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----------

Indications and Usage (1)	09/2021
Dosage and Administration (2.1, 2.2)	09/2021
Contraindications (4)	09/2021
Warnings and Precautions (5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.9)	09/2021

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

Limitations of Use:

- Not for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis. It may increase the risk of diabetic ketoacidosis in these patients. (1)
- Has not been studied in patients with a history of pancreatitis. (1, 5.1)

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

- Assess renal function before initiating STEGLUJAN and as clinically indicated (2.1):
- Correct volume depletion before initiating STEGLUJAN (2.1)
- Recommended starting dose is 5 mg ertugliflozin/100 mg sitagliptin once daily, taken in the morning, with or without food. (2.2)
- Increase dose to 15 mg ertugliflozin/100 mg sitagliptin once daily in those tolerating STEGLUJAN and needing additional glycemic control. (2.2)
- Use is not recommended in patients with an eGFR less than 45 mL/min/1.73 m^2. (2.2)

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

Tablets:

- Ertugliflozin 5 mg and sitagliptin 100 mg (3)
- Ertugliflozin 15 mg and sitagliptin 100 mg (3)

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

- Patients with severe renal impairment (<30 mL/min/1.73 m^2), end-stage renal disease, or dialysis. (4, 5.4)
- Hypersensitivity to sitagliptin, ertugliflozin, or any excipient, such as anaphylaxis or angioedema. (4, 5.11, 6.2)

---------- 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)
- *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)
- *Lower Limb Amputation:* Consider factors that may increase the risk of amputation before initiating STEGLUJAN. Monitor patients for infections or ulcers of lower limbs, and discontinue if these occur. (5.3)
- *Acute Renal Failure:* There have been postmarketing reports of acute renal failure in patients taking sitagliptin, sometimes requiring dialysis. Monitor renal function. (5.4)
- *Volume Depletion:* May result in acute kidney injury. Before initiating, assess and correct volume status in patients with renal impairment, or low systolic blood pressure elderly patients, or patients on diuretics. Monitor for signs and symptoms during therapy. (5.5)
- *Urosepsis and Pyelonephritis:* Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated. (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)
- *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. (5.12)
- *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. (5.13)

---------- 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 LLC 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. (5.5, 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: 06/2022

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.

Limitations of Use

- Not recommended in patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients *[see Warnings and Precautions (5.2)]*.
- 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 Prior to Initiation of STEGLUJAN

- Assess renal function prior to initiation of STEGLUJAN and as clinically indicated *[see Warnings and Precautions (5.4)]*.
- In patients with volume depletion, correct this condition before initiating STEGLUJAN *[see Warnings and Precautions (5.5), Use in Specific Populations (8.5, 8.6)]*.

2.2 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.
- For patients treated with ertugliflozin who are being switched to STEGLUJAN, the dose of ertugliflozin can be maintained.
- For additional glycemic control, the dose may be increased to 15 mg ertugliflozin/100 mg sitagliptin once daily in patients tolerating STEGLUJAN.
- Use is not recommended in patients with an eGFR less than 45 mL/min/1.73 m^2.
- Use of STEGLUJAN is contraindicated in patients with severe renal impairment (<30 mL/min/1.73 m^2), end-stage renal disease (ESRD) or on dialysis *[see Contraindications (4)]*.

3 DOSAGE FORMS AND STRENGTHS

- STEGLUJAN 5 mg/100 mg tablets: contain ertugliflozin 5 mg and sitagliptin 100 mg and are beige, almond-shaped debossed with “554” on one side and plain on the other side.
- STEGLUJAN 15 mg/100 mg tablets: contain ertugliflozin 15 mg and sitagliptin 100 mg and are brown, almond-shaped debossed with “555” on one side and plain on the other side.

4 CONTRAINDICATIONS

- Patients with severe renal impairment (<30 mL/min/1.73 m^2), end-stage renal disease (ESRD), or on dialysis *[see Warnings and Precautions (5.4)* and *Use in Specific Populations (8.6)]*.
- Hypersensitivity to sitagliptin, ertugliflozin, or any excipient, in STEGLUJAN, reactions such as anaphylaxis or angioedema have occurred *[see Warnings and Precautions (5.11) and Adverse Reactions (6.2)]*.

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 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 including ertugliflozin *[see Adverse Reactions (6.1)].* Fatal cases of ketoacidosis have been reported in patients taking SGLT2 inhibitors. In placebo-controlled trials of patients with type 1 diabetes, the risk of ketoacidosis was increased in patients who received SGLT2 inhibitors compared to patients who received placebo. The risk of ketoacidosis may be greater with higher doses. 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.

5.3 Lower Limb Amputation

In a long-term cardiovascular outcomes study *[see Clinical Studies 14.2]*, in patients with type 2 diabetes and established cardiovascular disease, the occurrence of non-traumatic lower limb amputations was reported with event rates of 4.7, 5.7, and 6.0 events per 1000 patient-years in the placebo, ertugliflozin 5 mg, and ertugliflozin 15 mg treatment arms, respectively.

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

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

Across seven ertugliflozin clinical trials, 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.

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.

5.4 Acute Renal Failure

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 Volume Depletion

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

5.6 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. 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)]*.

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, may increase the risk of hypoglycemia when used in combination with insulin and/or an insulin secretagogue *[see Adverse Reactions (6.1)]*. When sitagliptin, was used in combination with a sulfonylurea or with insulin, the incidence of hypoglycemia was increased over that of placebo used in combination with a sulfonylurea or with insulin *[see Adverse Reactions (6.1)]*. A lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with STEGLUJAN.

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

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

Patients treated with STEGLUJAN 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

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