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
Necrotizing Fasciitis of the Perineum (5.9) 10/2018

----------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: 06/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Recommended Dosage
2.2 Patients with Renal Impairment
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Pancreatitis
5.2 Hypotension
5.3 Ketoacidosis
5.4 Acute Kidney Injury and Impairment in Renal Function
5.5 Urosepsis and Pyelonephritis
5.6 Lower Limb Amputation
5.7 Heart Failure
5.8 Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues
5.9 Necrotizing Fasciitis of the Perineum
5.10 Genital Mycotic Infections
5.11 Hypersensitivity Reactions
5.12 Increases in Low-Density Lipoprotein Cholesterol (LDL-C)
5.13 Severe and Disabling Arthralgia
5.14 Bullous Pemphigoid
5.15 Macrovascular Outcomes
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Postmarketing Experience
7 DRUG INTERACTIONS
7.1 Concomitant Use with Insulin and Insulin Secretagogues
7.2 Positive Urine Glucose Test
7.3 Interference with 1,5-anhydroglucitol (1,5-AG) Assay
7.4 Digoxin
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Renal Impairment
8.7 Hepatic Impairment
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
14.1 Overview of Clinical Studies in Patients with Type 2 Diabetes Mellitus
14.2 In Combination with Sitagliptin versus Ertugliflozin Alone and Sitagliptin Alone, as Add-on to Metformin
14.3 Ertugliflozin as Add-on Combination Therapy with Metformin and Sitagliptin
14.4 Initial Combination Therapy of Ertugliflozin and Sitagliptin
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

***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 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 STEGLUJAN, 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 STEGLUJAN consider monitoring for ketoacidosis and temporarily discontinuing STEGLUJAN in clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or surgery).

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.

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. 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 debridement. Discontinue STEGLUJAN, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.

5.10 Genital Mycotic Infections

Ertugliflozin, a component of STEGLUJAN, 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.

5.11 Hypersensitivity Reactions

There have been postmarketing reports of serious hypersensitivity reactions in patients treated with sitagliptin, a component of STEGLUJAN. These reactions include anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. Onset of these reactions occurred within the first 3 months after initiation of treatment with sitagliptin, with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, discontinue STEGLUJAN, assess for other potential causes for the event, and institute alternative treatment for diabetes. *[See Adverse Reactions (6.2).]*

Angioedema has also been reported with other dipeptidyl peptidase-4 (DPP-4) inhibitors. Use caution in a patient with a history of angioedema with another DPP-4 inhibitor because it is unknown whether such patients will be predisposed to angioedema with STEGLUJAN.

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

Dose-related increases in LDL-C can occur with ertugliflozin, a component of STEGLUJAN *[see Adverse Reactions (6.1)]*. Monitor and treat as appropriate.

5.13 Severe and Disabling Arthralgia

There have been postmarketing reports of severe and disabling arthralgia in patients taking DPP-4 inhibitors. The time to onset of symptoms following initiation of drug therapy varied from one day to years. Patients experienced relief of symptoms upon discontinuation of the medication. A subset of patients experienced a recurrence of symptoms when restarting the same drug or a different DPP-4 inhibitor. Consider DPP-4 inhibitors as a possible cause for severe joint pain and discontinue drug if appropriate.

5.14 Bullous Pemphigoid

Postmarketing cases of bullous pemphigoid requiring hospitalization have been reported with DPP-4 inhibitor use. In reported cases, patients typically recovered with topical or systemic immunosuppressive treatment and discontinuation of the DPP-4 inhibitor. Tell patients to report development of blisters or erosions while receiving STEGLUJAN. If bullous pemphigoid is suspected, STEGLUJAN should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

5.15 Macrovascular Outcomes

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

6 ADVERSE REACTIONS

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

- Pancreatitis *[see Warnings and Precautions (5.1)]*
- Hypotension *[see Warnings and Precautions (5.2)]*
- Ketoacidosis *[see Warnings and Precautions (5.3)]*
- Acute Kidney Injury and Impairment in Renal Function *[see Warnings and Precautions (5.4)]*
- Urosepsis and Pyelonephritis *[see Warnings and Precautions (5.5)]*
- Lower Limb Amputation *[see Warnings and Precautions (5.6)]*

- Heart Failure *[see Warnings and Precautions (5.7)]*
- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues *[see Warnings and Precautions (5.8)]*
- Necrotizing Fasciitis of the Perineum (Fournier's gangrene) *[see Warnings and Precautions (5.9)]*
- Genital Mycotic Infections *[see Warnings and Precautions (5.10)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.11)]*
- Increases in Low-Density Lipoprotein (LDL-C) *[see Warnings and Precautions (5.12)]*
- Severe and Disabling Arthralgia *[see Warnings and Precautions (5.13)]*
- Bullous Pemphigoid *[see Warnings and Precautions (5.14)]*

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.

Ertugliflozin and Sitagliptin

The safety of concomitantly administered ertugliflozin and sitagliptin has been evaluated in 990 patients with type 2 diabetes mellitus treated for 26 weeks in three studies; a factorial study of ertugliflozin 5 mg or 15 mg in combination with sitagliptin 100 mg once daily compared to the individual components, a placebo-controlled study of ertugliflozin 5 mg or 15 mg as add-on therapy to sitagliptin 100 mg and metformin once daily, and a placebo-controlled study of initial therapy with ertugliflozin 5 mg or 15 mg once daily in combination with sitagliptin 100 mg once daily *[see Clinical Studies (14)]*. The incidence and type of adverse reactions in these three studies were similar to the adverse reactions seen with ertugliflozin and described below in Table 1.

Ertugliflozin

Pool of Placebo-Controlled Trials

The data in Table 1 are derived from a pool of three 26-week, placebo-controlled trials. Ertugliflozin 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 ertugliflozin with a mean exposure duration of approximately 25 weeks. Patients received ertugliflozin 5 mg (N=519), ertugliflozin 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 ertugliflozin. These adverse reactions were not present at baseline, occurred more commonly on ertugliflozin than on placebo, and occurred in at least 2% of patients treated with either ertugliflozin 5 mg or ertugliflozin 15 mg.

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

	Number (%) of Patients		
	Placebo N = 515	**Ertugliflozin 5 mg N = 519**	**Ertugliflozin 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%
Thirstᵇ	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), ertugliflozin 5 mg (N=252), ertugliflozin 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), ertugliflozin 5 mg (N=267), ertugliflozin 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.

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

Volume Depletion

Ertugliflozin 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, ertugliflozin 5 mg, and ertugliflozin 15 mg, respectively. Ertugliflozin 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 (5.3)].*

Impairment in Renal Function

Treatment with ertugliflozin 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	**Ertugliflozin 5 mg N=519**	**Ertugliflozin 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	**Ertugliflozin 5 mg N=158**	**Ertugliflozin 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 ertugliflozin, 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, ertugliflozin 5 mg, and ertugliflozin 15 mg, respectively.

Lower Limb Amputation

Across seven Phase 3 clinical trials in which ertugliflozin 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-ertugliflozin group, 3 of 1,716 (0.2%) in the ertugliflozin 5 mg group, and 8 of 1,693 (0.5%) in the ertugliflozin 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

Factorial Study with Sitagliptin as Add-on Combination Therapy with Metformin (26 weeks)		**Ertugliflozin 5 mg + Sitagliptin (N = 243)**	**Ertugliflozin 15 mg + Sitagliptin (N = 244)**
Overall [N (%)]		13 (5.3)	22 (9.0)
Severe [N (%)]		0 (0.0)	1 (0.4)
Add-on Combination Therapy with Metformin and Sitagliptin (26 weeks)	**Placebo (N = 153)**	**Ertugliflozin 5 mg (N = 156)**	**Ertugliflozin 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)
Initial Combination Therapy with Sitagliptin (26 weeks)	**Placebo (N = 97)**	**Ertugliflozin 5 mg + Sitagliptin (N = 98)**	**Ertugliflozin 15 mg + Sitagliptin (N = 96)**
Overall [N (%)]	1 (1.0)	6 (6.1)	3 (3.1)
Severe [N (%)]	0 (0.0)	0 (0.0)	2 (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, ertugliflozin 5 mg, and ertugliflozin 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 ertugliflozin, 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, ertugliflozin 5 mg, ertugliflozin 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 ertugliflozin, respectively. Phimosis was reported in 8 of 1,729 (0.5%) male ertugliflozin-treated patients, of which four required circumcision.

<u>Sitagliptin</u>

The following additional adverse reactions have been reported in clinical studies with sitagliptin: upper respiratory tract infection, nasopharyngitis, headache, abdominal pain, nausea, diarrhea. In addition, in a study of sitagliptin as add-on combination therapy with metformin and rosiglitazone, peripheral edema was noted with a higher incidence than placebo.

In a pooled analysis of the two monotherapy studies, the add-on to metformin study, and the add-on to pioglitazone study, the overall incidence of adverse reactions of hypoglycemia was 1.2% in patients treated with sitagliptin 100 mg and 0.9% in patients treated with placebo. 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. In the add-on to glimepiride (+/- metformin) study, the overall incidence of hypoglycemia was 12.2% in patients treated with sitagliptin 100 mg and 1.8% in patients treated with placebo. In the add-on to insulin (+/- metformin) study, the overall incidence of hypoglycemia was 15.5% in patients treated with sitagliptin 100 mg and 7.8% in patients treated with placebo. In all studies, adverse reactions of hypoglycemia were based on all reports of symptomatic hypoglycemia. A concurrent blood glucose measurement was not required although most (74%) reports of hypoglycemia were accompanied by a blood glucose measurement ≤70 mg/dL.

In a pooled analysis of 19 double-blind clinical trials that included data from 10,246 patients randomized to receive sitagliptin 100 mg/day (N=5,429) or corresponding (active or placebo) control (N=4,817), the incidence of non-adjudicated acute pancreatitis events was 0.1 per 100 patient-years in each group (4 patients with an event in 4,708 patient-years for sitagliptin and 4 patients with an event in 3,942 patient-years for control).

Laboratory Tests

Ertugliflozin

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 ertugliflozin. Mean percent changes from baseline to Week 26 in LDL-C relative to placebo were 2.6% and 5.4% with ertugliflozin 5 mg and ertugliflozin 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 (5.12)].*

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 ertugliflozin 5 mg, and 0.48 g/dL (3.5%) with ertugliflozin 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, ertugliflozin 5 mg, and ertugliflozin 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 ertugliflozin 5 mg, and 0.26 mg/dL (8.5%) with ertugliflozin 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 ertugliflozin 5 mg, and 0.24 mg/dL (7.8%) with ertugliflozin 15 mg.

Sitagliptin

Across clinical studies, the incidence of laboratory adverse reactions was similar in patients treated with sitagliptin 100 mg compared to patients treated with placebo. A small increase in white blood cell count (WBC) was observed due to an increase in neutrophils. This increase in WBC (of approximately 200 cells/microL vs. placebo, in four pooled placebo-controlled clinical studies, with a mean baseline WBC count of approximately 6,600 cells/microL) is not considered to be clinically relevant. In a 12-week study of 91 patients with chronic renal insufficiency, 37 patients with moderate renal insufficiency were randomized to sitagliptin 50 mg daily, while 14 patients with the same magnitude of renal impairment were randomized to placebo. Mean (SE) increases in serum creatinine were observed in patients treated with sitagliptin [0.12 mg/dL (0.04)] and in patients treated with placebo [0.07 mg/dL (0.07)]. The clinical significance of this added increase in serum creatinine relative to placebo is not known.

6.2 Postmarketing Experience

Sitagliptin

Additional adverse reactions have been identified during postapproval use of sitagliptin, a component of STEGLUJAN, as monotherapy and/or in combination with other antihyperglycemic agents. 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.

Hypersensitivity reactions including anaphylaxis, angioedema, rash, urticaria, cutaneous vasculitis, and exfoliative skin conditions including Stevens-Johnson syndrome *[see Warnings and Precautions (5.11)]*; hepatic enzyme elevations; acute pancreatitis, including fatal and non-fatal hemorrhagic and necrotizing pancreatitis *[see Indications and Usage (1) and Warnings and Precautions (5.1)]*; worsening renal function, including acute renal failure (sometimes requiring dialysis) *[see Warnings and Precautions (5.4)]*; severe and disabling arthralgia *[see Warnings and Precautions (5.13)]*; bullous pemphigoid *[see Warnings and Precautions (5.14)];* constipation; vomiting; headache; myalgia; pain in extremity; back pain; pruritus; mouth ulceration; stomatitis; rhabdomyolysis.

Ertugliflozin

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 (5.9)]*

7 DRUG INTERACTIONS

7.1 Concomitant Use with Insulin and Insulin Secretagogues

STEGLUJAN 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 STEGLUJAN *[see Warnings and Precautions (5.8)]*.

7.2 Positive Urine Glucose Test

Monitoring glycemic control with urine glucose tests is not recommended in patients taking medicines containing an SGLT2 inhibitor 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 medicines containing an SGLT2 inhibitor. Use alternative methods to monitor glycemic control.

7.4 Digoxin

There was a slight increase in the area under the curve (AUC, 11%) and mean peak drug concentration (C_{max}, 18%) of digoxin with the coadministration of 100 mg sitagliptin for 10 days. Patients receiving digoxin should be monitored appropriately. No dosage adjustment of digoxin or STEGLUJAN is recommended.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to sitagliptin during pregnancy. Health care providers are encouraged to report any prenatal exposure to STEGLUJAN by calling the Pregnancy Registry at 1-800-986-8999.

Risk Summary

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

The limited available data with ertugliflozin and sitagliptin use during pregnancy 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)*.

In rats and rabbits, sitagliptin doses of 250 and 125 mg/kg, respectively (approximately 30 and 20 times the human exposure at the maximum recommended human dose) did not adversely affect development outcomes of either species.

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

Ertugliflozin

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).

Sitagliptin

Sitagliptin administered to pregnant female rats and rabbits from gestation day 6 to 20 (organogenesis) did not adversely affect developmental outcomes at oral doses up to 250 mg/kg (rats) and 125 mg/kg (rabbits), or approximately 30 and 20 times human exposure at the maximum recommended human dose (MRHD) of 100 mg/day based on AUC comparisons. Higher doses increased the incidence of rib malformations in offspring at 1,000 mg/kg, or approximately 100 times human exposure at the MRHD.

Sitagliptin administered to female rats from gestation day 6 to lactation day 21 decreased body weight in male and female offspring at 1,000 mg/kg. No functional or behavioral toxicity was observed in offspring of rats.

Placental transfer of sitagliptin administered to pregnant rats was approximately 45% at 2 hours and 80% at 24 hours postdose. Placental transfer of sitagliptin administered to pregnant rabbits was approximately 66% at 2 hours and 30% at 24 hours.

8.2 Lactation

Risk Summary

There is no information regarding the presence of STEGLUJAN, in human milk, the effects on the breastfed infant, or the effects on milk production. Ertugliflozin and sitagliptin are 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, based on data with ertugliflozin. Because of the potential for serious adverse reactions in a breastfed infant, advise women that the use of STEGLUJAN is not recommended while breastfeeding.

Data

Animal Data

Ertugliflozin

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 ertugliflozin 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).

Sitagliptin

Sitagliptin is secreted in the milk of lactating rats at a milk to plasma ratio of 4:1.

8.4 Pediatric Use

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

8.5 Geriatric Use

STEGLUJAN

No dosage adjustment of STEGLUJAN is recommended based on age. Elderly patients are more likely to have decreased renal function. Because renal function abnormalities can occur after initiating ertugliflozin, and sitagliptin is known to be substantially excreted by the kidneys, renal function should be assessed more frequently in elderly patients *[see Dosage and Administration (2.2) and Warnings and Precautions (5.4)]*. STEGLUJAN is expected to have diminished efficacy in elderly patients with renal impairment *[see Use in Specific Populations (8.6)]*.

Ertugliflozin

Across the clinical program, a total of 876 (25.7%) patients treated with ertugliflozin were 65 years and older, and 152 (4.5%) patients treated with ertugliflozin 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, ertugliflozin 5 mg, and ertugliflozin 15 mg, respectively *[see Warnings and Precautions (5.2) and Adverse Reactions (6.1)]*.

Sitagliptin

Of the total number of subjects (N=3,884) in pre-approval clinical safety and efficacy studies of sitagliptin, 725 patients were 65 years and over, while 61 patients were 75 years and over. No overall differences in safety or effectiveness were observed between subjects 65 years and over and younger subjects. While this and other reported clinical experience have not identified differences in responses between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

The safety and efficacy of ertugliflozin have not been established in patients with type 2 diabetes mellitus and moderate renal impairment. Compared to placebo-treated patients, patients with moderate renal impairment treated with ertugliflozin did not have improvement in glycemic control, 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 (5.4), and Adverse Reactions (6.1)]*. Therefore, STEGLUJAN is not recommended in this population.

STEGLUJAN is contraindicated in patients with severe renal impairment, ESRD, or receiving dialysis. STEGLUJAN 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 STEGLUJAN is necessary in patients with mild or moderate hepatic impairment. STEGLUJAN 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

STEGLUJAN

In the event of an overdose with STEGLUJAN, contact the Poison Control Center. Employ the usual supportive measures as dictated by the patient's clinical status.

Ertugliflozin

Removal of ertugliflozin by hemodialysis has not been studied.

Sitagliptin

In the event of an overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring (including obtaining an electrocardiogram), and institute supportive therapy as dictated by the patient's clinical status.

Sitagliptin is modestly dialyzable. In clinical studies, approximately 13.5% of the dose was removed over a 3- to 4-hour hemodialysis session. Prolonged hemodialysis may be considered if clinically appropriate. It is not known if sitagliptin is dialyzable by peritoneal dialysis.

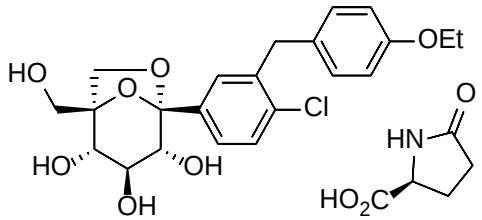
11 DESCRIPTION

STEGLUJAN (ertugliflozin and sitagliptin) tablet for oral use contains ertugliflozin L-pyroglutamic acid, a SGLT2 inhibitor, and sitagliptin phosphate, a DPP-4 inhibitor.

Ertugliflozin

The chemical name of ertugliflozin L-pyroglutamic acid is (1*S*,2*S*,3*S*,4*R*,5*S*)-5-(4-chloro-3-(4-ethoxybenzyl)phenyl)-1-(hydroxymethyl)-6,8-dioxabicyclo[3.2.1]octane-2,3,4-triol, compound with (2*S*)-5-oxopyrrolidine-2-carboxylic acid. The molecular formula is $C_{27}H_{32}ClNO_{10}$ and the molecular weight is 566.00.

The chemical structure is:

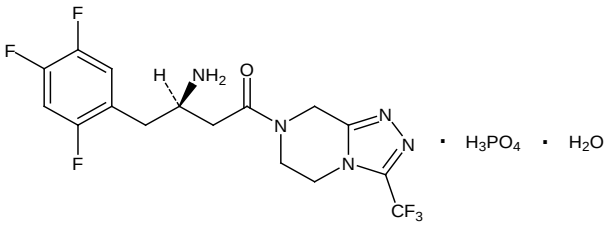


Ertugliflozin L-pyroglutamic acid is a white to off-white powder that is soluble in ethyl alcohol and acetone, slightly soluble in ethyl acetate and acetonitrile and very slightly soluble in water.

Sitagliptin

Sitagliptin phosphate monohydrate is described chemically as 7-[(3*R*)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8-tetrahydro-3-(trifluoromethyl)-1,2,4-triazolo[4,3-*a*]pyrazine phosphate (1:1) monohydrate.

The empirical formula is $C_{16}H_{15}F_6N_5O \bullet H_3PO_4 \bullet H_2O$ and the molecular weight is 523.32. The structural formula is:



Sitagliptin phosphate monohydrate is a white to off-white, crystalline, non-hygroscopic powder. It is soluble in water and N,N-dimethyl formamide; slightly soluble in methanol; very slightly soluble in ethanol, acetone, and acetonitrile; and insoluble in isopropanol and isopropyl acetate.

STEGLUJAN is available for oral use as film-coated tablets containing:

- 6.48 mg ertugliflozin L-pyroglutamic acid equivalent to 5 mg of ertugliflozin and 128.5 mg sitagliptin phosphate monohydrate equivalent to 100 mg sitagliptin (STEGLUJAN 5/100)
- 19.43 mg ertugliflozin L-pyroglutamic acid equivalent to 15 mg of ertugliflozin and 128.5 mg sitagliptin phosphate monohydrate equivalent to 100 mg sitagliptin (STEGLUJAN 15/100)

Inactive ingredients are microcrystalline cellulose, dibasic calcium phosphate anhydrous, croscarmellose sodium, sodium stearyl fumarate, and magnesium stearate.

The film coating contains: hypromellose, hydroxypropyl cellulose, titanium dioxide, iron oxide red, iron oxide yellow, ferrosoferric oxide/black iron oxide, and carnauba wax.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

STEGLUJAN

STEGLUJAN combines two antihyperglycemic agents with complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes mellitus: ertugliflozin, a SGLT2 inhibitor, and sitagliptin, a DPP-4 inhibitor.

Ertugliflozin

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.

Sitagliptin

Sitagliptin is a DPP-4 inhibitor, which is believed to exert its actions in patients with type 2 diabetes mellitus by slowing the inactivation of incretin hormones. Concentrations of the active intact hormones are increased by sitagliptin, thereby increasing and prolonging the action of these hormones. Incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are released by the intestine throughout the day, and levels are increased in response to a meal. These hormones are rapidly inactivated by the enzyme, DPP-4. The incretins are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells by intracellular signaling pathways involving cyclic AMP. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, leading to reduced hepatic glucose production. By increasing and prolonging active incretin levels, sitagliptin increases insulin release and decreases glucagon levels in the circulation in a glucose-dependent manner. Sitagliptin demonstrates selectivity for DPP-4 and does not inhibit DPP-8 or DPP-9 activity *in vitro* at concentrations approximating those from therapeutic doses.

12.2 Pharmacodynamics

Ertugliflozin

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 ertugliflozin 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, ertugliflozin does not prolong QTc to any clinically relevant extent.

Sitagliptin

General

In patients with type 2 diabetes mellitus, administration of sitagliptin led to inhibition of DPP-4 enzyme activity for a 24-hour period. After an oral glucose load or a meal, this DPP-4 inhibition resulted in a 2- to 3-fold increase in circulating levels of active GLP-1 and GIP, decreased glucagon concentrations, and increased responsiveness of insulin release to glucose, resulting in higher C-peptide and insulin concentrations. The rise in insulin with the decrease in glucagon was associated with lower fasting glucose concentrations and reduced glucose excursion following an oral glucose load or a meal.

In a two-day study in healthy subjects, sitagliptin alone increased active GLP-1 concentrations, whereas metformin alone increased active and total GLP-1 concentrations to similar extents. Coadministration of sitagliptin and metformin had an additive effect on active GLP-1 concentrations. Sitagliptin, but not metformin, increased active GIP concentrations. It is unclear how these findings relate to changes in glycemic control in patients with type 2 diabetes mellitus.

In studies with healthy subjects, sitagliptin did not lower blood glucose or cause hypoglycemia.

Cardiac Electrophysiology

In a randomized, placebo controlled crossover study, 79 healthy subjects were administered a single oral dose of sitagliptin 100 mg, sitagliptin 800 mg (8 times the recommended dose), and placebo. At the recommended dose of 100 mg, there was no effect on the QTc interval obtained at the peak plasma concentration, or at any other time during the study. Following the 800 mg dose, the maximum increase in the placebo corrected mean change in QTc from baseline was observed at 3 hours postdose and was 8.0 msec. This increase is not considered to be clinically significant. At the 800 mg dose, peak sitagliptin plasma concentrations were approximately 11 times higher than the peak concentrations following a 100-mg dose.

In patients with type 2 diabetes mellitus administered sitagliptin 100 mg (N=81) or sitagliptin 200 mg (N=63) daily, there were no meaningful changes in QTc interval based on ECG data obtained at the time of expected peak plasma concentration.

12.3 Pharmacokinetics

General Introduction

Ertugliflozin

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.

Sitagliptin

The pharmacokinetics of sitagliptin have been extensively characterized in healthy subjects and patients with type 2 diabetes mellitus. After oral administration of a 100-mg dose to healthy subjects, sitagliptin was rapidly absorbed, with peak plasma concentrations (median T_{max}) occurring 1 to 4 hours postdose. Plasma AUC of sitagliptin increased in a dose proportional manner. Following a single oral 100-mg dose to healthy volunteers, mean plasma AUC of sitagliptin was 8.52 μM•hr, C_{max} was 950 nM, and apparent terminal half-life ($t_{1/2}$) was 12.4 hours. Plasma AUC of sitagliptin increased approximately 14% following 100-mg doses at steady state compared to the first dose. The intra subject and inter subject coefficients of variation for sitagliptin AUC were small (5.8% and 15.1%). The pharmacokinetics of sitagliptin was generally similar in healthy subjects and in patients with type 2 diabetes mellitus.

Absorption

STEGLUJAN

The effects of a high-fat meal on the pharmacokinetics of ertugliflozin and sitagliptin when administered as STEGLUJAN tablets are comparable to those reported for the individual tablets. Administration of STEGLUJAN with food decreased ertugliflozin C_{max} by 29% and had no meaningful effect on ertugliflozin AUC_{inf}, and on sitagliptin AUC_{inf} and C_{max}.

Ertugliflozin

Following single-dose oral administration of 5 mg and 15 mg of ertugliflozin, peak plasma concentrations of ertugliflozin occur at 1 hour postdose (median T_{max}) 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 ertugliflozin 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, ertugliflozin was administered without regard to meals.

Sitagliptin

The absolute bioavailability of sitagliptin is approximately 87%. Because coadministration of a high fat meal with sitagliptin had no effect on the pharmacokinetics, sitagliptin may be administered with or without food.

Distribution

Ertugliflozin

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.

Sitagliptin

The mean volume of distribution at steady state following a single 100-mg intravenous dose of sitagliptin to healthy subjects is approximately 198 L. The fraction of sitagliptin reversibly bound to plasma proteins is low (38%).

Elimination

Metabolism

Ertugliflozin

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%).

Sitagliptin

Approximately 79% of sitagliptin is excreted unchanged in the urine with metabolism being a minor pathway of elimination.

Following a [^{14}C]sitagliptin oral dose, approximately 16% of the radioactivity was excreted as metabolites of sitagliptin. Six metabolites were detected at trace levels and are not expected to contribute to the plasma DPP-4 inhibitory activity of sitagliptin. *In vitro* studies indicated that the primary enzyme responsible for the limited metabolism of sitagliptin was CYP3A4, with contribution from CYP2C8.

Excretion

Ertugliflozin

The mean systemic plasma clearance following an intravenous 100 µg dose was 11.2 L/hr. The mean elimination half-life in type 2 diabetic patients with normal renal function was estimated to be 16.6 hours based on the population pharmacokinetic analysis. Following administration of an oral [^{14}C]-ertugliflozin solution to healthy subjects, approximately 40.9% and 50.2% of the drug-related radioactivity was eliminated in feces and urine, respectively. Only 1.5% of the administered dose was excreted as unchanged ertugliflozin in urine and 33.8% as unchanged ertugliflozin in feces, which is likely due to biliary excretion of glucuronide metabolites and subsequent hydrolysis to parent.

Sitagliptin

Following administration of an oral [^{14}C]sitagliptin dose to healthy subjects, approximately 100% of the administered radioactivity was eliminated in feces (13%) or urine (87%) within one week of dosing. The apparent terminal $t_{1/2}$ following a 100-mg oral dose of sitagliptin was approximately 12.4 hours and renal clearance was approximately 350 mL/min.

Elimination of sitagliptin occurs primarily via renal excretion and involves active tubular secretion. Sitagliptin is a substrate for human organic anion transporter-3 (hOAT-3), which may be involved in the renal elimination of sitagliptin. The clinical relevance of hOAT-3 in sitagliptin transport has not been established. Sitagliptin is also a substrate of p-glycoprotein, which may also be involved in mediating the renal elimination of sitagliptin. However, cyclosporine, a p-glycoprotein inhibitor, did not reduce the renal clearance of sitagliptin.

Specific Populations

Patients with Renal Impairment

STEGLUJAN

Studies characterizing the pharmacokinetics of ertugliflozin and sitagliptin after administration of STEGLUJAN in renally impaired patients have not been performed *[see Dosage and Administration (2.2)].*

Ertugliflozin

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 ertugliflozin, 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 (5.4) and Use in Specific Populations (8.6)]*. The plasma protein binding of ertugliflozin was unaffected in patients with renal impairment.

Sitagliptin

An approximately 2-fold increase in the plasma AUC of sitagliptin was observed in patients with moderate renal impairment with eGFR of 30 to less than 45 mL/min/1.73 m^2, and an approximately 4-fold increase was observed in patients with severe renal impairment, including patients with ESRD on hemodialysis, as compared to normal healthy control subjects.

Patients with Hepatic Impairment

Ertugliflozin

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)]*.

Sitagliptin

In patients with moderate hepatic insufficiency (Child Pugh score 7 to 9), mean AUC and C_{max} of sitagliptin increased approximately 21% and 13%, respectively, compared to healthy matched controls following administration of a single 100-mg dose of sitagliptin. These differences are not considered to be clinically meaningful. No dosage adjustment for sitagliptin is necessary for patients with mild or moderate hepatic insufficiency.

There is no clinical experience in patients with severe hepatic insufficiency (Child Pugh score >9) *[see Use in Specific Populations (8.7)].*

Pediatric Patients

No studies with STEGLUJAN, ertugliflozin, and sitagliptin have been performed in pediatric patients.

Effects of Age, Body Weight/ Body Mass Index (BMI), Gender, and Race

Ertugliflozin

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

Sitagliptin

Based on a population pharmacokinetic analysis or a composite analysis of available pharmacokinetic data, BMI, gender, and race do not have a clinically meaningful effect on the pharmacokinetics of sitagliptin. When the effects of age on renal function are taken into account, age alone did not have a clinically meaningful impact on the pharmacokinetics of sitagliptin based on a population pharmacokinetic analysis. Elderly subjects (65 to 80 years) had approximately 19% higher plasma concentrations of sitagliptin compared to younger subjects.

Drug Interaction Studies

STEGLUJAN

Coadministration of single dose of ertugliflozin (15 mg) and sitagliptin (100 mg) did not meaningfully alter the pharmacokinetics of either ertugliflozin or metformin in healthy subjects.

Pharmacokinetic drug interaction studies with STEGLUJAN have not been performed; however, such studies have been conducted with ertugliflozin and sitagliptin, the individual components of STEGLUJAN.

Ertugliflozin

In Vitro Assessment of Drug Interactions

In *in vitro* studies, ertugliflozin and ertugliflozin glucuronides did not inhibit CYP450 isoenzymes (CYPs) 1A2, 2C9, 2C19, 2C8, 2B6, 2D6, or 3A4, and did not induce CYPs 1A2, 2B6, or 3A4. Ertugliflozin was not a time-dependent inhibitor of CYP3A *in vitro*. Ertugliflozin did not inhibit UGT1A6, 1A9, or 2B7 *in vitro* and was a weak inhibitor (IC_{50} >39 µM) of UGT1A1 and 1A4. Ertugliflozin glucuronides did not inhibit UGT1A1, 1A4, 1A6, 1A9, or 2B7 *in vitro*. Overall, ertugliflozin is unlikely to affect the pharmacokinetics of drugs eliminated by these enzymes. Ertugliflozin is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) transporters and is not a substrate of organic anion transporters (OAT1, OAT3), organic cation transporters (OCT1, OCT2), or organic anion transporting polypeptides (OATP1B1, OATP1B3). Ertugliflozin or ertugliflozin glucuronides do not meaningfully inhibit P-gp, OCT2, OAT1, or OAT3 transporters, or transporting polypeptides OATP1B1 and OATP1B3, at clinically relevant concentrations. Overall, ertugliflozin is unlikely to affect the pharmacokinetics of concurrently administered medications that are substrates of these transporters.

In Vivo Assessment of Drug Interactions

No dose adjustment of STEGLUJAN 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

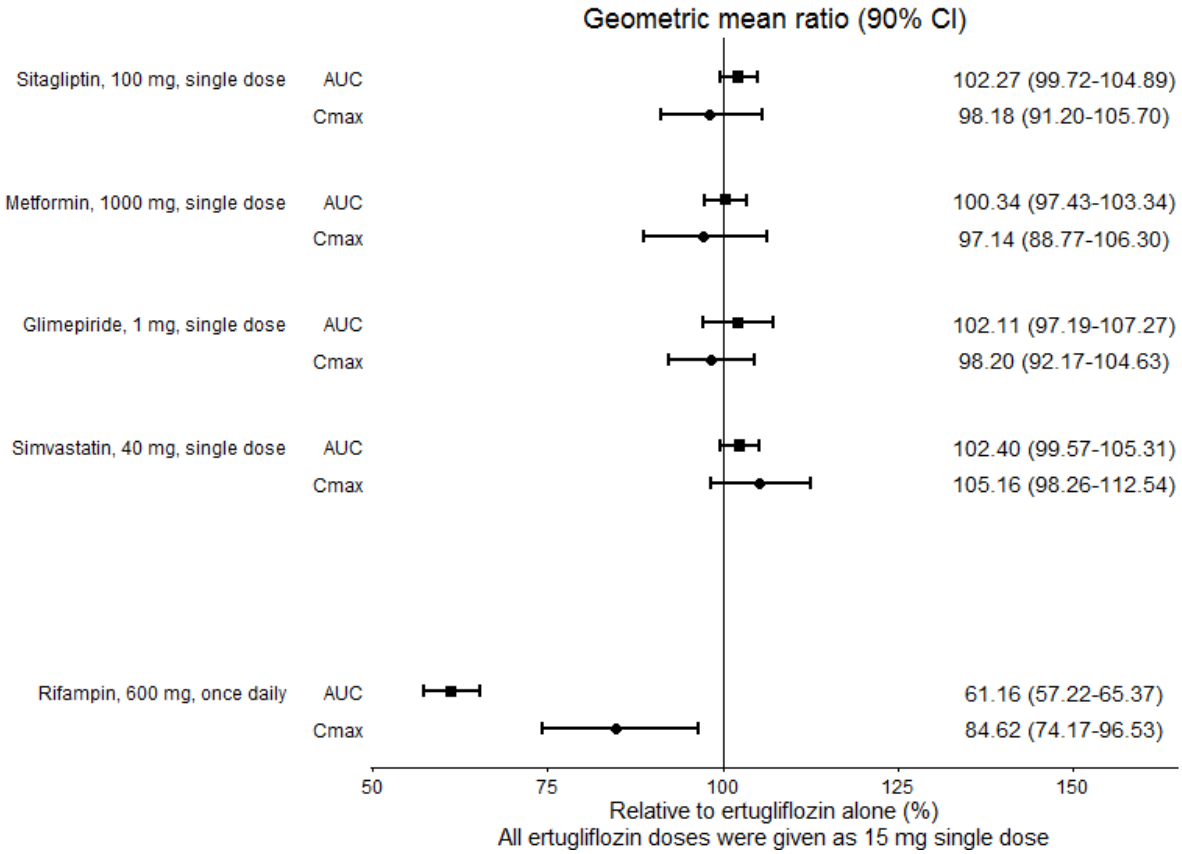
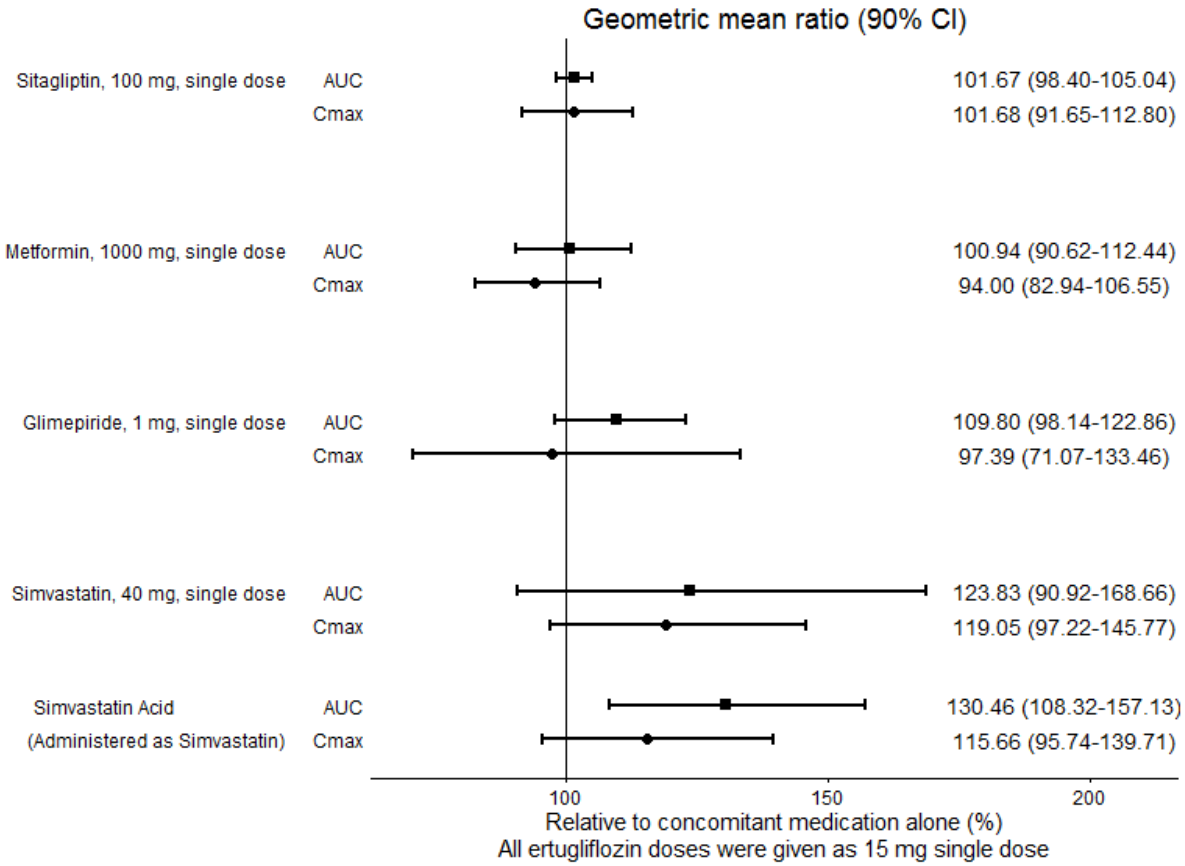


Figure 2: Effects of Ertugliflozin on the Pharmacokinetics of Other Drugs



Sitagliptin

In Vitro Assessment of Drug Interactions

Sitagliptin is not an inhibitor of CYP isozymes CYP3A4, 2C8, 2C9, 2D6, 1A2, 2C19 or 2B6, and is not an inducer of CYP3A4. Sitagliptin is a p-glycoprotein substrate, but does not inhibit p-glycoprotein mediated transport of digoxin. Based on these results, sitagliptin is considered unlikely to cause interactions with other drugs that utilize these pathways.

Sitagliptin is not extensively bound to plasma proteins. Therefore, the propensity of sitagliptin to be involved in clinically meaningful drug-drug interactions mediated by plasma protein binding displacement is very low.

In Vivo Assessment of Drug Interactions

Table 4: Effect of Coadministered Drugs on Systemic Exposure of Sitagliptin

Coadministered Drug	**Dose of Coadministered Drug***	**Dose of Sitagliptin***	**Geometric Mean Ratio (ratio with/without coadministered drug) No Effect = 1.00**		
				AUC†	**C_{max}**
No dosing adjustments required for the following:					
Cyclosporine	600 mg once daily	100 mg once daily	Sitagliptin	1.29	1.68
Metformin	1,000 mg‡ twice daily for 14 days	50 mg‡ twice daily for 7 days	Sitagliptin	1.02§	1.05

* All doses administered as single dose unless otherwise specified.
† AUC is reported as $AUC_{0-\infty}$ unless otherwise specified.
‡ Multiple dose.
§ AUC_{0-12hr}.

Table 5: Effect of Sitagliptin on Systemic Exposure of Coadministered Drugs

Coadministered Drug	Dose of Coadministered Drug*	Dose of Sitagliptin*	Geometric Mean Ratio (ratio with/without sitagliptin) No Effect = 1.00		
				AUC†	C_{max}
No dosing adjustments required for the following:					
Digoxin	0.25 mg‡ once daily for 10 days	100 mg‡ once daily for 10 days	Digoxin	1.11§	1.18
Glyburide	1.25 mg	200 mg‡ once daily for 6 days	Glyburide	1.09	1.01
Simvastatin	20 mg	200 mg‡ once daily for 5 days	Simvastatin	0.85¶	0.80
			Simvastatin Acid	1.12¶	1.06
Rosiglitazone	4 mg	200 mg‡ once daily for 5 days	Rosiglitazone	0.98	0.99
Warfarin	30 mg single dose on day 5	200 mg‡ once daily for 11 days	S(-) Warfarin	0.95	0.89
			R(+) Warfarin	0.99	0.89
Ethinyl estradiol and norethindrone	21 days once daily of 35 µg ethinyl estradiol with norethindrone 0.5 mg x 7 days, 0.75 mg x 7 days, 1.0 mg x 7 days	200 mg‡ once daily for 21 days	Ethinyl estradiol	0.99	0.97
			Norethindrone	1.03	0.98
Metformin	1,000 mg‡ twice daily for 14 days	50 mg‡ twice daily for 7 days	Metformin	1.02#	0.97

* All doses administered as single dose unless otherwise specified. The 200 mg dose is 2 times the maximum recommended daily dose of sitagliptin.
† AUC is reported as $AUC_{0-\infty}$ unless otherwise specified.
‡ Multiple dose.
§ AUC_{0-24hr}.
¶ AUC_{0-last}.
# AUC_{0-12hr}.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Ertugliflozin

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 relevance 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).

Sitagliptin

A two year carcinogenicity study was conducted in male and female rats given oral doses of sitagliptin of 50, 150, and 500 mg/kg/day. There was an increased incidence of combined liver adenoma/carcinoma in males and females and of liver carcinoma in females at 500 mg/kg. This dose results in exposures approximately 60 times the human exposure at the maximum recommended daily adult human dose (MRHD) of 100 mg/day based on AUC comparisons. Liver tumors were not observed at 150 mg/kg, approximately 20 times the human exposure at the MRHD.

A two year carcinogenicity study was conducted in male and female mice given oral doses of sitagliptin of 50, 125, 250, and 500 mg/kg/day. There was no increase in the incidence of tumors in any organ up to 500 mg/kg, approximately 70 times human exposure at the MRHD.

Mutagenesis

Ertugliflozin

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.

Sitagliptin

Sitagliptin was not mutagenic or clastogenic with or without metabolic activation in the Ames bacterial mutagenicity assay, a Chinese hamster ovary (CHO) chromosome aberration assay, an *in vitro* cytogenetics assay in CHO, an *in vitro* rat hepatocyte DNA alkaline elution assay, and an *in vivo* micronucleus assay.

Impairment of Fertility

Ertugliflozin

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).

Sitagliptin

In rat fertility studies with oral gavage doses of 125, 250, and 1,000 mg/kg, males were treated for 4 weeks prior to mating, during mating, up to scheduled termination (approximately 8 weeks total) and females were treated 2 weeks prior to mating through gestation day 7. No adverse effect on fertility was observed at 125 mg/kg (approximately 12 times human exposure at the MRHD of 100 mg/day based on AUC comparisons). At higher doses, nondose-related increased resorptions in females were observed (approximately 25 and 100 times human exposure at the MRHD 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 ertugliflozin in combination with sitagliptin have been studied in 3 multi-center, randomized, double-blind, placebo- and active comparator-controlled, clinical studies involving 1,985 patients with type 2 diabetes mellitus. These studies included white, Hispanic, black, Asian, and other racial and ethnic groups, and patients with an age range of 21 to 85 years.

In patients with type 2 diabetes mellitus, treatment with ertugliflozin in combination with sitagliptin reduced HbA1c compared to placebo or active comparator.

In patients with type 2 diabetes mellitus treated with ertugliflozin in combination with sitagliptin, the change in HbA1c was generally similar across subgroups defined by age, sex, and race.

14.2 In Combination with Sitagliptin versus Ertugliflozin 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 (≥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 ertugliflozin 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: ertugliflozin 5 mg, ertugliflozin 15 mg, sitagliptin 100 mg, ertugliflozin 5 mg + sitagliptin 100 mg, or ertugliflozin 15 mg + sitagliptin 100 mg.

At Week 26, ertugliflozin 5 mg or 15 mg + sitagliptin 100 mg provided statistically significantly greater reductions in HbA1c compared to the individual components. More patients achieved an HbA1c < 7% on the combination as compared to the individual components (see Table 6 and Figure 3).

Table 6: Results at Week 26 from a Factorial Study with Ertugliflozin and Sitagliptin as Add-on Combination Therapy with Metformin Compared to Individual Components Alone*

	Sitagliptin 100 mg	**Ertugliflozin 5 mg**	**Ertugliflozin 15 mg**	**Ertugliflozin 5 mg +Sitagliptin 100 mg**	**Ertugliflozin 15 mg + Sitagliptin 100 mg**
HbA1c (%)	**N = 242**	**N = 244**	**N = 247**	**N = 237**	**N = 241**
Baseline (mean)	8.5	8.6	8.6	8.6	8.6
Change from baseline (LS mean†)	-1.0	-1.0	-1.0	-1.4	-1.4
Difference from					
Sitagliptin				-0.4‡ (-0.6, -0.2)	-0.4‡ (-0.5, -0.2)
Ertugliflozin 5 mg				-0.4‡ (-0.5, -0.2)	
Ertugliflozin 15 mg					-0.4‡ (-0.6, -0.2)
(LS mean†, 95% CI)					
Patients [N (%)] with HbA1c <7%	93 (38.5)	72 (29.3)	83 (33.7)	126 (53.3)	123 (50.9)
FPG (mg/dL)	**N = 246**	**N = 250**	**N = 247**	**N = 240**	**N = 241**
Baseline (mean)	177.4	184.1	179.5	183.8	177.2
Change from baseline (LS mean†)	-24.3	-34.0	-34.6	-41.1	-44.3
Difference from					
Sitagliptin				-16.8‡ (-23.2, -10.4)	-20.0‡ (-26.4, -13.6)
Ertugliflozin 5 mg				-7.0§ (-13.3, -0.7)	
Ertugliflozin 15 mg					-9.8§ (-16.1, -3.4)
(LS mean†, 95% CI)					

* 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 13%, 10%, 11% , 11%, and 12% of patients and during the trial rescue medication was initiated by 6%, 6%, 3%, 2%, and 0% of patients randomized to sitagliptin, ertugliflozin 5 mg, ertugliflozin 15 mg, ertugliflozin 5 mg + sitagliptin, and ertugliflozin 15 mg + sitagliptin, respectively. Missing Week 26 measurements were imputed using multiple imputation with a mean equal to the baseline value of the patient. Results included measurements collected after initiation of rescue medication. For those subjects who did not receive rescue medication and had values measured at 26 weeks, the mean change from baseline for HbA1c was -1.1%, -1.1%, -1.1%, -1.5% and -1.6% for sitagliptin, ertugliflozin 5 mg, ertugliflozin 15 mg, ertugliflozin 5 mg + sitagliptin, and ertugliflozin 15 mg + sitagliptin, respectively.

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

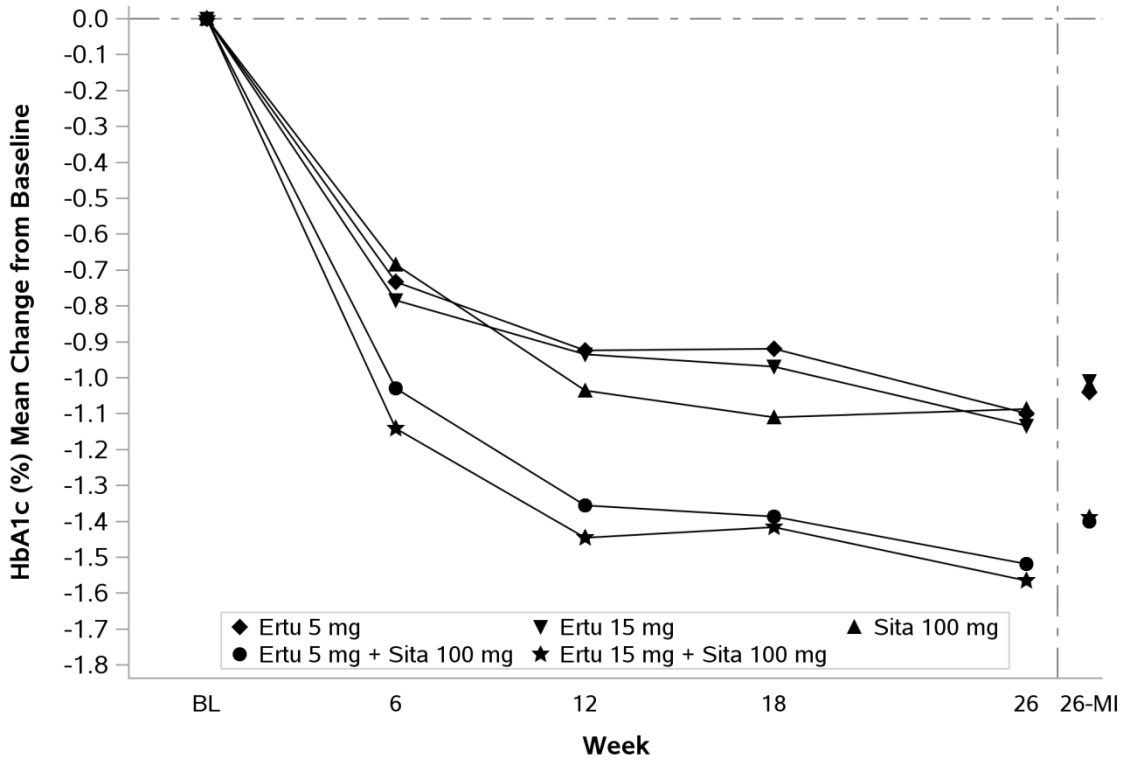
‡ p<0.001 compared to control group.

§ p<0.03 compared to control group.

The mean baseline body weight was 89.8 kg, 88.6 kg, 88.0 kg, 89.5 kg, and 87.5 kg in the sitagliptin 100 mg, ertugliflozin 5 mg, ertugliflozin15 mg, ertugliflozin 5 mg + sitagliptin 100 mg, and ertugliflozin 15 mg + sitagliptin 100 mg groups, respectively. The mean changes from baseline to Week 26 were -0.4 kg, -2.6 kg, -3.4 kg, -2.4 kg, and -2.7 kg in the sitagliptin 100 mg, ertugliflozin 5 mg, ertugliflozin 15 mg, ertugliflozin 5 mg + sitagliptin 100 mg, and ertugliflozin 15 mg + sitagliptin 100 mg groups, respectively. The difference from sitagliptin 100 mg (95% CI) for ertugliflozin 5 mg + sitagliptin 100 mg was -1.9 kg (-2.6, -1.3) and for ertugliflozin 15 mg + sitagliptin 100 mg was -2.3 kg (-3.0, -1.6).

The mean baseline systolic blood pressure was 128.4 mmHg, 129.7 mmHg, 128.9 mmHg, 130.2 mmHg, and 129.1 mmHg in the sitagliptin 100 mg, ertugliflozin 5 mg, ertugliflozin 15 mg , ertugliflozin 5 mg + sitagliptin 100 mg, and ertugliflozin 15 mg + sitagliptin 100 mg groups, respectively. The mean changes from baseline to Week 26 were -0.5 mmHg, -4.0 mmHg, -3.6 mmHg, -2.8 mmHg, and -3.4 mmHg in the sitagliptin 100 mg, ertugliflozin 5 mg, ertugliflozin 15 mg, ertugliflozin 5 mg + sitagliptin 100 mg, and ertugliflozin 15 mg + sitagliptin 100 mg groups, respectively. The difference from sitagliptin 100 mg (95% CI) for ertugliflozin 5 mg + sitagliptin 100 mg was -2.3 mmHg (-4.3, -0.4) and for ertugliflozin 15 mg + sitagliptin 100 mg was -2.9 mmHg (-4.8, -1.0).

Figure 3: HbA1c (%) Change over Time in a Factorial Study with Ertugliflozin and Sitagliptin as Add-on Combination Therapy with Metformin Compared to Individual Components Alone*



	BL	6	12	18	26
Ertu 5 mg (N)	244	236	231	223	211
Ertu 15 mg (N)	247	239	232	226	214
Sita 100 mg (N)	242	236	226	212	203
Ertu 5 mg + Sita 100 mg (N)	237	227	223	220	212
Ertu 15 mg + Sita 100 mg (N)	241	229	226	225	215

*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 6).

14.3 Ertugliflozin as 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 (≥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 ertugliflozin. Patients entered a 2-week, single-blind, placebo run-in period and were randomized to placebo, ertugliflozin 5 mg, or ertugliflozin 15 mg.

At Week 26, treatment with ertugliflozin at 5 mg or 15 mg daily provided statistically significant reductions in in HbA1c. Ertugliflozin 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 Ertugliflozin in Combination with Metformin and Sitagliptin in Patients with Type 2 Diabetes Mellitus*

	Placebo	Ertugliflozin 5 mg	Ertugliflozin 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, ertugliflozin 5 mg, and ertugliflozin 15 mg, respectively. Missing Week 26 measurements were imputed using multiple imputation with a mean equal to the baseline value of the patient. Results included 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, ertugliflozin 5 mg, and ertugliflozin 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, ertugliflozin 5 mg, and ertugliflozin 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, ertugliflozin 5 mg and ertugliflozin 15 mg groups, respectively. The difference from placebo (95% CI) for ertugliflozin 5 mg was -1.9 kg (-2.6, -1.3) and for ertugliflozin 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, ertugliflozin 5 mg, and ertugliflozin 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, ertugliflozin 5 mg and ertugliflozin 15 mg groups, respectively. The difference from placebo (95% CI) for ertugliflozin 5 mg was -3.7 mmHg (-6.1, -1.2) and for ertugliflozin 15 mg was -4.3 mmHg (-6.7, -1.9).

14.4 Initial Combination Therapy of Ertugliflozin and 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 ertugliflozin 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, ertugliflozin 5 mg, ertugliflozin 15 mg in combination with sitagliptin (100 mg), once daily.

At Week 26, treatment with ertugliflozin 5 mg and 15 mg in combination with sitagliptin at 100 mg daily provided statistically significant reductions in HbA1c compared to placebo. Ertugliflozin 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% compared with placebo (see Table 8).

Table 8: Results at Week 26 from an Initial Combination Therapy Study of Ertugliflozin and Sitagliptin*

	Placebo	Ertugliflozin 5 mg + Sitagliptin 100 mg	Ertugliflozin 15 mg + Sitagliptin 100 mg
HbA1c (%)	**N = 96**	**N = 98**	**N = 96**
Baseline (mean)	9.0	8.9	9.0
Change from baseline (LS mean†)	-0.6	-1.6	-1.5
Difference from placebo (LS mean† and 95% CI)		-1.0‡ (-1.3, -0.7)	-0.9‡ (-1.3, -0.6)
Patients [N (%)] with HbA1c <7%	9 (9.3)	36 (37.1)	32 (32.9)
FPG (mg/dL)	**N = 96**	**N = 98**	**N = 96**
Baseline (mean)	207.5	198.0	187.7
Change from baseline (LS mean†)	-11.8	-47.1	-50.8
Difference from placebo (LS mean†, 95% CI)		-35.4‡ (-47.3, -23.4)	-39.1‡ (-51.4, -26.8)

* 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 22%, 7% and 10% of patients and during the trial rescue medication was initiated by 32%, 6%, and 0% of patients randomized to placebo, ertugliflozin 5 mg and ertugliflozin 15 mg, respectively. Missing Week 26 measurements were imputed using multiple imputation with a mean equal to the baseline value of the patient. Results included measurements collected after initiation of rescue medication. For those subjects who did not receive rescue medication and had values measured at 26 weeks, the mean change from baseline for HbA1c was -0.8%, -1.7%, -1.7% for placebo, ertugliflozin 5 mg and ertugliflozin 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 95.0 kg, 90.8 kg, and 91.2 kg in the placebo, ertugliflozin 5 mg + sitagliptin 100 mg, and ertugliflozin 15 mg + sitagliptin 100 mg groups, respectively. The mean changes from baseline to Week 26 were -0.5 kg, -2.7 kg, and -2.8 kg in the placebo, ertugliflozin 5 mg + sitagliptin 100 mg, and ertugliflozin 15 mg + sitagliptin 100 mg groups, respectively. The difference from placebo (95% CI) for ertugliflozin 5 mg + sitagliptin 100 mg was -2.1 kg (-3.1, -1.2) and for ertugliflozin 15 mg + sitagliptin 100 mg was -2.3 kg (-3.3, -1.3).

The mean baseline systolic blood pressure was 127.4 mmHg, 130.7 mmHg, and 129.2 mmHg in the placebo, ertugliflozin 5 mg + sitagliptin 100 mg, and ertugliflozin 15 mg + sitagliptin 100 mg groups, respectively. The mean changes from baseline to Week 26 were 1.6 mmHg, -2.4 mmHg, and -3.5 mmHg in the placebo, ertugliflozin 5 mg + sitagliptin 100 mg, and ertugliflozin 15 mg + sitagliptin 100 mg, respectively. The difference from placebo (95% CI) for ertugliflozin 5 mg + sitagliptin 100 mg was -4.0 mmHg (-7.2, -0.8) and for ertugliflozin 15 mg + sitagliptin 100 mg was -5.2 mmHg (-8.4, -1.9).

16 HOW SUPPLIED/STORAGE AND HANDLING

STEGLUJAN (ertugliflozin and sitagliptin) tablets are available in the strengths listed below:

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. They are supplied as follows:

NDC 0006-5367-03 unit-of-use bottles of 30
NDC 0006-5367-06 unit-of-use bottles of 90
NDC 0006-5367-07 bulk bottles of 500

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. They are supplied as follows:

NDC 0006-5368-03 unit-of-use bottles of 30
NDC 0006-5368-06 unit-of-use bottles of 90
NDC 0006-5368-07 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 STEGLUJAN (ertugliflozin and sitagliptin) and to reread it each time the prescription is renewed.

Inform patients of the potential risks and benefits of STEGLUJAN 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 STEGLUJAN 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 STEGLUJAN at the same time.

Pancreatitis

Inform patients that acute pancreatitis has been reported during use of sitagliptin, a component of STEGLUJAN. Inform patients that persistent severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting, is the hallmark symptom of acute pancreatitis. Instruct patients to promptly discontinue STEGLUJAN and contact their physician if persistent severe abdominal pain occurs *[see Warnings and Precautions (5.1)]*.

Heart Failure

Inform patients of the signs and symptoms of heart failure. Instruct patients to contact their health care provider as soon as possible if they experience symptoms of heart failure, including increasing shortness of breath, rapid increase in weight or swelling of the feet *[see Warnings and Precautions (5.7)]*.

Hypersensitivity Reactions

Inform patients that allergic reactions have been reported during postmarketing use of sitagliptin, a component of STEGLUJAN. If symptoms of allergic reactions (including rash, hives, and swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing) occur, instruct patients that they must stop taking STEGLUJAN and seek medical advice promptly *[see Warnings and Precautions (5.11)]*.

Severe and Disabling Arthralgia

Inform patients that severe and disabling joint pain may occur with this class of drugs. The time to onset of symptoms can range from one day to years. Instruct patients to seek medical advice if severe joint pain occurs *[see Warnings and Precautions (5.13)]*.

Bullous Pemphigoid

Inform patients that bullous pemphigoid may occur with the DPP-4 class of drugs. Instruct patients to seek medical advice if blisters or erosions occur *[see Warnings and Precautions (5.14)]*.

Hypoglycemia with Concomitant Use of Insulin and Insulin Secretagogue

Inform patients that the incidence of hypoglycemia may increase when STEGLUJAN 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 (5.8)]*.

Fetal Toxicity

Advise pregnant patients of the potential risk to a fetus with treatment with STEGLUJAN. 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 STEGLUJAN is not recommended while breastfeeding *[see Use in Specific Populations (8.2)].*

Hypotension

Inform patients that symptomatic hypotension may occur with STEGLUJAN and advise them to contact their doctor if they experience such symptoms *[see Warnings and Precautions (5.2)]*. 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 medicines containing SGLT2 inhibitors, including ertugliflozin. 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 STEGLUJAN and seek medical advice immediately *[see Warnings and Precautions (5.3)]*.

Acute Kidney Injury

Inform patients that acute kidney injury has been reported during use of STEGLUJAN. 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 STEGLUJAN use in those settings *[see Warnings and Precautions (5.4)]*.

Monitoring of Renal Function

Inform patients about the importance of regular testing of renal function when receiving treatment with STEGLUJAN *[see Warnings and Precautions (5.4)]*.

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 (5.5)]*.

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 (5.6)]*.

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 (5.9)]*.

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 (5.10)]*.

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 (5.10)]*.

Laboratory Tests

Due to the mechanism of action of ertugliflozin, inform patients that their urine will test positive for glucose while taking STEGLUJAN.

Manufactured for: Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

For patent information: www.merck.com/product/patent/home.html

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Medication Guide
STEGLUJAN™ (STEG-loo-jan)
(ertugliflozin and sitagliptin)
tablets, for oral use

Read this Medication Guide carefully before you start taking STEGLUJAN and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment.

What is the most important information I should know about STEGLUJAN?
STEGLUJAN may cause serious side effects, including:

- **Inflammation of the pancreas (pancreatitis)** which may be severe and lead to death. Certain medical problems make you more likely to get pancreatitis.
  Before you start taking STEGLUJAN, tell your doctor if you have ever had:
  - pancreatitis
  - a history of alcoholism
  - kidney problems
  - stones in your gallbladder (gallstones)
  - high blood triglyceride levels

  Stop taking STEGLUJAN and call your doctor right away if you have pain in your stomach area (abdomen) that is severe and will not go away. The pain may be felt going from your abdomen through to your back. The pain may happen with or without vomiting. These may be symptoms of pancreatitis.
- **Dehydration.** STEGLUJAN can cause some people to become dehydrated (the loss of body water and salt)**.** Dehydration may cause you to feel dizzy, faint, lightheaded, or weak, especially when you stand up (orthostatic hypotension).

You may be at risk of dehydration if you:

- have low blood pressure
- take medicines to lower your blood pressure, including water pills (diuretics)
- have kidney problems
- are on a low sodium (salt) diet
- are 65 years of age or older

Talk to your doctor about what you can do to prevent dehydration including how much fluid you should drink on a daily basis.

- **Vaginal yeast infection.** Women who take STEGLUJAN may get vaginal yeast infections. Symptoms of a vaginal yeast infection include:
  - vaginal odor
  - white or yellowish vaginal discharge (discharge may be lumpy or look like cottage cheese)
  - vaginal itching
- **Yeast infection of the penis (balanitis or balanoposthitis).** Men who take STEGLUJAN may get a yeast infection of the skin around the penis. Certain men who are not circumcised may have swelling of the penis that makes it difficult to pull back the skin around the tip of your penis. Other symptoms of yeast infection of the penis include:
  - redness, itching, or swelling of the penis
  - foul smelling discharge from the penis
  - rash of the penis
  - pain in the skin around your penis

Talk to your doctor about what to do if you get symptoms of a yeast infection of the vagina or penis. Your doctor may suggest you use an over-the-counter antifungal medicine. Talk to your doctor right away if you use an over-the-counter antifungal medicine and your symptoms do not go away.

- **Heart failure.** Heart failure means your heart does not pump blood well enough.
  Before you start taking STEGLUJAN, tell your doctor if you have ever had heart failure or have problems with your kidneys. Contact your doctor right away if you have any of the following symptoms:
  - increasing shortness of breath or trouble breathing, especially when you lie down

- swelling or fluid retention, especially in the feet, ankles or legs
- an unusually fast increase in weight
- unusual tiredness

These may be symptoms of heart failure.

What is STEGLUJAN?

- STEGLUJAN contains 2 prescription diabetes medicines called ertugliflozin (STEGLATRO™) and sitagliptin (JANUVIA®). STEGLUJAN can be used along with diet and exercise to lower blood sugar in adults with type 2 diabetes.
- STEGLUJAN is not for people with type 1 diabetes.
- STEGLUJAN is not for people with diabetic ketoacidosis (increased ketones in your blood or urine).
- If you have had pancreatitis (inflammation of the pancreas) in the past, it is not known if you have a higher chance of getting pancreatitis while you take STEGLUJAN.
- It is not known if STEGLUJAN is safe and effective in children under 18 years of age.

Do not take STEGLUJAN if you:

- have severe kidney problems or are on dialysis.
- are allergic to ertugliflozin, sitagliptin, or any of the ingredients in STEGLUJAN. See the end of this Medication Guide for a list of ingredients in STEGLUJAN. Symptoms of a **serious** allergic reaction to STEGLUJAN may include skin rash, raised red patches on your skin (hives), swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing.

Before you take STEGLUJAN, tell your doctor about all of your medical conditions, including if you:

- have type 1 diabetes or have had diabetic ketoacidosis.
- have kidney problems.
- have liver problems.
- have or have had problems with your pancreas, including pancreatitis or surgery on your pancreas.
- have a history of urinary tract infections or problems with urination.
- are eating less due to illness, surgery, or a change in your diet.
- have a history of amputation.
- have had blocked or narrowed blood vessels, usually in the leg.
- have damage to the nerves (neuropathy) in your leg.
- have had diabetic foot ulcers or sores.
- are going to have surgery.
- drink alcohol very often, or drink a lot of alcohol in the short term (“binge” drinking).
- are pregnant or plan to become pregnant. STEGLUJAN may harm your unborn baby. If you become pregnant while taking STEGLUJAN, your doctor may switch you to a different medicine to control your blood sugar. Talk to your doctor about the best way to control your blood sugar if you plan to become pregnant or while you are pregnant.
  Pregnancy Registry: If you take STEGLUJAN at any time during your pregnancy, talk with your doctor about how you can join the STEGLUJAN pregnancy registry. The purpose of this registry is to collect information about the health of you and your baby. You can enroll in this registry by calling 1-800-986-8999.
- are breastfeeding or plan to breastfeed. It is not known if STEGLUJAN passes into your breast milk. You should not breastfeed if you take STEGLUJAN.

Tell your doctor about all of the medicines you take, including prescription and over-the-counter

medicines, vitamins, and herbal supplements.

How should I take STEGLUJAN?

- Take STEGLUJAN exactly as your doctor tells you to take it.
- Take STEGLUJAN by mouth 1 time in the morning each day, with or without food.
- Your doctor may change your dose if needed.
- If you miss a dose, take it as soon as you remember. If it is almost time for your next dose, skip the missed dose and take the medicine at the next regularly scheduled time. **Do not** take 2 doses of STEGLUJAN at the same time.
- Your doctor may tell you to take STEGLUJAN along with other diabetes medicines. Low blood sugar can happen more often when STEGLUJAN is taken with certain other diabetes medicines. See "What are the possible side effects of STEGLUJAN?".
- Stay on your prescribed diet and exercise program while taking STEGLUJAN.
- Check your blood sugar as your doctor tells you to.
- Your doctor will check your diabetes with regular blood tests, including your blood sugar levels and your HbA1c.
- Talk to your doctor about how to prevent, recognize and manage low blood sugar (hypoglycemia), high blood sugar (hyperglycemia), complications of diabetes.
- Your doctor will do blood tests to check how well your kidneys are working before and during your treatment with STEGLUJAN.
- When your body is under some types of stress, such as fever, trauma (such as a car accident), infection, or surgery, the amount of diabetes medicine you need may change. Tell your doctor right away if you have any of these conditions and follow your doctor's instructions.
- When taking STEGLUJAN, you may have sugar in your urine, which will show up on a urine test.
- If you take too much STEGLUJAN, call your doctor or go to the nearest hospital emergency room right away.

What are the possible side effects of STEGLUJAN?

STEGLUJAN may cause serious side effects, including:

See "**What is the most important information I should know about STEGLUJAN?**"

- ketoacidosis **(increased ketones in your blood or urine).** Ketoacidosis has happened in people who have **type 1 diabetes or type 2 diabetes** during treatment with STEGLUJAN. Ketoacidosis is a serious condition, which may need to be treated in a hospital. Ketoacidosis may lead to death. **Ketoacidosis can happen even if your blood sugar is less than 250 mg/dL. Stop taking STEGLUJAN and call your doctor right away if you get any of the following symptoms:**
  - nausea
  - vomiting
  - stomach area (abdominal) pain
  - tiredness
  - trouble breathing

If you get any of these symptoms during treatment with STEGLUJAN, if possible check for ketones in your urine, even if your blood sugar is less than 250 mg/dL.

- **kidney problems (sometimes requiring dialysis).** Sudden kidney injury has happened to people treated with STEGLUJAN. Talk to your doctor right away if you:
  - reduce the amount of food or liquid you drink, for example, if you are sick or cannot eat or
  - you start to lose liquids from your body, for example, from vomiting, diarrhea or being in the sun too long
- **serious urinary tract infections.** Serious urinary tract infections that may lead to hospitalization have happened in people who are taking STEGLUJAN. Tell your doctor if you

have any signs or symptoms of a urinary tract infection such as a burning feeling when passing urine, a need to urinate often, the need to urinate right away, pain in the lower part of your stomach (pelvis), or blood in the urine. Sometimes people may also have a fever, back pain, nausea, or vomiting.

- **amputations**. STEGLUJAN may increase your risk of lower limb amputations. Amputations mainly involve removal of the toe.

You may be at a higher risk of lower limb amputation if you:

- have a history of amputation
- have had blocked or narrowed blood vessels, usually in your leg
- have damage to the nerves (neuropathy) in your leg
- have had diabetic foot ulcers or sores

Call your doctor right away if you have new pain or tenderness, any sores, ulcers, or infections in your leg or foot. Your doctor may decide to stop your STEGLUJAN for a while if you have any of these signs or symptoms. Talk to your doctor about proper foot care.

- **low blood sugar (hypoglycemia).** If you take STEGLUJAN with another medicine that can cause low blood sugar such as a sulfonylurea or insulin, your risk of getting low blood sugar is higher. The dose of your sulfonylurea or insulin may need to be lowered while you take STEGLUJAN. Signs and symptoms of low blood sugar may include:
  - headache
  - drowsiness
  - hunger
  - irritability
  - dizziness
  - confusion
  - sweating
  - feeling jittery or shaky
  - weakness
  - fast heartbeat
- **a rare but serious bacterial infection that causes damage to the tissue under the skin (necrotizing fasciitis) in the area between and around the anus and genitals (perineum).** Necrotizing fasciitis of the perineum has happened in women and men who take medicines that lower blood sugar in the same way as one of the medicines in STEGLUJAN. Necrotizing fasciitis of the perineum may lead to hospitalization, may require multiple surgeries, and may lead to death. **Seek medical attention immediately if you have fever or you are feeling very weak, tired or uncomfortable (malaise) and you develop any of the following symptoms in the area between and around your anus and genitals:**
  - pain or tenderness
  - swelling
  - redness of skin (erythema)
- **increased fats in your blood (bad cholesterol or LDL).**
- **serious allergic reactions.** If you have any symptoms of a serious allergic reaction, stop taking STEGLUJAN and call your doctor right away. See "**Do not take STEGLUJAN if you:**". Your doctor may give you a medicine for your allergic reaction and prescribe a different medicine for your diabetes.
- **joint pain.** Some people who take medicines called DPP-4 inhibitors, one of the medicines in STEGLUJAN, may develop joint pain that can be severe. Call your doctor if you have severe joint pain.
- **skin reaction.** Some people who take medicines called DPP-4 inhibitors, one of the medicines in STEGLUJAN, may develop a skin reaction called bullous pemphigoid that can require treatment in a hospital. Tell your doctor right away if you develop blisters or the breakdown of the outer layer of your skin (erosion). Your doctor may tell you to stop taking STEGLUJAN.

The most common side effects of ertugliflozin include:

- vaginal yeast infections and yeast infections of the penis (**See "What is the most important information I should know about STEGLUJAN?")**
- changes in urination, including urgent need to urinate more often, in larger amounts, or at night.

The most common side effects of sitagliptin include:

- upper respiratory infection
- stuffy or runny nose and sore throat
- headache
- stomach upset and diarrhea

STEGLUJAN may have other side effects including swelling of the hands or legs. Swelling of the hands and legs can happen when sitagliptin, one of the medicines in STEGLUJAN, is used with rosiglitazone (Avandia®). Rosiglitazone is another type of diabetes medicine.
These are not all the possible side effects of STEGLUJAN.
Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088.

How should I store STEGLUJAN?

- Store STEGLUJAN at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep STEGLUJAN dry.
- Store blister packs of STEGLUJAN in the original package.

Keep STEGLUJAN and all medicines out of the reach of children.

General information about the safe and effective use of STEGLUJAN.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use STEGLUJAN for a condition for which it was not prescribed. Do not give STEGLUJAN to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or doctor for information about STEGLUJAN that is written for health professionals. For more information about STEGLUJAN, go to www.steglujan.com or call 1-800-622-4477.

What are the ingredients in STEGLUJAN?

Active ingredients: ertugliflozin and sitagliptin.
Inactive ingredients: microcrystalline cellulose, dibasic calcium phosphate anhydrous, croscarmellose sodium, sodium stearyl fumarate, and magnesium stearate.
The tablet film coating contains the following inactive ingredients: hypromellose, hydroxypropyl cellulose, titanium dioxide, iron oxide red, iron oxide yellow, ferrosoferric oxide/black iron oxide, and carnauba wax.

Manufactured for: Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

For patent information, go to: www.merck.com/product/patent/home.html.
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