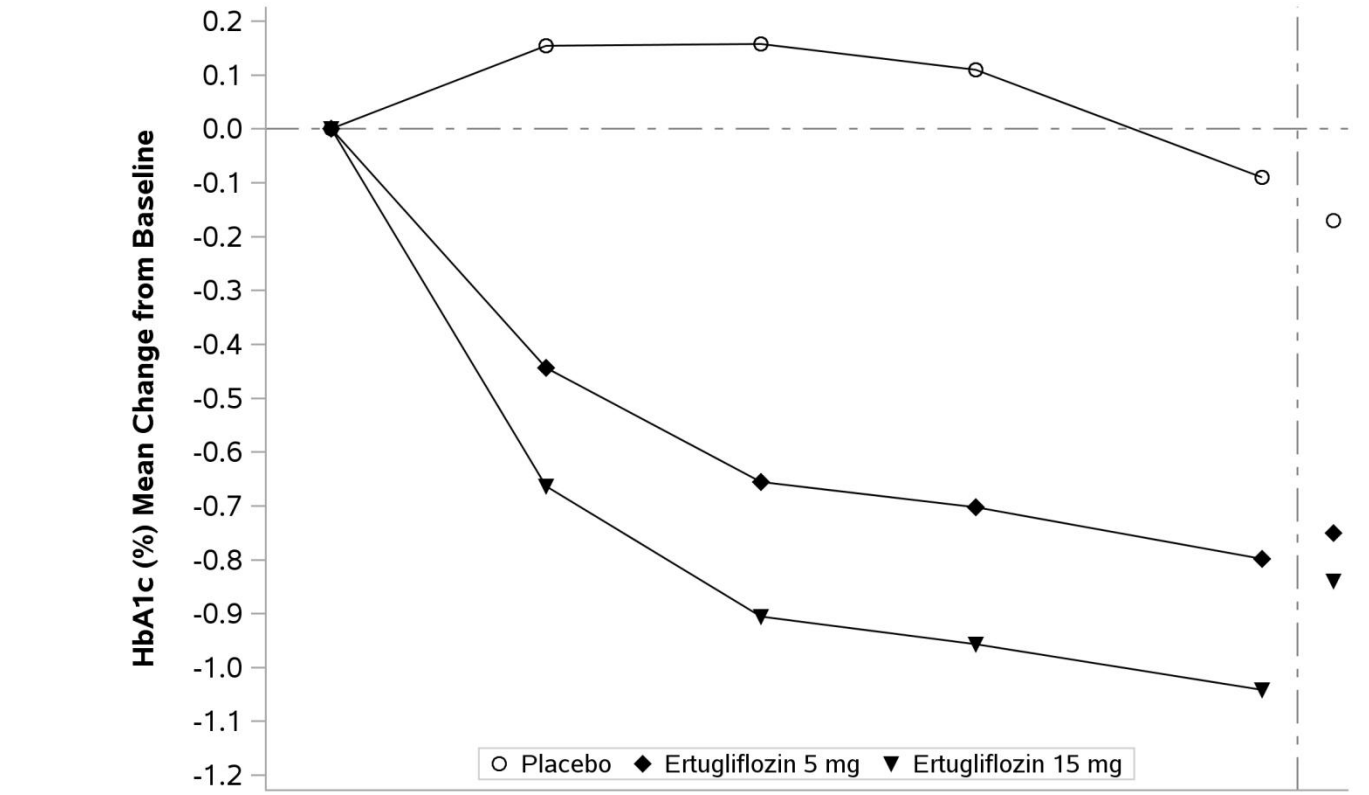
* N includes all randomized and treated patients with a baseline measurement of the outcome variable. At Week 26, the primary HbA1c endpoint was missing for 23%, 11%, and 16% of patients, and during the trial, rescue medication was initiated by 25%, 2%, and 3% of patients randomized to placebo, STEGLATRO 5 mg, and STEGLATRO 15 mg, respectively. Missing Week 26 measurements were imputed using multiple imputation with a mean equal to the baseline value of the patient. Results include measurements collected after initiation of rescue medication. For those patients who did not receive rescue medication and had values measured at 26 weeks, the mean changes from baseline for HbA1c were -0.1%, -0.8%, and -1.0% for placebo, STEGLATRO 5 mg, and STEGLATRO 15 mg, respectively.

† Intent-to-treat analysis using ANCOVA adjusted for baseline value, prior antihyperglycemic medication, and baseline eGFR.

‡ p<0.001 compared to placebo.

The mean baseline body weight was 94.2 kg, 94.0 kg, and 90.6 kg in the placebo, STEGLATRO 5 mg, and STEGLATRO 15 mg groups, respectively. The mean changes from baseline to Week 26 were -1.0 kg, -3.0 kg, and -3.1 kg in the placebo, STEGLATRO 5 mg, and STEGLATRO 15 mg groups, respectively. The difference from placebo (95% CI) for STEGLATRO 5 mg was -2.0 kg (-2.8, -1.2) and for STEGLATRO 15 mg was -2.1 kg (-2.9, -1.3).

Figure 3: HbA1c (%) Change Over Time in a 26-Week Placebo-Controlled Monotherapy Study of STEGLATRO in Patients with Type 2 Diabetes Mellitus*



Placebo (N)	153	137	124	105	89
Ertugliflozin 5 mg (N)	155	143	140	140	136
Ertugliflozin 15 mg (N)	151	144	142	134	123

* Data to the left of the vertical line are observed means (non-model-based) excluding values occurring post glycemic rescue. Data to the right of the vertical line represent the final Week 26 data, including all values regardless of use of glycemic rescue medication and use of study drug, with missing Week 26 values imputed using multiple imputation (26-MI) with a mean equal to the baseline value of the patient (see Table 4).

Combination Therapy

Add-on Combination Therapy with Metformin HCl

A total of 621 patients with type 2 diabetes mellitus inadequately controlled (HbA1c between 7% and 10.5%) on metformin HCl monotherapy (≥1,500 mg/day for ≥8 weeks) participated in a randomized, double-blind, multi-center, 26-week, placebo-controlled study (NCT02033889) to evaluate the efficacy and safety of STEGLATRO in combination with metformin HCl. Patients entered a 2-week, single-blind, placebo run-in, and were randomized to placebo, STEGLATRO 5 mg, or STEGLATRO 15 mg administered once daily in addition to continuation of background metformin HCl therapy.

At Week 26, treatment with STEGLATRO at 5 mg or 15 mg orally once daily provided statistically significant reductions in HbA1c compared to placebo. STEGLATRO also resulted in a greater proportion of patients achieving an HbA1c <7% compared to placebo (see Table 5).

Table 5: Results at Week 26 from a Placebo-Controlled Study for STEGLATRO Used in Combination with Metformin HCl in Patients with Type 2 Diabetes Mellitus*

	Placebo	STEGLATRO 5 mg	STEGLATRO 15 mg
HbA1c (%)	**N = 207**	**N = 205**	**N = 201**
Baseline (mean)	8.2	8.1	8.1
Change from baseline (LS mean†)	-0.2	-0.7	-0.9
Difference from placebo (LS mean†, 95% CI)		-0.5‡ (-0.7, -0.4)	-0.7‡ (-0.9, -0.5)
Patients [N (%)] with HbA1c <7%	38 (18.4)	74 (36.3)	87 (43.3)
FPG (mg/dL)	**N = 202**	**N = 199**	**N = 201**
Baseline (mean)	169.1	168.1	167.9
Change from baseline (LS mean†)	-8.7	-30.3	-40.9
Difference from placebo (LS mean†, 95% CI)		-21.6‡ (-27.8, -15.5)	-32.3‡ (-38.5, -26.0)

* N includes all randomized and treated patients with a baseline measurement of the outcome variable. At Week 26, the primary HbA1c endpoint was missing for 12%, 6%, and 9% of patients, and during the trial, rescue medication was initiated by 18%, 3%, and 1% of patients randomized to placebo, STEGLATRO 5 mg, and STEGLATRO 15 mg, respectively. Missing Week 26 measurements were imputed using multiple imputation with a mean equal to the baseline value of the patient. Results include measurements collected after initiation of rescue medication. For those patients who did not receive rescue medication and had values measured at 26 weeks, the mean changes from baseline for HbA1c were -0.2%, -0.7%, and -1.0% for placebo, STEGLATRO 5 mg, and STEGLATRO 15 mg, respectively.

† Intent-to-treat analysis using ANCOVA adjusted for baseline value, prior antihyperglycemic medication, menopausal status and baseline eGFR.

‡ p<0.001 compared to placebo.

The mean baseline body weight was 84.5 kg, 84.9 kg, and 85.3 kg in the placebo, STEGLATRO 5 mg, and STEGLATRO 15 mg groups, respectively. The mean changes from baseline to Week 26 were -1.4 kg, -3.2 kg, and -3.0 kg in the placebo, STEGLATRO 5 mg, and STEGLATRO 15 mg groups, respectively. The difference from placebo (95% CI) for STEGLATRO 5 mg was -1.8 kg (-2.4, -1.2) and for STEGLATRO 15 mg was -1.7 kg (-2.2, -1.1).

The mean baseline systolic blood pressure was 129.3 mmHg, 130.5 mmHg, and 130.2 mmHg in the placebo, STEGLATRO 5 mg, and STEGLATRO 15 mg groups, respectively. The mean changes from baseline to Week 26 were -1.8 mmHg, -5.1 mmHg, and -5.7 mmHg in the placebo, STEGLATRO 5 mg, and STEGLATRO 15 mg groups, respectively. The difference from placebo (95% CI) for STEGLATRO 5 mg was -3.3 mmHg (-5.6, -1.1) and for STEGLATRO 15 mg was -3.8 mmHg (-6.1, -1.5).

Active Controlled Study versus Glimepiride as Add-on Combination Therapy with Metformin HCl

A total of 1,326 patients with type 2 diabetes mellitus inadequately controlled (HbA1c between 7% and 9%) on metformin HCl monotherapy participated in a randomized, double-blind, multi-center, 52-week, active comparator controlled study (NCT01999218) to evaluate the efficacy and safety of STEGLATRO in combination with metformin HCl. These patients, who were receiving metformin HCl monotherapy (≥1,500 mg/day for ≥8 weeks), entered a 2-week, single-blind, placebo run-in period and were randomized to glimepiride, STEGLATRO 5 mg, or STEGLATRO 15 mg administered orally once daily in addition to continuation of background metformin HCl 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 hypoglycemia. The mean daily dose of glimepiride was 3.0 mg.

STEGLATRO 15 mg was non-inferior to glimepiride after 52 weeks of treatment. (See Table 6.)

Table 6: Results at Week 52 from an Active-Controlled Study Comparing STEGLATRO to Glimepiride as Add-on Therapy in Patients with Type 2 Diabetes Mellitus Inadequately Controlled on Metformin HCl*

	Glimepiride	STEGLATRO 5 mg	STEGLATRO 15 mg
HbA1c (%)	**N = 437**	**N = 447**	**N = 440**
Baseline (mean)	7.8	7.8	7.8
Change from baseline (LS mean†)	-0.6	-0.5	-0.5
Difference from glimepiride (LS mean†, 95% CI)		0.2‡ (0.0, 0.3)	0.1‡ (-0.0, 0.2)
Patients [N (%)] with HbA1c <7%	208 (47.7)	177 (39.5)	186 (42.2)

* N includes all randomized and treated patients with a baseline measurement of the outcome variable. At Week 52, the primary HbA1c endpoint was missing for 15%, 20%, and 16% of patients and during the trial, rescue medication was initiated by 3%, 6%, and 4% of patients randomized to glimepiride, STEGLATRO 5 mg, and STEGLATRO 15 mg, respectively. Missing Week 52 measurements were imputed using multiple imputation with a mean equal to the baseline value of the patient. Results include measurements collected after initiation of rescue medication. For those patients who did not receive rescue medication and had values measured at 52 weeks, the mean changes from baseline for HbA1c were -0.8%, -0.6%, and -0.7% for glimepiride, STEGLATRO 5 mg, and STEGLATRO 15 mg, respectively.

† Intent-to-treat analysis using ANCOVA adjusted for baseline value, prior antihyperglycemic medication and baseline eGFR.

‡ 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%.

The mean baseline body weight was 86.8 kg, 87.9 kg, and 85.6 kg in the glimepiride, STEGLATRO 5 mg, and STEGLATRO 15 mg groups, respectively. The mean changes from baseline to Week 52 were 0.6 kg, -2.6 kg, and -3.0 kg in the glimepiride, STEGLATRO 5 mg, and STEGLATRO 15 mg groups, respectively. The difference from glimepiride (95% CI) for STEGLATRO 5 mg was -3.2 kg (-3.7, -2.7) and for STEGLATRO 15 mg was -3.6 kg (-4.1, -3.1).

In Combination with Sitagliptin versus STEGLATRO Alone and Sitagliptin Alone, as Add-on to Metformin HCl

A total of 1,233 patients with type 2 diabetes mellitus with inadequate glycemic control (HbA1c between 7.5% and 11%) on metformin HCl monotherapy (≥1,500 mg/day for ≥8 weeks) participated in a randomized, double-blind, 26-week, active controlled study (NCT02099110) to evaluate the efficacy and safety of STEGLATRO 5 mg or 15 mg orally once daily in combination with sitagliptin 100 mg orally once daily compared to the individual components. Patients were randomized to one of five treatment arms: STEGLATRO 5 mg, STEGLATRO 15 mg, sitagliptin 100 mg, STEGLATRO 5 mg + sitagliptin 100 mg, or STEGLATRO 15 mg + sitagliptin 100 mg.

At Week 26, STEGLATRO 5 mg or 15 mg + sitagliptin 100 mg provided statistically significantly greater reductions in HbA1c compared to STEGLATRO (5 mg or 15 mg) alone or sitagliptin 100 mg alone. The mean change from baseline in HbA1c was -1.4% for STEGLATRO 5 mg or 15 mg + sitagliptin 100 mg versus -1.0%, for STEGLATRO 5 mg, STEGLATRO 15 mg, or sitagliptin 100 mg, respectively. More patients receiving STEGLATRO 5 mg or 15 mg + sitagliptin 100 mg achieved an HbA1c <7% (53.3% and 50.9%, for STEGLATRO 5 mg or 15 mg, respectively, + sitagliptin 100 mg) compared to the individual components (29.3%, 33.7%, and 38.5% for STEGLATRO 5 mg, STEGLATRO 15 mg, or sitagliptin 100 mg, respectively).

Add-on Combination Therapy with Metformin HCl and Sitagliptin

A total of 463 patients with type 2 diabetes mellitus inadequately controlled (HbA1c between 7% and 10.5%) on metformin HCl (≥1,500 mg/day for ≥8 weeks) and sitagliptin 100 mg once daily participated in a randomized, double-blind, multi-center, 26-week, placebo-controlled study (NCT02036515) to evaluate the efficacy and safety of STEGLATRO. Patients entered a 2-week, single-blind, placebo run-in period and were randomized to placebo, STEGLATRO 5 mg, or STEGLATRO 15 mg orally once daily.

At Week 26, treatment with STEGLATRO at 5 mg or 15 mg daily provided statistically significant reductions in HbA1c. STEGLATRO also resulted in a higher proportion of patients achieving an HbA1c <7% compared to placebo (see Table 7).

Table 7: Results at Week 26 from an Add-on Study of STEGLATRO in Combination with Metformin HCl and Sitagliptin in Patients with Type 2 Diabetes Mellitus*

	Placebo	STEGLATRO 5 mg	STEGLATRO 15 mg
HbA1c (%)	**N = 152**	**N = 155**	**N = 152**
Baseline (mean)	8.0	8.1	8.0
Change from baseline (LS mean†)	-0.2	-0.7	-0.8
Difference from placebo (LS mean†, 95% CI)		-0.5‡ (-0.7, -0.3)	-0.6‡ (-0.8, -0.4)
Patients [N (%)] with HbA1c <7%	31 (20.2)	54 (34.6)	64 (42.3)
FPG (mg/dL)	**N = 152**	**N = 156**	**N = 152**
Baseline (mean)	169.6	167.7	171.7
Change from baseline (LS mean†)	-6.5	-25.7	-32.1
Difference from placebo (LS mean†, 95% CI)		-19.2‡ (-26.8, -11.6)	-25.6‡ (-33.2, -18.0)

* N includes all randomized and treated patients with a baseline measurement of the outcome variable. At Week 26, the primary HbA1c endpoint was missing for 10%, 11%, and 7% of patients and during the trial, rescue medication was initiated by 16%, 1%, and 2% of patients randomized to placebo, STEGLATRO 5 mg, and STEGLATRO 15 mg, respectively. Missing Week 26 measurements were imputed using multiple imputation with a mean equal to the baseline value of the patient. Results include measurements collected after initiation of rescue medication. For those patients who did not receive rescue medication and had values measured at 26 weeks, the mean changes from baseline for HbA1c were -0.2%, -0.8%, and -0.9% for placebo, STEGLATRO 5 mg, and STEGLATRO 15 mg, respectively.

† Intent-to-treat analysis using ANCOVA adjusted for baseline value, prior antihyperglycemic medication and baseline eGFR.

‡ p<0.001 compared to placebo.

The mean baseline body weight was 86.5 kg, 87.6 kg, and 86.6 kg in the placebo, STEGLATRO 5 mg, and STEGLATRO 15 mg groups, respectively. The mean changes from baseline to Week 26 were -1.0 kg, -3.0 kg, and -2.8 kg in the placebo, STEGLATRO 5 mg, and STEGLATRO 15 mg groups, respectively. The difference from placebo (95% CI) for STEGLATRO 5 mg was -1.9 kg (-2.6, -1.3) and for STEGLATRO 15 mg was -1.8 kg (-2.4, -1.2).

The mean baseline systolic blood pressure was 130.2 mmHg, 132.1 mmHg, and 131.6 mmHg in the placebo, STEGLATRO 5 mg, and STEGLATRO 15 mg groups, respectively. The mean changes from baseline to Week 26 were -0.2 mmHg, -3.8 mmHg, and -4.5 mmHg in the placebo, STEGLATRO 5 mg, and STEGLATRO 15 mg groups, respectively. The difference from placebo (95% CI) for STEGLATRO 5 mg was -3.7 mmHg (-6.1, -1.2) and for STEGLATRO 15 mg was -4.3 mmHg (-6.7, -1.9).

Initial Combination Therapy with Sitagliptin

A total of 291 patients with type 2 diabetes mellitus inadequately controlled (HbA1c between 8% and 10.5%) on diet and exercise participated in a randomized, double-blind, multi-center, placebo-controlled 26-week study (NCT02226003) to evaluate the efficacy and safety of STEGLATRO in combination with sitagliptin. These patients, who were not receiving any background antihyperglycemic treatment for ≥8 weeks, entered a 2-week, single-blind, placebo run-in period and were randomized to placebo, STEGLATRO 5 mg or STEGLATRO 15 mg, in combination with sitagliptin (100 mg) orally once daily.

At Week 26, treatment with STEGLATRO 5 mg and 15 mg in combination with sitagliptin at 100 mg daily provided statistically significant reductions in HbA1c compared to placebo. STEGLATRO 5 mg and 15 mg in combination with sitagliptin at 100 mg daily also resulted in a higher proportion of patients achieving an HbA1c <7% and greater reductions in FPG compared with placebo.

Add-on Combination Therapy with Insulin (with or without Metformin HCl)

In an 18-week randomized, double-blind, multi-center, placebo-controlled, glycemic sub-study of VERTIS CV (eValuation of ERTugliflozin efficacy and Safety CardioVascular, NCT01986881, study details see 14.2), a total of 1,065 patients with type 2 diabetes mellitus and established atherosclerotic

cardiovascular disease with inadequate glycemic control (HbA1c between 7% and 10.5%) on background therapy of insulin ≥20 units/day (59% also on metformin HCl ≥1,500 mg/day) were randomized to placebo, STEGLATRO 5 mg or STEGLATRO 15 mg orally once daily treatment.

At Week 18, treatment with STEGLATRO at 5 mg or 15 mg daily provided statistically significant reductions in HbA1c compared to placebo (see Table 8).

Table 8: Results at Week 18 from an Add-on Study of STEGLATRO in Combination with Insulin (with or without Metformin HCl) in Patients with Type 2 Diabetes Mellitus*

	Placebo	STEGLATRO 5 mg	STEGLATRO 15 mg
HbA1c (%)	**N = 346**	**N = 346**	**N = 367**
Baseline (mean)	8.4	8.4	8.4
Change from baseline (LS mean†, SE)	-0.2 (0.05)	-0.7 (0.05)	-0.7 (0.05)
Difference from placebo (LS mean†, 95% CI)		-0.5‡ (-0.6, -0.4)	-0.5‡ (-0.7, -0.4)
Patients [N (%)] with HbA1c <7%§	37 (10.7)	79 (22.8)	81 (22.1)
FPG (mg/dL)	**N = 343**	**N = 346**	**N = 368**
Baseline (mean)	167.4	173.8	175.4
Change from baseline (LS mean†, SE)	-6.3 (2.91)	-25.6 (2.90)	-29.8 (2.86)
Difference from placebo (LS mean†, 95% CI)		-19.2‡ (-26.8, -11.6)	-23.4‡ (-30.9, -16.0)

* N includes all randomized and treated patients with a baseline measurement of the outcome variable. At Week 18, the primary HbA1c endpoint was missing for 10%, 9%, and 12% of patients and during the trial, rescue medication was initiated by 12%, 7%, and 6% of patients randomized to placebo, STEGLATRO 5 mg, and STEGLATRO 15 mg, respectively. Results include measurements collected after initiation of rescue medication. Prior to Week 18, background antidiabetic medication was held stable. Missing Week 18 measurements were imputed using multiple imputation with a mean equal to the baseline value of the patient (Return to Baseline analysis).

† Intent-to-treat analysis using ANCOVA adjusted for baseline value, insulin stratum, and baseline eGFR.

‡ p<0.001 compared to placebo.

§ Missing values imputed as not meeting the <7% criterion.

SE: standard error.

The mean baseline body weights were 93.3 kg, 93.8 kg, and 92.1 kg in the placebo, STEGLATRO 5 mg, and STEGLATRO 15 mg groups, respectively. The mean changes from baseline to Week 18 were - 0.2 kg, -1.6 kg, and -1.9 kg in the placebo, STEGLATRO 5 mg, and STEGLATRO 15 mg groups, respectively. The differences from placebo (95% CI) for STEGLATRO 5 mg were - 1.4 kg (- 1.9, - 0.9) and for STEGLATRO 15 mg was -1.6 kg (-2.1, -1.1).

The mean baseline systolic blood pressures were 134.0 mmHg, 135.6 mmHg, and 133.7 mmHg in the placebo, STEGLATRO 5 mg, and STEGLATRO 15 mg groups, respectively. The mean changes from baseline to Week 18 were 0.7 mmHg, -2.2 mmHg, and -1.7 mmHg in the placebo, STEGLATRO 5 mg, and STEGLATRO 15 mg groups, respectively. The differences from placebo (95% CI) for STEGLATRO 5 mg was – 2.9 mmHg (-4.9, -1.0) and for STEGLATRO 15 mg were -2.5 mmHg (- 4.4, - 0.5).

Add-on Combination Therapy with Metformin HCl and Sulfonylurea

In an 18-week randomized, double-blind, multi-center, placebo-controlled, glycemic sub-study of VERTIS CV (NCT01986881, study details see 14.2), a total of 330 patients with type 2 diabetes mellitus and established atherosclerotic cardiovascular disease with inadequate glycemic control (HbA1c between 7% and 10.5%) with background therapy of metformin HCl ≥1,500 mg/day and a sulfonylurea (SU) were randomized to placebo, STEGLATRO 5 mg or STEGLATRO 15 mg orally once daily treatment.

At Week 18, treatment with STEGLATRO at 5 mg or 15 mg daily provided statistically significant reductions in HbA1c compared to placebo (see Table 9).

Table 9: Results at Week 18 from an Add-on Study of STEGLATRO in Combination with Metformin HCl and a SU in Patients with Type 2 Diabetes Mellitus*

	Placebo	STEGLATRO 5 mg	STEGLATRO 15 mg
HbA1c (%)	**N = 116**	**N = 99**	**N = 113**
Baseline (mean)	8.3	8.4	8.3
Change from baseline (LS mean†, SE)	-0.3 (0.08)	-0.8 (0.09)	-0.9 (0.08)
Difference from placebo (LS mean†, 95% CI)		-0.6‡ (-0.8, -0.3)	-0.7‡ (-0.9, -0.4)
Patients [N (%)] with HbA1c <7%§	17 (14.7)	39 (39.4)	38 (33.6)
FPG (mg/dL)	**N = 117**	**N = 99**	**N = 113**
Baseline (mean)	177.3	183.5	174.0
Change from baseline (LS mean†, SE)	-3.5 (3.65)	-31.3 (3.87)	-33.0 (3.67)
Difference from placebo (LS mean†, 95% CI)		-27.9‡ (-37.8, -17.9)	-29.5‡ (-39.0, -19.9)

* N includes all randomized and treated patients with a baseline measurement of the outcome variable. At Week 18, the primary HbA1c endpoint was missing for 9%, 8%, and 6% of patients and during the trial, rescue medication was initiated by 10%, 7%, and 3% of patients randomized to placebo, STEGLATRO 5 mg, and STEGLATRO 15 mg, respectively. Results include measurements collected after initiation of rescue medication. Missing Week 18 measurements were imputed using multiple imputation with a mean equal to the baseline value of the patient (Return to Baseline analysis).

† Intent-to-treat analysis using ANCOVA adjusted for baseline value and baseline eGFR.

‡ p<0.001 compared to placebo.

§ Missing values imputed as not meeting the <7% criterion.

SE: standard error

The mean baseline body weights were 90.5 kg, 92.1 kg, and 92.9 kg in the placebo, STEGLATRO 5 mg, and STEGLATRO 15 mg groups, respectively. The mean changes from baseline to Week 18 were - 0.6 kg, -2.0 kg, and - 2.2 kg in the placebo, STEGLATRO 5 mg, and STEGLATRO 15 mg groups, respectively. The differences from placebo (95% CI) for STEGLATRO 5 mg were - 1.4 kg (- 2.2, - 0.7) and for STEGLATRO 15 mg was - 1.6 kg (- 2.3, - 0.9).

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

26-Week Placebo-Controlled Study

The efficacy of STEGLATRO was assessed in a multicenter, randomized, double-blind, placebo-controlled study (NCT01986855) of patients with type 2 diabetes mellitus and moderate renal impairment (468 patients with eGFR ≥30 to <60 mL/min/1.73 m^2). In this study, 202 patients exposed to STEGLATRO (5 mg or 15 mg) had an eGFR between 45 and 60 mL/min/1.73 m^2 and 111 patients exposed to STEGLATRO (5 mg or 15 mg orally once daily) had an eGFR between 30 and 45 mL/min/1.73 m^2. The mean duration of diabetes for the study population was approximately 14 years, and the majority of patients were receiving background insulin (55.9%) and/or sulfonylurea (40.3%) therapy. Approximately 50% had a history of cardiovascular disease or heart failure.

STEGLATRO did not show efficacy in this study. The HbA1c reductions from baseline to Week 26 were not significantly different between placebo and STEGLATRO 5 mg or 15 mg *[see Use in Specific Populations (8.6)]*.

14.2 Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus and Established Cardiovascular Disease

The effect of STEGLATRO on cardiovascular risk in adult patients with type 2 diabetes and established atherosclerotic cardiovascular disease was evaluated in the VERTIS CV study (NCT01986881), a multicenter, multi-national, randomized, double-blind, placebo-controlled, event-driven trial. The study compared the risk of experiencing a major adverse cardiovascular event (MACE) between STEGLATRO and placebo when these were added to and used concomitantly with standard of care treatments for diabetes and atherosclerotic cardiovascular disease.

A total of 8,246 patients were randomized to placebo (N=2,747), oral once daily STEGLATRO 5 mg (N=2,752) or oral once daily STEGLATRO 15 mg (N=2,747) and followed for a median of 3 years.

Approximately 88% of the study population was White, 6% Asian, and 3% Black or African American. The mean age was 64 years and approximately 70% were male.

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

Almost all patients (99%) had established atherosclerotic cardiovascular disease at baseline including: a documented history of coronary artery disease (76%), cerebrovascular disease (23%) or peripheral artery disease (19%). Approximately 24% patients had a history of heart failure (HF). At baseline, the mean systolic blood pressure was 133 mmHg, the mean diastolic blood pressure was 77 mmHg, the mean LDL was 89 mg/dL, and the mean HDL was 44 mg/dL. At baseline, approximately 81% of patients were treated with renin angiotensin system inhibitors, 69% with beta-blockers, 43% with diuretics, 82% with statins, 4% with ezetimibe, and 89% with antiplatelet agents.

The primary endpoint in VERTIS CV was the time to first occurrence of MACE. A major adverse cardiovascular event was defined as occurrence of either a cardiovascular death or a nonfatal myocardial infarction (MI) or a nonfatal stroke. The statistical analysis plan pre-specified that the 5 and 15 mg doses would be combined for the analysis. A Cox proportional hazards model was used to test for non-inferiority against the pre-specified risk margin of 1.3 for the hazard ratio of MACE. Type-1 error was controlled across multiple tests using a hierarchical testing strategy.

The incidence rate of MACE was similar between the STEGLATRO-treated and placebo-treated patients. The estimated hazard ratio of MACE associated with STEGLATRO relative to placebo was 0.97 with 95.6% confidence interval (0.85, 1.11). The upper bound of this confidence interval excluded a risk larger than 1.3 (Table 10). Results for the individual 5 mg and 15 mg doses were consistent with results for the combined dose group.

Table 10: Analysis of MACE and its Components from the VERTIS-CV Study*

Endpoint†	Placebo (N=2747)		STEGLATRO (N=5499)		Hazard Ratio vs Placebo (CI)‡
	N (%)	Event Rate (per 100 person-years)	N (%)	Event Rate (per 100 person-years)	
MACE (CV death, non-fatal MI, or non-fatal stroke) Composite	327 (11.9)	4.0	653 (11.9)	3.9	0.97 (0.85, 1.11)
Components of Composite Endpoint					
Non-fatal MI	148 (5.4)	1.6	310 (5.6)	1.7	1.04 (0.86, 1.27)
Non-fatal Stroke	78 (2.8)	0.8	157 (2.9)	0.8	1.00 (0.76, 1.32)
CV death	184 (6.7)	1.9	341 (6.2)	1.8	0.92 (0.77, 1.11)

N=Number of patients, CI=Confidence interval, CV=Cardiovascular, MI=Myocardial infarction.

* Intent-to-treat analysis set.

† MACE was evaluated in subjects who took at least one dose of study medication and, for subjects who discontinued study medication prior to the end of the study, censored events that occurred more than 365 days after the last dose of study medication. Other endpoints were evaluated using all randomized subjects and events that occurred any time after the first dose of study medication until the last contact date. The total number of first events was analyzed for each endpoint.

‡ HR and CI are based on Cox proportional hazards regression model, stratified by cohorts. For MACE a 95.6% CI is presented, for other endpoints a 95% CI is presented.

16 HOW SUPPLIED/STORAGE AND HANDLING

STEGLATRO (ertugliflozin) tablets are available as follows:

Strength	Description	How Supplied	NDC
5 mg tablets	pink, triangular-shaped, biconvex tablets, with “701” debossed on one side and plain on the other side	unit-of-use bottles of 30	0006-5363-03
		unit-of-use bottles of 90	0006-5363-06

15 mg tablets	red, triangular-shaped, biconvex tablets, with “702” debossed on one side and plain on the other side	unit-of-use bottles of 30	0006-5364-03
		unit-of-use bottles of 90	0006-5364-06

Store at 20°C-25°C (68°F-77°F), excursions permitted between 15°C-30°C (between 59°F-86°F) [see USP Controlled Room Temperature]. Protect from moisture. Store in a dry place.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Diabetic Ketoacidosis in Patients with Type 1 Diabetes Mellitus and Other Ketoacidosis

Inform patients that STEGLATRO can cause potentially fatal ketoacidosis and that type 2 diabetes mellitus and pancreatic disorders (e.g., history of pancreatitis or pancreatic surgery) are risk factors.

Educate all patients on precipitating factors (such as insulin dose reduction or missed insulin doses, infection, reduced caloric intake, ketogenic diet, surgery, dehydration, and alcohol abuse) and symptoms of ketoacidosis (including nausea, vomiting, abdominal pain, tiredness, and labored breathing). Inform patients that blood glucose may be normal even in the presence of ketoacidosis.

Advise patients that they may be asked to monitor ketones. If symptoms of ketoacidosis occur, instruct patients to discontinue STEGLATRO and seek medical attention immediately *[see Warnings and Precautions (5.1)]*.

Lower Limb Amputation

Inform patients of the potential for an increased risk of amputations. Counsel patients about the importance of routine preventative foot care. Instruct patients to monitor for new pain or tenderness, sores or ulcers, or infections involving the leg or foot and to seek medical advice immediately if such signs or symptoms develop *[see Warnings and Precautions (5.2)]*.

Volume Depletion

Inform patients that symptomatic hypotension may occur with STEGLATRO and advise them to contact their doctor if they experience such symptoms *[see Warnings and Precautions (5.3)]*. Inform patients that dehydration may increase the risk for hypotension, and to have adequate fluid intake.

Serious Urinary Tract Infections

Inform patients of the potential for urinary tract infections, which may be serious. Provide them with information on the symptoms of urinary tract infections. Advise them to seek medical advice if such symptoms occur *[see Warnings and Precautions (5.4)]*.

Hypoglycemia with Concomitant Use of Insulin or Insulin Secretagogue

Inform patients that the incidence of hypoglycemia may increase when STEGLATRO is used with insulin or an insulin secretagogue. Educate patients or caregivers on the signs and symptoms of hypoglycemia *[see Warnings and Precautions (5.5)].*

Necrotizing Fasciitis of the Perineum (Fournier’s Gangrene)

Inform patients that necrotizing infections of the perineum (Fournier’s Gangrene) have occurred with SGLT2 inhibitors. Counsel patients to promptly seek medical attention if they develop pain or tenderness, redness, or swelling of the genitals or the area from the genitals back to the rectum, along with a fever above 100.4°F or malaise *[see Warnings and Precautions (5.6)]*.

Genital Mycotic Infections in Females (e.g., Vulvovaginitis)

Inform female patients that vaginal yeast infections may occur and provide them with information on the signs and symptoms of vaginal yeast infection. Advise them of treatment options and when to seek medical advice *[see Warnings and Precautions (5.7)]*.

Genital Mycotic Infections in Males (e.g., Balanitis or Balanoposthitis)

Inform male patients that yeast infections of the penis (e.g., balanitis or balanoposthitis) may occur, especially in uncircumcised males. Provide them with information on the signs and symptoms of balanitis

and balanoposthitis (rash or redness of the glans or foreskin of the penis). Advise them of treatment options and when to seek medical advice *[see Warnings and Precautions (5.7)]*.

Fetal Toxicity

Advise pregnant patients of the potential risk to a fetus with treatment with STEGLATRO. Instruct patients to immediately inform their healthcare provider if pregnant or planning to become pregnant *[see Use in Specific Populations (8.1)]*.

Lactation

Advise patients that use of STEGLATRO is not recommended while breastfeeding *[see Use in Specific Populations (8.2)]*.

Laboratory Tests

Due to its mechanism of action, inform patients that their urine will test positive for glucose while taking STEGLATRO.

Missed Dose

Instruct patients to take STEGLATRO only as prescribed. If a dose is missed, it should be taken as soon as the patient remembers. Advise patients not to double their next dose.

Manufactured for: Merck Sharp & Dohme LLC
Rahway, NJ 07065, USA

For patent information: www.msd.com/research/patent

Copyright © 2017-2024 Merck & Co., Inc., Rahway, NJ, USA, and its affiliates.
All rights reserved.

uspi-mk8835-t-2412r010