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

----------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 m^2.
  - Initiation is not recommended in patients with an eGFR of 30 to less than 60 mL/minute/1.73 m^2.
  - Continued use is not recommended in patients with an eGFR persistently between 30 and less than 60 mL/min/1.73 m^2.

---------- 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)
- *Genital Mycotic Infections:* Monitor and treat if indicated. (5.7)
- *Increased LDL-C:* Monitor and treat as appropriate. (5.8)

---------- 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: 12/2017

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

- 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 m^2 *[see Contraindications (4)]*.
- Initiation of STEGLATRO is not recommended in patients with an eGFR of 30 mL/minute/1.73 m^2 to less than 60 mL/minute/1.73 m^2 *[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 m^2.

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 m^2) *[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 m^2) 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 m^2 and is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m^2 *[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 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.

5.8 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.

5.9 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)]*
- Genital Mycotic Infections *[see Warnings and Precautions (5.7)]*
- Increases in Low-Density Lipoprotein Cholesterol (LDL-C) *[see Warnings and Precautions (5.8)]*

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 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%
Thirst[Þ]	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.

Þ 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)]*.

Ketoacidosis

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