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

STEGLUJAN™ (ertugliflozin and sitagliptin) tablets, for oral use
Initial U.S. Approval: 2017

----------RECENT MAJOR CHANGES----------
Warnings and Precautions
Ketoacidosis (5.3) 01/2020

----------INDICATIONS AND USAGE----------
STEGLUJAN is a combination of ertugliflozin, a sodium glucose co-transporter 2 (SGLT2) inhibitor, and sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both ertugliflozin and sitagliptin is appropriate. (1)

Limitations of Use:
- Not for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis. (1)
- Has not been studied in patients with a history of pancreatitis. (1, 5.1)

---------- DOSAGE AND ADMINISTRATION ----------
- Recommended starting dose is 5 mg ertugliflozin/100 mg sitagliptin once daily, taken in the morning, with or without food. (2.1)
- Increase dose to 15 mg ertugliflozin/100 mg sitagliptin once daily in those tolerating STEGLUJAN and needing additional glycemic control. (2.1)
- Assess renal function before initiating STEGLUJAN and periodically thereafter (2.2):
  - Do not use in patients with an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m^2.
  - Initiation is not recommended in patients with an eGFR of 30 to less than 60 mL/min/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:
- Ertugliflozin 5 mg and sitagliptin 100 mg (3)
- Ertugliflozin 15 mg and sitagliptin 100 mg (3)

----------CONTRAINDICATIONS----------
- Severe renal impairment, end stage renal disease, or dialysis. (4, 5.4)
- History of a serious hypersensitivity reaction to sitagliptin, such as anaphylaxis or angioedema. (4, 5.11, 6.2)
- History of serious hypersensitivity reaction to ertugliflozin. (4)

---------- WARNINGS AND PRECAUTIONS----------
- *Pancreatitis:* There have been postmarketing reports of acute pancreatitis in patients taking sitagliptin, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. If pancreatitis is suspected, promptly discontinue. (5.1)
- *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. (5.2)
- *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. (5.3)
- *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. There have been postmarketing reports of acute renal failure in patients taking sitagliptin, sometimes requiring dialysis. Monitor renal function. (5.4)
- *Urosepsis and Pyelonephritis:* Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated. (5.5)
- *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. (5.6)
- *Heart Failure:* Heart failure has been observed with two other members of the DPP-4 inhibitor class. Consider risks and benefits in patients who have known risk factors for heart failure. Monitor patients for signs and symptoms. (5.7)
- *Hypoglycemia:* Consider a lower dose of insulin or insulin secretagogue to reduce risk of hypoglycemia when used in combination. (5.8)
- *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. (5.9)
- *Genital Mycotic Infections:* Monitor and treat if indicated. (5.10)
- *Hypersensitivity:* There have been postmarketing reports of serious allergic and hypersensitivity reactions in patients treated with sitagliptin such as anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. In such cases, promptly discontinue, assess for other potential causes, institute appropriate monitoring and treatment, and initiate alternative treatment for diabetes. (5.11)
- *Increased LDL-C:* Monitor and treat as appropriate. (5.12)
- *Severe and Disabling Arthralgia:* Severe and disabling arthralgia has been reported in patients taking DPP-4 inhibitors. Consider as a possible cause for severe joint pain and discontinue if appropriate. (5.13)
- *Pemphigoid:* There have been postmarketing reports of bullous pemphigoid requiring hospitalization in patients taking DPP-4 inhibitors. Tell patients to report development of blisters or erosions. If bullous pemphigoid is suspected, discontinue. (5.14)

---------- ADVERSE REACTIONS ----------
- Most common adverse reactions associated with ertugliflozin (incidence ≥5%): female genital mycotic infections. (6.1)
- Most common adverse reactions associated with sitagliptin (incidence ≥5%): upper respiratory tract infection, nasopharyngitis and headache. In the add-on to sulfonylurea and add-on to insulin studies, hypoglycemia was also more commonly reported in patients treated with sitagliptin compared to placebo. (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. (5.2, 8.5)
- *Renal Impairment:* Higher incidence of adverse reactions related to reduced intravascular volume and renal function. (5.2, 5.4, 8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 01/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

STEGLUJAN™ is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both ertugliflozin and sitagliptin is appropriate.

Limitations of Use

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

STEGLUJAN has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using STEGLUJAN. *[See Warnings and Precautions (5.1).]*

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

- The recommended starting dose of STEGLUJAN is 5 mg ertugliflozin/100 mg sitagliptin once daily, taken in the morning, with or without food. In patients tolerating STEGLUJAN, the dose may be increased to a maximum recommended dose of 15 mg ertugliflozin/100 mg sitagliptin, once daily, if additional glycemic control is needed.
- For patients treated with ertugliflozin who are being switched to STEGLUJAN, the dose of ertugliflozin can be maintained.
- In patients with volume depletion, correct this condition prior to initiation of STEGLUJAN *[see Warnings and Precautions (5.2)]*.

2.2 Patients with Renal Impairment

- Assess renal function prior to initiation of STEGLUJAN and periodically thereafter *[see Warnings and Precautions (5.4)]*.
- Use of STEGLUJAN is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m^2 *[see Contraindications (4)]*.
- Initiation of STEGLUJAN is not recommended in patients with an eGFR of 30 mL/min/1.73 m^2 to less than 60 mL/min/1.73 m^2 *[see Warnings and Precautions (5.4) and Use in Specific Populations (8.6)]*.
- Continued use of STEGLUJAN is not recommended when eGFR is persistently between 30 and less than 60 mL/min/1.73 m^2.
- No dose adjustment is needed in patients with mild renal impairment.

3 DOSAGE FORMS AND STRENGTHS

- STEGLUJAN 5 mg/100 mg: ertugliflozin 5 mg and sitagliptin 100 mg tablets are beige, almond-shaped debossed with “554” on one side and plain on the other side.
- STEGLUJAN 15 mg/100 mg: ertugliflozin 15 mg and sitagliptin 100 mg tablets are brown, almond-shaped debossed with “555” 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 (5.4) and Use in Specific Populations (8.6)]*.
- History of a serious hypersensitivity reaction to sitagliptin, such as anaphylaxis or angioedema *[see Warnings and Precautions (5.11) and Adverse Reactions (6.2)].*
- History of a serious hypersensitivity reaction to ertugliflozin.

5 WARNINGS AND PRECAUTIONS

5.1 Pancreatitis

There have been postmarketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, in patients taking sitagliptin, a component of STEGLUJAN. After initiation of STEGLUJAN, patients should be observed carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, STEGLUJAN should promptly be discontinued and appropriate management

should be initiated. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using STEGLUJAN.

5.2 Hypotension

Ertugliflozin, a component of STEGLUJAN, causes intravascular volume contraction. Therefore, symptomatic hypotension may occur after initiating STEGLUJAN *[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 STEGLUJAN, volume status should be assessed and corrected if indicated. Monitor for signs and symptoms of hypotension after initiating therapy.

5.3 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 medicines containing sodium glucose co-transporter-2 (SGLT2) inhibitors and cases have been reported in ertugliflozin-treated patients in clinical trials. Across the clinical program, ketoacidosis was identified in 3 of 3,409 (0.1%) of ertugliflozin-treated patients and 0% of comparator-treated patients. Fatal cases of ketoacidosis have been reported in patients taking medicines containing SGLT2 inhibitors. STEGLUJAN is not indicated for the treatment of patients with type 1 diabetes mellitus *[see Indications and Usage (1)]*.

Patients treated with STEGLUJAN 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 STEGLUJAN may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, STEGLUJAN 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, surgery, pancreatic disorders suggesting insulin deficiency (e.g., type 1 diabetes, history of pancreatitis or pancreatic surgery), and alcohol abuse were identified.

Before initiating STEGLUJAN, consider factors in the patient history that may predispose to ketoacidosis, including pancreatic insulin deficiency from any cause, caloric restriction, and alcohol abuse.

For patients who undergo scheduled surgery, consider temporarily discontinuing STEGLUJAN for at least 4 days prior to surgery *[see Clinical Pharmacology (12.2, 12.3)]*.

Consider monitoring for ketoacidosis and temporarily discontinuing STEGLUJAN in other clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or post-surgery). Ensure risk factors for ketoacidosis are resolved prior to restarting STEGLUJAN.

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

5.4 Acute Kidney Injury and Impairment in Renal Function

STEGLUJAN 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 STEGLUJAN, 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 STEGLUJAN 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 STEGLUJAN promptly and institute treatment.

Ertugliflozin, a component of STEGLUJAN, 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 STEGLUJAN *[see Adverse Reactions (6.1)]*. Renal function should be evaluated prior to initiating STEGLUJAN and periodically thereafter. Use of STEGLUJAN 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)]*.

There have been postmarketing reports with sitagliptin of worsening renal function, including acute renal failure, sometimes requiring dialysis. A subset of these reports involved patients with renal insufficiency, some of whom were prescribed inappropriate doses of sitagliptin. A return to baseline levels of renal insufficiency has been observed with supportive treatment and discontinuation of potentially causative agents. Consideration can be given to cautiously reinitiating STEGLUJAN if another etiology is deemed likely to have precipitated the acute worsening of renal function.

Sitagliptin has not been found to be nephrotoxic in preclinical studies at clinically relevant doses, or in clinical trials.

5.5 Urosepsis and Pyelonephritis

There have been postmarketing reports of serious urinary tract infections, including urosepsis and pyelonephritis, requiring hospitalization in patients receiving medicines containing SGLT2 inhibitors. Cases of pyelonephritis also have been reported in ertugliflozin-treated patients in clinical trials. Treatment with medicines containing 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)]*.

5.6 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 ertugliflozin development program, non-traumatic lower limb amputations were reported in 1 (0.1%) patient in the comparator group, 3 (0.2%) patients in the ertugliflozin 5 mg group, and 8 (0.5%) patients in the ertugliflozin 15 mg group. A causal association between ertugliflozin and lower limb amputation has not been definitively established.

Before initiating STEGLUJAN, 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 STEGLUJAN for signs and symptoms of infection (including osteomyelitis), new pain or tenderness, sores or ulcers involving the lower limbs, and discontinue STEGLUJAN if these complications occur.

5.7 Heart Failure

An association between dipeptidyl peptidase-4 (DPP-4) inhibitor treatment and heart failure has been observed in cardiovascular outcomes trials for two other members of the DPP-4 inhibitor class. These trials evaluated patients with type 2 diabetes mellitus and atherosclerotic cardiovascular disease. Consider the risks and benefits of STEGLUJAN prior to initiating treatment in patients at risk for heart failure, such as those with a prior history of heart failure and a history of renal impairment, and observe these patients for signs and symptoms of heart failure during therapy. Advise patients of the characteristic symptoms of heart failure and to immediately report such symptoms. If heart failure develops, evaluate and manage according to current standards of care and consider discontinuation of STEGLUJAN.

5.8 Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues

Insulin and insulin secretagogues (e.g., sulfonylurea) are known to cause hypoglycemia. Ertugliflozin, a component of STEGLUJAN, may increase the risk of hypoglycemia when used in combination with insulin and/or an insulin secretagogue *[see Adverse Reactions (6.1)]*. When sitagliptin, a component of STEGLUJAN, was used in combination with a sulfonylurea or with insulin, medications known to cause hypoglycemia, the incidence of hypoglycemia was increased over that of placebo used in combination with a sulfonylurea or with insulin. *[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 STEGLUJAN.

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