

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

Warnings and Precautions

Necrotizing Fasciitis of the Perineum (5.7) 10/2018

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 for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis. (1)

DOSAGE AND ADMINISTRATION

- Recommended starting dose is 5 mg once daily, taken in the morning, with or without food. (2.1)
- Increase dose to 15 mg once daily in those tolerating STEGLATRO and needing additional glycemic control. (2.1)
- Assess renal function before initiating STEGLATRO and periodically thereafter (2.2):
 - Do not use in patients with an estimated glomerular filtration rate (eGFR) below 30 mL/minute/1.73 m².
 - Initiation is not recommended in patients with an eGFR of 30 to less than 60 mL/minute/1.73 m².
 - Continued use is not recommended in patients with an eGFR persistently between 30 and less than 60 mL/min/1.73 m².

DOSAGE FORMS AND STRENGTHS

Tablets: 5 mg and 15 mg (3)

CONTRAINDICATIONS

- Severe renal impairment, end-stage renal disease, or dialysis. (4, 5.3)
- History of serious hypersensitivity reaction to STEGLATRO. (4)

WARNINGS AND PRECAUTIONS

- **Hypotension:** May occur particularly in patients with renal impairment, the elderly, or patients on diuretics. Before initiating, assess and correct volume status. Monitor for signs and symptoms during therapy. (5.1)

- **Ketoacidosis:** Assess patients who present with signs and symptoms of metabolic acidosis for ketoacidosis, regardless of blood glucose level. If suspected, discontinue, evaluate, and treat promptly. Before initiating, consider risk factors for ketoacidosis. Patients may require monitoring and temporary discontinuation of therapy in clinical situations known to predispose to ketoacidosis. (5.2)
- **Acute Kidney Injury and Impairment in Renal Function:** Consider temporarily discontinuing in settings of reduced oral intake or fluid losses. If acute kidney injury occurs, discontinue and promptly treat. Monitor renal function. (5.3)
- **Urosepsis and Pyelonephritis:** Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated. (5.4)
- **Lower Limb Amputation:** Before initiating, consider factors that may increase risk of amputation. Monitor patients for infections or ulcers of lower limbs, and discontinue if these occur. (5.5)
- **Hypoglycemia:** Consider a lower dose of insulin or insulin secretagogue to reduce risk of hypoglycemia when used in combination. (5.6)
- **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. (5.7)
- **Genital Mycotic Infections:** Monitor and treat if indicated. (5.8)
- **Increased LDL-C:** Monitor and treat as appropriate. (5.9)

ADVERSE REACTIONS

- The most common adverse reactions associated with STEGLATRO (incidence ≥ 5%) were female genital mycotic infections. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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. (5.1, 8.5)
- **Renal Impairment:** Higher incidence of adverse reactions related to reduced intravascular volume and renal function. (5.1, 5.3, 8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2018

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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

- STEGLATRO is not recommended in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

- 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 volume depletion, correct this condition prior to initiation of STEGLATRO [see *Warnings and Precautions (5.1)*].

2.2 Patients with Renal Impairment

- Assess renal function prior to initiation of STEGLATRO and periodically thereafter [see *Warnings and Precautions (5.3)*].
- Use of STEGLATRO is contraindicated in patients with an eGFR less than 30 mL/minute/1.73 m² [see *Contraindications (4)*].
- Initiation of STEGLATRO is not recommended in patients with an eGFR of 30 mL/minute/1.73 m² to less than 60 mL/minute/1.73 m² [see *Warnings and Precautions (5.3) and Use in Specific Populations (8.6)*].
- Continued use of STEGLATRO is not recommended when eGFR is persistently between 30 and less than 60 mL/minute/1.73 m².

No dose adjustment is needed in patients with mild renal impairment.

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

- Severe renal impairment, end-stage renal disease (ESRD), or dialysis [see *Warnings and Precautions (5.3) and Use in Specific Populations (8.6)*].
- History of a serious hypersensitivity reaction to STEGLATRO.

5 WARNINGS AND PRECAUTIONS

5.1 Hypotension

STEGLATRO causes intravascular volume contraction. Therefore, symptomatic hypotension may occur after initiating STEGLATRO [see *Adverse Reactions (6.1)*] particularly in patients with impaired renal function (eGFR less than 60 mL/min/1.73 m²) [see *Use in Specific Populations (8.6)*], elderly patients (≥65 years), in patients with low systolic blood pressure, and in patients on diuretics. Before initiating STEGLATRO, volume status should be assessed and corrected if indicated. Monitor for signs and symptoms of hypotension after initiating therapy.

5.2 Ketoacidosis

Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization, have been identified in clinical trials and postmarketing surveillance in patients with type 1 and type 2 diabetes mellitus receiving sodium glucose co-transporter-2 (SGLT2) inhibitors and cases have been reported in

STEGLATRO-treated patients in clinical trials. Across the clinical program, ketoacidosis was identified in 3 of 3,409 (0.1%) of STEGLATRO-treated patients and 0% of comparator-treated patients. Fatal cases of ketoacidosis have been reported in patients taking SGLT2 inhibitors. STEGLATRO is not indicated for the treatment of patients with type 1 diabetes mellitus [see *Indications and Usage (1)*].

Patients treated with STEGLATRO who present with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of presenting blood glucose levels, as ketoacidosis associated with STEGLATRO may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, STEGLATRO should be discontinued, patient should be evaluated, and prompt treatment should be instituted. Treatment of ketoacidosis may require insulin, fluid and carbohydrate replacement.

In many of the reported cases, and particularly in patients with type 1 diabetes, the presence of ketoacidosis was not immediately recognized and institution of treatment was delayed because presenting blood glucose levels were below those typically expected for diabetic ketoacidosis (often less than 250 mg/dL). Signs and symptoms at presentation were consistent with dehydration and severe metabolic acidosis and included nausea, vomiting, abdominal pain, generalized malaise, and shortness of breath. In some but not all cases, factors predisposing to ketoacidosis such as insulin dose reduction, acute febrile illness, reduced caloric intake due to illness or surgery, pancreatic disorders suggesting insulin deficiency (e.g., type 1 diabetes, history of pancreatitis or pancreatic surgery), and alcohol abuse were identified.

Before initiating STEGLATRO, consider factors in the patient history that may predispose to ketoacidosis, including pancreatic insulin deficiency from any cause, caloric restriction, and alcohol abuse. In patients treated with STEGLATRO consider monitoring for ketoacidosis and temporarily discontinuing STEGLATRO in clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or surgery).

5.3 Acute Kidney Injury and Impairment in Renal Function

STEGLATRO causes intravascular volume contraction and can cause renal impairment [see *Adverse Reactions (6.1)*]. There have been postmarketing reports of acute kidney injury some requiring hospitalization and dialysis in patients receiving SGLT2 inhibitors.

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.

STEGLATRO increases serum creatinine and decreases eGFR. Patients with moderate renal impairment (eGFR 30 to less than 60 mL/min/1.73 m²) may be more susceptible to these changes. Renal function abnormalities can occur after initiating STEGLATRO [see *Adverse Reactions (6.1)*]. Renal function should be evaluated prior to initiating STEGLATRO and periodically thereafter. Use of STEGLATRO is not recommended when eGFR is persistently between 30 and less than 60 mL/min/1.73 m² and is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m² [see *Dosage and Administration (2.2)*, *Contraindications (4)*, and *Use in Specific Populations (8.6)*].

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. Cases of pyelonephritis also have been reported in STEGLATRO-treated patients in clinical trials. 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 Lower Limb Amputation

An increased risk for lower limb amputation (primarily of the toe) has been observed in clinical studies with another SGLT2 inhibitor. Across seven Phase 3 clinical trials in the STEGLATRO development program, 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. A causal association between STEGLATRO and lower limb amputation has not been definitively established.

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. 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.

5.6 Hypoglycemia with Concomitant Use with Insulin and 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 and/or an insulin secretagogue [see *Adverse Reactions (6.1)*]. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with STEGLATRO.

5.7 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. 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.

5.8 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.

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

Dose-related increases in LDL-C can occur with STEGLATRO [see *Adverse Reactions (6.1)*]. Monitor and treat as appropriate.

5.10 Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with STEGLATRO.

6 ADVERSE REACTIONS

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

- Hypotension [see *Warnings and Precautions (5.1)*]
- Ketoacidosis [see *Warnings and Precautions (5.2)*]
- Acute Kidney Injury and Impairment in Renal Function [see *Warnings and Precautions (5.3)*]
- Urosepsis and Pyelonephritis [see *Warnings and Precautions (5.4)*]
- Lower Limb Amputation [see *Warnings and Precautions (5.5)*]
- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues [see *Warnings and Precautions (5.6)*]
- Necrotizing Fasciitis of the Perineum (Fournier's gangrene) [see *Warnings and Precautions (5.7)*]
- Genital Mycotic Infections [see *Warnings and Precautions (5.8)*]

- Increases in Low-Density Lipoprotein Cholesterol (LDL-C) [see *Warnings and Precautions (5.9)*]

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 Caucasian, 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 m²) 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%
Thirst [♯]	0.6%	2.7%	1.4%

* 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: 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.

[♯] 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 m²). 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)].

Ketoacidosis

Across the clinical program, ketoacidosis was identified in 3 of 3,409 (0.1%) ertugliflozin-treated patients and 0.0% of comparator-treated patients [see *Warnings and Precautions* (5.2)].

Impairment in Renal Function

Treatment with STEGLATRO was associated with increases in serum creatinine and decreases in eGFR (see Table 2). Patients with moderate renal impairment at baseline had larger mean changes. In a study in patients with moderate renal impairment, these abnormal laboratory findings were observed to reverse after treatment discontinuation [see *Use in Specific Populations* (8.5, 8.6)].

Table 2: Changes from Baseline in Serum Creatinine and eGFR in the Pool of Three 26-Week Placebo-Controlled Studies, and a 26-Week Moderate Renal Impairment Study in Patients with Type 2 Diabetes Mellitus

		Pool of 26-Week Placebo-Controlled Studies		
		Placebo N=515	STEGLATRO 5 mg N=519	STEGLATRO 15 mg N=510
Baseline Mean	Creatinine (mg/dL)	0.83	0.82	0.82
	eGFR (mL/min/1.73 m ²)	89.5	88.2	89.0
Week 6 Change	Creatinine (mg/dL)	0.00	0.03	0.03
	eGFR (mL/min/1.73 m ²)	-0.3	-2.7	-3.1
Week 26 Change	Creatinine (mg/dL)	-0.01	0.00	0.01
	eGFR (mL/min/1.73 m ²)	0.7	0.5	-0.6
		Moderate Renal Impairment Study		
		Placebo N=154	STEGLATRO 5 mg N=158	STEGLATRO 15 mg N=155
Baseline	Creatinine (mg/dL)	1.39	1.38	1.37
	eGFR (mL/min/1.73 m ²)	46.0	46.8	46.9
Week 6 Change	Creatinine (mg/dL)	-0.02	0.11	0.12
	eGFR (mL/min/1.73 m ²)	0.6	-3.2	-4.1
Week 26 Change	Creatinine (mg/dL)	0.02	0.08	0.10
	eGFR (mL/min/1.73 m ²)	0.0	-2.7	-2.6

Renal-related adverse reactions (e.g., acute kidney injury, renal impairment, acute prerenal failure) may occur in patients treated with STEGLATRO, particularly in patients with moderate renal impairment where the incidence of renal-related adverse reactions was 0.6%, 2.5%, and 1.3% in patients treated with placebo, STEGLATRO 5 mg, and STEGLATRO 15 mg, 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 of 1,450 (0.1%) in the non-STEGLATRO group, 3 of 1,716 (0.2%) in the STEGLATRO 5 mg group, and 8 of 1,693 (0.5%) in the STEGLATRO 15 mg group.

Hypoglycemia

The incidence of hypoglycemia by study is shown in Table 3.

Table 3: 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 (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 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	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)

* 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.

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.

Laboratory Tests

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 [see *Warnings and Precautions* (5.9)].

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. 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.

- Cases of necrotizing fasciitis of the perineum (Fournier's gangrene) have been seen with SGLT2 inhibitors [see *Warnings and Precautions* (5.7)]

7 DRUG INTERACTIONS

7.1 Concomitant Use with Insulin and Insulin Secretagogues

STEGLATRO may increase the risk of hypoglycemia when used in combination with insulin and/or an insulin secretagogue [see *Adverse Reactions* (6.1)]. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with STEGLATRO [see *Warnings and Precautions* (5.6)].

7.2 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.

7.3 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.

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, stillbirth, 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

Animal 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. Across the clinical program, 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 (5.1) and Adverse Reactions (6.1)*]. STEGLATRO is expected to have diminished efficacy in elderly patients with renal impairment [see *Use in Specific Populations (8.6)*].

8.6 Renal Impairment

The safety and efficacy of STEGLATRO have not been established in patients with type 2 diabetes mellitus and moderate renal impairment [see *Clinical Studies (14.4)*]. Compared to placebo-treated patients, patients with moderate renal impairment treated with STEGLATRO did not have improvement in glycemic control [see *Clinical Studies (14.4)*], and had increased risks for renal impairment, renal-related adverse reactions and volume depletion adverse reactions [see *Dosage and Administration (2.2)*, *Warnings and Precautions (5.3)* and *Adverse Reactions (6.1)*]. Therefore, STEGLATRO is not recommended in this population.

STEGLATRO is contraindicated in patients with severe renal impairment, ESRD, or receiving dialysis. STEGLATRO is not expected to be effective in these patient populations [see *Contraindications (4)*].

No dosage adjustment or increased monitoring is needed in patients with mild renal impairment.

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

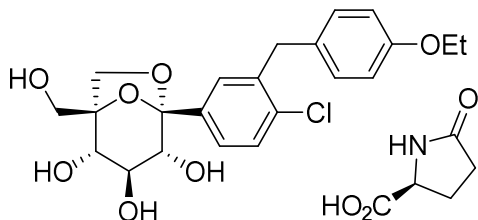
In the event of an overdose with STEGLATRO, contact the Poison Control Center. Employ the usual supportive measures as dictated by the patient's clinical status. Removal of ertugliflozin by hemodialysis has not been studied.

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 (1S,2S,3S,4R,5S)-5-(4-chloro-3-(4-ethoxybenzyl)phenyl)-1-(hydroxymethyl)-6,8-dioxabicyclo[3.2.1]octane-2,3,4-triol, compound with (2S)-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 [¹⁴C]-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 Phase 1 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)*].

Pediatric Patients

No studies with STEGLATRO have been performed in pediatric patients.

Effects of Age, Body Weight, Gender, and Race

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

Drug 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 (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.

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

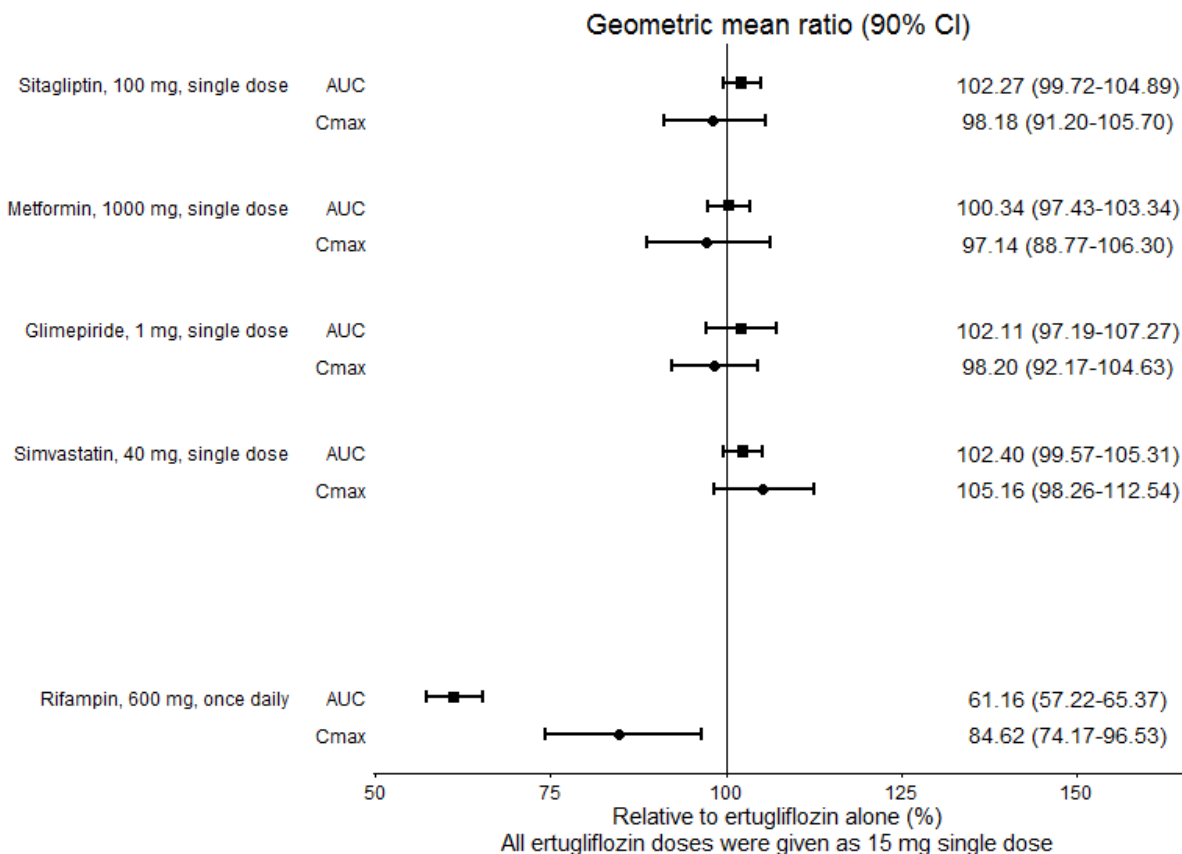
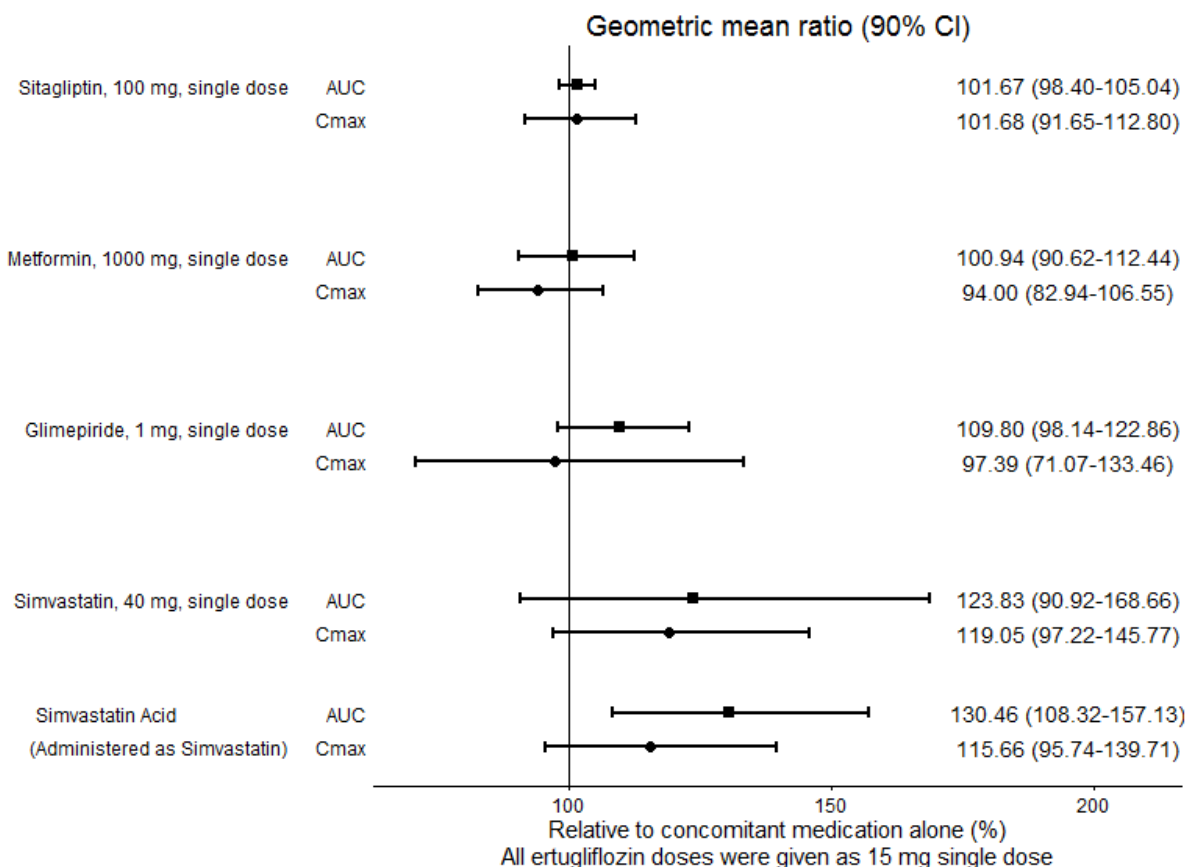


Figure 2: Effects of Ertugliflozin on the Pharmacokinetics of Other Drugs



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 Overview of Clinical Studies in Patients with Type 2 Diabetes Mellitus

The efficacy and safety of STEGLATRO have been studied in 7 multicenter, randomized, double-blind, placebo- or active comparator-controlled, clinical studies involving 4,863 patients with type 2 diabetes mellitus. These studies included White, Hispanic, Black, Asian, and other racial and ethnic groups, and patients with an average age of approximately 57.8 years.

STEGLATRO has been studied as monotherapy and in combination with metformin and/or a dipeptidyl peptidase 4 (DPP-4) inhibitor. STEGLATRO has also been studied in combination with antidiabetic medications, including insulin and a sulfonylurea, in patients with type 2 diabetes mellitus with moderate renal impairment.

In patients with type 2 diabetes mellitus treatment with STEGLATRO reduced hemoglobin A1c (HbA1c) compared to placebo.

In patients with type 2 diabetes mellitus treated with STEGLATRO, the 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. In patients with type 2 diabetes mellitus and moderate renal impairment, treatment with STEGLATRO did not result in a reduction in HbA1c compared to placebo.

14.2 Clinical Study of Monotherapy Use of STEGLATRO in Patients with Type 2 Diabetes Mellitus

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 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)

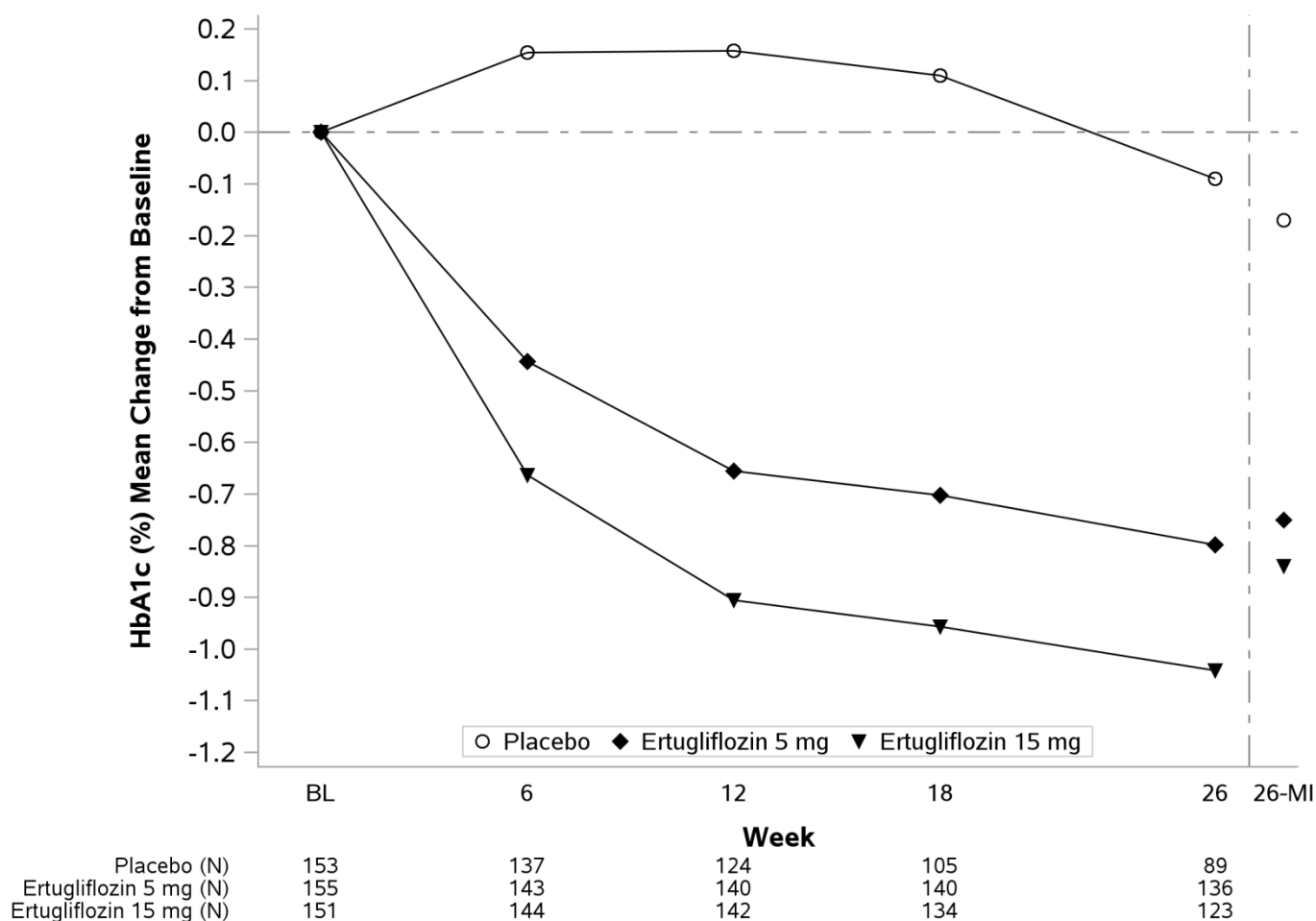
* N includes all randomized and treated patients with a baseline measurement of the outcome variable. At Week 26, the primary HbA1c endpoint was missing for 23%, 11%, and 16% of patients, and during the trial, rescue medication was initiated by 25%, 2%, and 3% of patients randomized to placebo, STEGLATRO 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*



* 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).

14.3 Clinical Studies of Combination Therapy Use of STEGLATRO in Patients with Type 2 Diabetes Mellitus

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 ($\geq 1,500$ 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. 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 therapy.

At Week 26, treatment with STEGLATRO at 5 mg or 15 mg 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 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

A total of 1,326 patients with type 2 diabetes mellitus inadequately controlled (HbA1c between 7% and 9%) on metformin 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. These patients, who were receiving metformin 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 once daily in addition to continuation of background metformin therapy. Glimepiride was initiated at 1 mg/day and titrated up to a maximum dose of 6 or 8 mg/day (depending on maximum approved dose in each country) or a maximum tolerated dose or down-titrated to avoid or manage 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*

	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

A total of 1,233 patients with type 2 diabetes mellitus with inadequate glycemic control (HbA1c between 7.5% and 11%) on metformin monotherapy ($\geq 1,500$ 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 in combination with sitagliptin 100 mg 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 and Sitagliptin

A total of 463 patients with type 2 diabetes mellitus inadequately controlled (HbA1c between 7% and 10.5%) on metformin ($\geq 1,500$ 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.

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 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) 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.

14.4 Clinical Study of STEGLATRO in Patients with Moderate Renal Impairment and Type 2 Diabetes Mellitus

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 m²). In this study, 202 patients exposed to STEGLATRO (5 mg or 15 mg) had an eGFR between 45 and 60 mL/min/1.73 m² and 111 patients exposed to STEGLATRO (5 mg or 15 mg) had an eGFR between 30 and 45 mL/min/1.73 m². 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)].

16 HOW SUPPLIED/STORAGE AND HANDLING

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

5 mg tablets, are pink, triangular-shaped, biconvex, with “701” debossed on one side and plain on the other side. They are supplied as follows:

NDC 0006-5363-03 unit-of-use bottles of 30

NDC 0006-5363-06 unit-of-use bottles of 90

NDC 0006-5363-07 bulk bottles of 500

15 mg tablets, are red, triangular-shaped, biconvex, with “702” debossed on one side and plain on the other side. They are supplied as follows:

NDC 0006-5364-03 unit-of-use bottles of 30

NDC 0006-5364-06 unit-of-use bottles of 90

NDC 0006-5364-07 bulk bottles of 500

Storage of Bottles

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).

Instructions

Instruct patients to read the Medication Guide before starting STEGLATRO (ertugliflozin) and to reread it each time the prescription is renewed.

Inform patients of the potential risks and benefits of STEGLATRO and of alternative modes of therapy. Also inform patients about the importance of adherence to dietary instructions, regular physical activity, periodic blood glucose monitoring and HbA1c testing, recognition and management of hypoglycemia and hyperglycemia, and assessment for diabetes complications. Advise patients to seek medical advice promptly during periods of stress such as fever, trauma, infection, or surgery, as medication requirements may change.

Instruct patients to take STEGLATRO only as prescribed. If a dose is missed, advise patients to take it as soon as it is remembered unless it is almost time for the next dose, in which case patients should skip the missed dose and take the medicine at the next regularly scheduled time. Advise patients not to take two doses of STEGLATRO at the same time.

Hypoglycemia with Concomitant Use of Insulin and/or Insulin Secretagogue

Inform patients that the incidence of hypoglycemia may increase when STEGLATRO is added to insulin and/or an insulin secretagogue and that a lower dose of insulin or insulin secretagogue may be required to reduce the risk of hypoglycemia [see *Warnings and Precautions* (5.6)].

Hypotension

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* (5.1)]. Inform patients that dehydration may increase the risk for hypotension, and to have adequate fluid intake.

Ketoacidosis

Inform patients that ketoacidosis is a serious life-threatening condition. Cases of ketoacidosis have been reported during use of STEGLATRO. Instruct patients to check ketones (when possible) if symptoms consistent with ketoacidosis occur even if blood glucose is not elevated. If symptoms of

ketoacidosis (including nausea, vomiting, abdominal pain, tiredness, and labored breathing) occur, instruct patients to discontinue STEGLATRO and seek medical advice immediately [see *Warnings and Precautions* (5.2)].

Acute Kidney Injury

Inform patients that acute kidney injury has been reported during use of STEGLATRO. Advise patients to seek medical advice immediately if they have reduced oral intake (due to acute illness or fasting) or increased fluid losses (due to vomiting, diarrhea, or excessive heat exposure), as it may be appropriate to temporarily discontinue STEGLATRO use in those settings [see *Warnings and Precautions* (5.3)].

Monitoring of Renal Function

Inform patients about the importance of regular testing of renal function when receiving treatment with STEGLATRO [see *Warnings and Precautions* (5.3)].

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)].

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* (5.5)].

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* (5.7)].

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* (5.8)].

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* (5.8)].

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.

Manufactured for: Merck Sharp & Dohme Corp., a subsidiary of
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For patent information: www.merck.com/product/patent/home.html

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