

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

RECENT MAJOR CHANGES

Indications and Usage (1)	09/2023
Dosage and Administration (2.1, 2.3)	09/2023
Warnings and Precautions (5.1)	09/2023

INDICATIONS AND USAGE

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

Limitations of Use:

- Not recommended for use to improve glycemic control in patients with type 1 diabetes mellitus. (1)
- Has not been studied in patients with a history of pancreatitis. (1, 5.2)

DOSAGE AND ADMINISTRATION

- Assess renal function before initiating and as clinically indicated. (2.1)
- Correct volume depletion before initiating. (2.1)
- Recommended starting dose is 5 mg ertugliflozin/100 mg sitagliptin once daily, taken in the morning, with or without food. (2.2)
- Increase dose to 15 mg ertugliflozin/100 mg sitagliptin once daily in those tolerating STEGLUJAN and needing additional glycemic control. (2.2)
- Use is not recommended in patients with an eGFR less than 45 mL/min/1.73 m². (2.2)
- Withhold STEGLUJAN for at least 4 days, if possible, prior to major surgery or procedures associated with prolonged fasting. (2.3)

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 (<30 mL/min/1.73 m²), end-stage renal disease, or dialysis. (4)
- Hypersensitivity to sitagliptin, ertugliflozin, or any excipient in STEGLUJAN. (4, 5.11, 6.2)

WARNINGS AND PRECAUTIONS

- **Diabetic Ketoacidosis in Patients with Type 1 Diabetes Mellitus and Other Ketoacidosis:** Consider ketone monitoring in patients at risk for ketoacidosis, as indicated. Assess for ketoacidosis regardless of presenting blood glucose levels and discontinue STEGLUJAN if ketoacidosis is suspected. Monitor patients for resolution of ketoacidosis before restarting. (5.1)
- **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. (5.2)
- **Lower Limb Amputation:** Consider factors that may increase the risk of amputation before initiating STEGLUJAN. Monitor patients for infections or ulcers of lower limbs, and discontinue if these occur. (5.3)
- **Acute Renal Failure:** There have been postmarketing reports of acute renal failure in patients taking sitagliptin, sometimes requiring dialysis. Monitor renal function. (5.4)

- **Volume Depletion:** May result in acute kidney injury. Before initiating, assess and correct volume status in patients with renal impairment, or low systolic blood pressure elderly patients, or patients on diuretics. Monitor for signs and symptoms during therapy. (5.5)
- **Urosepsis and Pyelonephritis:** Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated. (5.6)
- **Heart Failure:** Heart failure has been observed with two other members of the DPP-4 inhibitor class. Consider risks and benefits in patients who have known risk factors for heart failure. Monitor patients for signs and symptoms. (5.7)
- **Hypoglycemia:** Consider a lower dose of insulin or insulin secretagogue to reduce risk of hypoglycemia when used in combination. (5.8)
- **Necrotizing Fasciitis of the Perineum (Fournier's Gangrene):** Serious, life-threatening cases have occurred in both females and males. Assess patients presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise. If suspected, institute prompt treatment. (5.9)
- **Genital Mycotic Infections:** Monitor and treat if indicated. (5.10)
- **Hypersensitivity:** There have been postmarketing reports of serious allergic and hypersensitivity reactions in patients treated with sitagliptin such as anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. In such cases, promptly discontinue, assess for other potential causes, institute appropriate monitoring and treatment, and initiate alternative treatment for diabetes. (5.11)
- **Severe and Disabling Arthralgia:** Severe and disabling arthralgia has been reported in patients taking DPP-4 inhibitors. Consider as a possible cause for severe joint pain and discontinue if appropriate. (5.12)
- **Pemphigoid:** There have been postmarketing reports of bullous pemphigoid requiring hospitalization in patients taking DPP-4 inhibitors. Tell patients to report development of blisters or erosions. If bullous pemphigoid is suspected, discontinue. (5.13)

ADVERSE REACTIONS

- Most common adverse reactions associated with ertugliflozin (incidence ≥5%): female genital mycotic infections. (6.1)
- Most common adverse reactions associated with sitagliptin (incidence ≥5%): upper respiratory tract infection, nasopharyngitis and headache. In the add-on to sulfonylurea and add-on to insulin studies, hypoglycemia was also more commonly reported in patients treated with sitagliptin compared to placebo. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme LLC at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

See full prescribing information for information on drug interactions and interference of STEGLUJAN with laboratory tests. (7)

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

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

Limitations of Use

- Not recommended for use to improve glycemic control in patients with type 1 diabetes mellitus [see *Warnings and Precautions (5.1)*].
- 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 (5.2)*].

2 DOSAGE AND ADMINISTRATION

2.1 Prior to Initiation of STEGLUJAN

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

2.2 Recommended Dosage

- The recommended starting dose of STEGLUJAN is 5 mg ertugliflozin/100 mg sitagliptin once daily, taken in the morning, with or without food.
- For patients treated with ertugliflozin who are being switched to STEGLUJAN, the dose of ertugliflozin can be maintained.
- For additional glycemic control, the dose may be increased to 15 mg ertugliflozin/100 mg sitagliptin once daily in patients tolerating STEGLUJAN.
- Use is not recommended in patients with an eGFR less than 45 mL/min/1.73 m².
- Use of STEGLUJAN is contraindicated in patients with severe renal impairment (<30 mL/min/1.73 m²), end-stage renal disease (ESRD) or on dialysis [see *Contraindications (4)*].

2.3 Temporary Interruption for Surgery

Withhold STEGLUJAN for at least 4 days, if possible, prior to major surgery or procedures associated with prolonged fasting. Resume STEGLUJAN when the patient is clinically stable and has resumed oral intake [see *Warnings and Precautions (5.1)* and *Clinical Pharmacology (12.2)*].

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

- Patients with severe renal impairment (<30 mL/min/1.73 m²), end-stage renal disease (ESRD), or on dialysis [see *Warnings and Precautions (5.4)* and *Use in Specific Populations (8.6)*].
- Hypersensitivity to sitagliptin, ertugliflozin, or any excipient, in STEGLUJAN, reactions such as anaphylaxis or angioedema have occurred [see *Warnings and Precautions (5.11)* and *Adverse Reactions (6.2)*].

5 WARNINGS AND PRECAUTIONS

5.1 Diabetic Ketoacidosis in Patients with Type 1 Diabetes Mellitus and Other Ketoacidosis

In patients with type 1 diabetes mellitus, STEGLUJAN significantly increases the risk of diabetic ketoacidosis, a life-threatening event, beyond the background rate. In placebo-controlled trials of patients with type 1 diabetes mellitus, the risk of ketoacidosis was markedly increased in patients who received sodium glucose transporter 2 (SGLT2) inhibitors compared to patients who received placebo; this risk may be greater with higher doses. STEGLUJAN is not indicated for glycemic control in patients with type 1 diabetes mellitus.

Type 2 diabetes mellitus and pancreatic disorders (e.g., history of pancreatitis or pancreatic surgery) are also risk factors for ketoacidosis. There have been postmarketing reports of fatal events of ketoacidosis in patients with type 2 diabetes mellitus using SGLT2 inhibitors.

Precipitating conditions for diabetic ketoacidosis or other ketoacidosis include under-insulinization due to insulin dose reduction or missed insulin doses, acute febrile illness, reduced caloric intake, ketogenic diet, surgery, volume depletion, and alcohol abuse.

Signs and symptoms are consistent with dehydration and severe metabolic acidosis and include nausea, vomiting, abdominal pain, generalized malaise, and shortness of breath. Blood glucose levels at presentation may be below those typically expected for diabetic ketoacidosis (e.g., less than 250 mg/dL). Ketoacidosis and glucosuria may persist longer than typically expected. Urinary glucose excretion persists for 4 days after discontinuing STEGLUJAN [see *Clinical Pharmacology (12.2)*]; however, there have been postmarketing reports of ketoacidosis and/or glucosuria lasting greater than 6 days and some up to 2 weeks after discontinuation of SGLT2 inhibitors.

Consider ketone monitoring in patients at risk for ketoacidosis if indicated by the clinical situation. Assess for ketoacidosis regardless of presenting blood glucose levels in patients who present with signs and symptoms consistent with severe metabolic acidosis. If ketoacidosis is suspected, discontinue STEGLUJAN, promptly evaluate, and treat ketoacidosis, if confirmed. Monitor patients for resolution of ketoacidosis before restarting STEGLUJAN.

Withhold STEGLUJAN, if possible, in temporary clinical situations that could predispose patients to ketoacidosis. Resume STEGLUJAN when the patient is clinically stable and has resumed oral intake [see *Dosage and Administration (2.3)*].

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

5.2 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.

5.3 Lower Limb Amputation

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

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

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

Across seven ertugliflozin clinical trials, non-traumatic lower limb amputations were reported in 1 (0.1%) patient in the comparator group, 3 (0.2%) patients in the ertugliflozin 5 mg group, and 8 (0.5%) patients in the ertugliflozin 15 mg group.

Before initiating STEGLUJAN, consider factors in the patient history that may predispose them to the need for amputations, such as a history of prior amputation, peripheral vascular disease, neuropathy and diabetic foot ulcers. Counsel patients about the importance of routine preventative foot care. Monitor patients receiving STEGLUJAN for signs and symptoms of infection (including osteomyelitis), new pain or tenderness, sores or ulcers involving the lower limbs, and discontinue STEGLUJAN if these complications occur.

5.4 Acute Renal Failure

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

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

5.5 Volume Depletion

STEGLUJAN can cause intravascular volume contraction which may sometimes manifest as symptomatic hypotension or acute transient changes in creatinine [see *Adverse Reactions (6.1)*]. There have been postmarketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients with type 2 diabetes mellitus receiving SGLT2 inhibitors, including STEGLUJAN. Patients with impaired renal function (eGFR less than 60 mL/min/1.73 m²) [see *Use in Specific Populations (8.6)*], elderly patients, patients with low systolic blood pressure, or patients on loop diuretics may be at increased risk for volume depletion or hypotension. Before initiating STEGLUJAN in patients with one or more of these characteristics, assess volume status and renal function. In patients with volume depletion, correct this condition before initiating STEGLUJAN. Monitor for signs and symptoms of volume depletion, and renal function after initiating therapy.

5.6 Urosepsis and Pyelonephritis

There have been postmarketing reports of serious urinary tract infections, including urosepsis and pyelonephritis, requiring hospitalization in patients receiving medicines containing SGLT2 inhibitors. Treatment with medicines containing SGLT2 inhibitors increases the risk for urinary tract infections. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated [see *Adverse Reactions (6)*].

5.7 Heart Failure

An association between dipeptidyl peptidase-4 (DPP-4) inhibitor treatment and heart failure has been observed in cardiovascular outcomes trials for two other members of the DPP-4 inhibitor class. These trials

evaluated patients with type 2 diabetes mellitus and atherosclerotic cardiovascular disease. Consider the risks and benefits of STEGLUJAN prior to initiating treatment in patients at risk for heart failure, such as those with a prior history of heart failure and a history of renal impairment, and observe these patients for signs and symptoms of heart failure during therapy. Advise patients of the characteristic symptoms of heart failure and to immediately report such symptoms. If heart failure develops, evaluate and manage according to current standards of care and consider discontinuation of STEGLUJAN.

5.8 Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues

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

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

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

Patients treated with STEGLUJAN presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise, should be assessed for necrotizing fasciitis. If suspected, start treatment immediately with broad-spectrum antibiotics and, if necessary, surgical debridement. Discontinue STEGLUJAN, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.

5.10 Genital Mycotic Infections

Ertugliflozin, 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. 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 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.

5.13 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.

6 ADVERSE REACTIONS

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

- Diabetic Ketoacidosis in Patients with Type 1 Diabetes and Other Ketoacidosis [see *Warnings and Precautions (5.1)*]
- Pancreatitis [see *Warnings and Precautions (5.2)*]
- Lower Limb Amputation [see *Warnings and Precautions (5.3)*]
- Acute Renal Failure [see *Warnings and Precautions (5.4)*]
- Volume Depletion [see *Warnings and Precautions (5.5)*]
- Urosepsis and Pyelonephritis [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)*]
- Severe and Disabling Arthralgia [see *Warnings and Precautions (5.12)*]
- Bullous Pemphigoid [see *Warnings and Precautions (5.13)*]

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 m²) was normal or mildly impaired in 97% of patients and moderately impaired in 3% of patients.

Table 1 shows common adverse reactions associated with the use of 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%
Thirst [♯]	0.6%	2.7%	1.4%

* The three placebo controlled studies included one monotherapy trial and two add-on combination trials with metformin or with metformin and sitagliptin.

[†] Includes: genital candidiasis, genital infection fungal, vaginal infection, vulvitis, vulvovaginal candidiasis, vulvovaginal mycotic infection, and vulvovaginitis. Percentages calculated with the number of female patients in each group as denominator: placebo (N=235), 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.

[♯] 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 m²). In patients with moderate renal impairment, adverse reactions related to volume depletion (e.g., dehydration, dizziness postural, presyncope, syncope, hypotension, and orthostatic hypotension) were reported in 0%, 4.4%, and 1.9% of patients treated with placebo, 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)*].

Hypoglycemia

The incidence of hypoglycemia by study is shown in Table 2.

Table 2: 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.

Urinary Tract Infections

In VERTIS CV, urinary tract infections (e.g., urinary tract infection, cystitis, dysuria) occurred in 10.2%, 12.2% and 12.0% of patients treated with placebo, ertugliflozin 5 mg and ertugliflozin 15 mg, respectively. The incidences of serious urinary tract infections were 0.8%, 0.9% and 0.4% with placebo, ertugliflozin 5 mg and ertugliflozin 15 mg, respectively.

Sitagliptin

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

Changes in Serum Creatinine and eGFR

Initiation of ertugliflozin causes an increase in serum creatinine and decrease in eGFR within weeks of starting therapy and then these changes stabilize. In a study of patients with moderate renal impairment, larger mean changes were observed. In a long-term cardiovascular outcomes trial, an initial increase in serum creatinine and a decrease in eGFR within weeks of starting therapy was observed (at Week 6 eGFR changes of -2.7, -3.8 and -0.4 mL/min/1.73 m² in the ertugliflozin 5 mg, ertugliflozin 15 mg and placebo arms, respectively). The initial decline was followed by a recovery toward baseline to Week 52 (eGFR change from baseline of -0.4, -1.1 and -0.2 mL/min/1.73 m² in ertugliflozin 5 mg, ertugliflozin 15 mg, and placebo arms, respectively). Acute hemodynamic changes may play a role in the early renal function changes observed with ertugliflozin since they are reversed after treatment discontinuation.

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.

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

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.

Sitagliptin

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

Ertugliflozin

- Necrotizing fasciitis of the perineum (Fournier's Gangrene)
- Angioedema

7 DRUG INTERACTIONS

Table 3: Clinically Significant Drug Interactions with STEGLUJAN

Insulin and Insulin Secretagogues	
<i>Clinical Impact:</i>	The risk of hypoglycemia when STEGLUJAN is used in combination with insulin and/or an insulin secretagogue.
<i>Intervention:</i>	A lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with STEGLUJAN.
Lithium	
<i>Clinical Impact:</i>	Concomitant use of an SGLT2 inhibitor with lithium may decrease serum lithium concentrations.
<i>Intervention:</i>	Monitor serum lithium concentration more frequently during STEGLUJAN initiation and dosage changes.
Positive Urine Glucose Test	
<i>Clinical Impact:</i>	SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests.
<i>Intervention:</i>	Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.
Interference with 1,5-anhydroglucitol (1,5-AG) Assay	
<i>Clinical Impact:</i>	Measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors.
<i>Intervention:</i>	Monitoring glycemic control with 1,5-AG assay is not recommended. Use alternative methods to monitor glycemic control.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on animal data showing adverse renal effects, 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, 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 \geq 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

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 (2.1) and Warnings and Precautions (5.4)*].

Ertugliflozin

In ertugliflozin clinical trials, 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 (5.5) and Adverse Reactions (6.1)*].

In VERTIS CV, a total of 2780 (50.5%) patients treated with ertugliflozin were 65 years and older, and 595 (10.8%) patients treated with ertugliflozin were 75 years and older. Safety and efficacy were generally similar for patients age 65 years and older compared to patients younger than 65.

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

A 26-week placebo-controlled study of 313 patients with Stage 3 Chronic Kidney Disease (eGFR \geq 30 to less than 60 mL/min/1.73 m²) treated with ertugliflozin did not demonstrate improvement in glycemic control. In the VERTIS CV study, there were 1370 patients (25%) with an eGFR \geq 90 mL/min/1.73 m², 2929 patients (53%) with an eGFR of \geq 60 to less than 90 mL/min/1.73 m², 879 patients (16%) with an eGFR of \geq 45 to less than 60 mL/min/1.73 m² and 299 patients (5%) with eGFR of 30 to $<$ 45 mL/min/1.73 m² treated with ertugliflozin. Similar effects on glycemic control at Week 18 were observed in patients treated with ertugliflozin in each eGFR subgroup and also in the overall patient population.

STEGLUJAN is contraindicated in patients with severe renal impairment ($<$ 30 mL/min/1.73 m²), ESRD, or on dialysis [see *Contraindications (4)*].

No dosage adjustment is needed in patients with eGFR \geq 45 mL/min/1.73 m².

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.

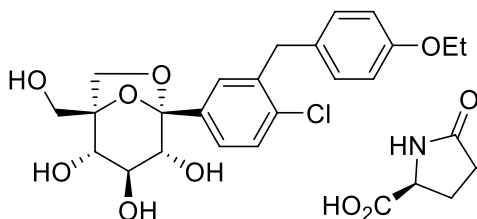
11 DESCRIPTION

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

The chemical structure is:

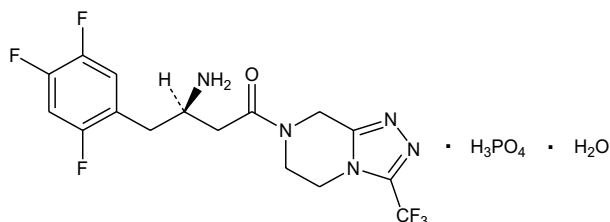


Ertugliflozin L-pyroglutamic acid is a white to off-white powder that is soluble in ethyl alcohol and acetone, slightly soluble in ethyl acetate and acetonitrile and very slightly soluble in water.

Sitagliptin

Sitagliptin phosphate monohydrate is described chemically as 7-[(3R)-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 $C_{16}H_{15}F_6N_5O \cdot H_3PO_4 \cdot H_2O$ 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, ferrosulfate 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 $\mu\text{M}\cdot\text{hr}$, 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 μ g 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 (2.1)*].

Ertugliflozin

In a 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 m², 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)*].

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 ($IC_{50} > 39 \mu M$) 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

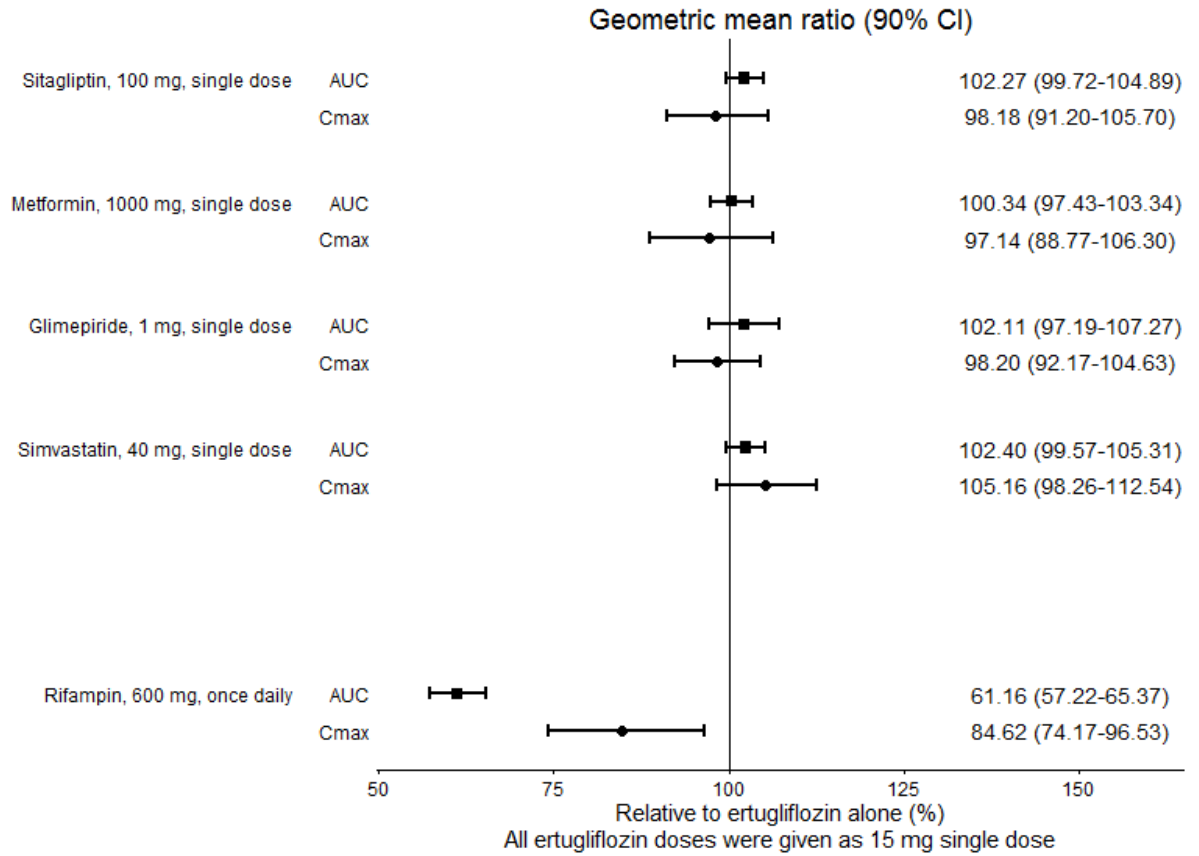
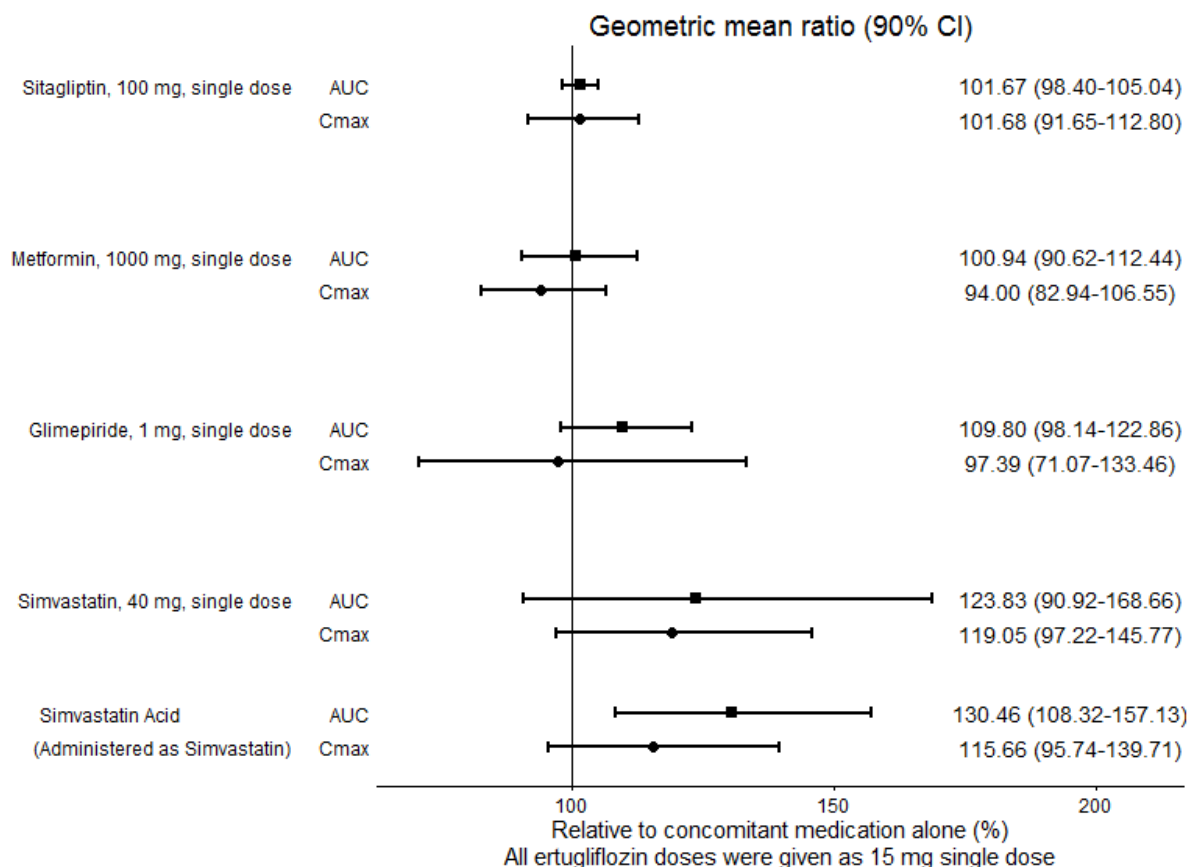


Figure 2: Effects of Ertugliflozin on the Pharmacokinetics of Other Drugs



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-∞} 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-∞} 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 Glycemic Control Trials 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.

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 ($\geq 1,500$ mg/day for ≥ 8 weeks) participated in a randomized, double-blind, 26-week, active controlled study (NCT02099110) to evaluate the efficacy and

safety of 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 (LS mean [†] , 95% CI)					-0.4 [‡] (-0.6, -0.2)
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 (LS mean [†] , 95% CI)					-9.8 [§] (-16.1, -3.4)

* N includes all randomized and treated patients with a baseline measurement of the outcome variable. At Week 26 the primary HbA1c endpoint was missing for 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.

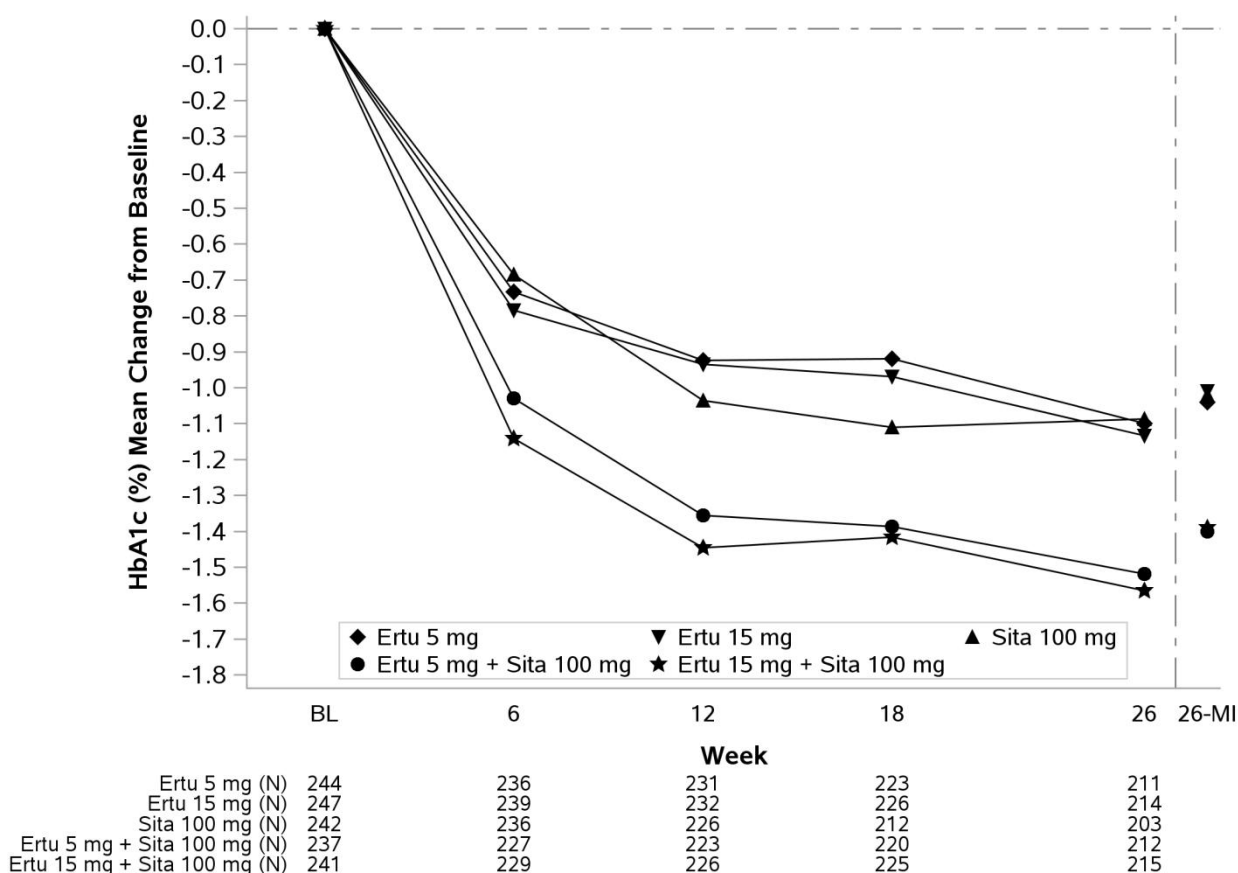
[‡] p<0.001 compared to control group.

[§] 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, 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 -0.4 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*



*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).

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 ($\geq 1,500$ mg/day for ≥ 8 weeks) and sitagliptin 100 mg once daily participated in a randomized, double-blind, multi-center, 26-week, placebo-controlled study (NCT02036515) to evaluate the

efficacy and safety of 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 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).

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).

14.2 Ertugliflozin Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus and Established Cardiovascular Disease

The effect of ertugliflozin on cardiovascular risk in adult patients with type 2 diabetes and established atherosclerotic cardiovascular disease was evaluated in the VERTIS CV study (NCT01986881), a multicenter, multi-national, randomized, double-blind, placebo-controlled, event driven trial. The study compared the risk of experiencing a major adverse cardiovascular event (MACE) between ertugliflozin and placebo when these were added to and used concomitantly with standard of care treatments for diabetes and atherosclerotic cardiovascular disease.

A total of 8246 patients were randomized (placebo N=2747, ertugliflozin 5 mg N=2752, ertugliflozin 15 mg N=2747) and followed for a median of 3 years. Approximately 88% of the study population was Caucasian, 6% Asian, and 3% Black. The mean age was 64 years and approximately 70% were male.

All patients in the study had inadequately controlled type 2 diabetes mellitus at baseline (HbA1c greater than or equal to 7%). The mean duration of type 2 diabetes mellitus was 13 years, the mean HbA1c at baseline was 8.2% and the mean eGFR was 76 mL/min/1.73 m². At baseline, patients were treated with one (32%) or more (67%) antidiabetic medications including biguanides (metformin) (76%), insulin (47%), sulfonylureas (41%), DPP-4 inhibitors (11%) and GLP-1 receptor agonists (3%).

Almost all patients (99%) had established atherosclerotic cardiovascular disease at baseline including: a documented history of coronary artery disease (76%), cerebrovascular disease (23%) or peripheral artery disease (19%). Approximately 24% patients had a history of heart failure (HF). At baseline, the mean systolic blood pressure was 133 mmHg, the mean diastolic blood pressure was 77 mmHg, the

mean LDL was 89 mg/dL, and the mean HDL was 44 mg/dL. At baseline, approximately 81% of patients were treated with renin angiotensin system inhibitors, 69% with beta-blockers, 43% with diuretics, 82% with statins, 4% with ezetimibe, and 89% with antiplatelet agents.

The primary endpoint in VERTIS CV was the time to first occurrence of a Major Adverse Cardiac Event (MACE). A major adverse cardiovascular event was defined as occurrence of either a cardiovascular death or a nonfatal myocardial infarction (MI) or a nonfatal stroke. The statistical analysis plan pre-specified that the 5 and 15 mg doses would be combined for the analysis. A Cox proportional hazards model was used to test for non-inferiority against the pre-specified risk margin of 1.3 for the hazard ratio of MACE. Type I error was controlled across multiple tests using a hierarchical testing strategy.

The incidence rate of MACE was similar between the ertugliflozin-treated and placebo-treated patients. The estimated hazard ratio of MACE associated with ertugliflozin relative to placebo was 0.97 with 95.6% confidence interval (0.85, 1.11). The upper bound of this confidence interval excluded a risk larger than 1.3. (Table 9). Results for the 5 mg and 15 mg doses were consistent with results for the combined dose group.

Table 9: Analysis of MACE and its Components from the VERTIS-CV Study*

Endpoint†	Placebo (N=2747)		Ertugliflozin (N=5499)		Hazard Ratio vs Placebo (CI) ‡
	N (%)	Event Rate (per 100 person-years)	N (%)	Event Rate (per 100 person-years)	
MACE (CV death, non-fatal MI, or non-fatal stroke) Composite	327 (11.9)	4.0	653 (11.9)	3.9	0.97 (0.85, 1.11)
Components of Composite Endpoint					
Non-fatal MI	148 (5.4)	1.6	310 (5.6)	1.7	1.04 (0.86, 1.27)
Non-fatal Stroke	78 (2.8)	0.8	157 (2.9)	0.8	1.00 (0.76, 1.32)
CV death	184 (6.7)	1.9	341 (6.2)	1.8	0.92 (0.77, 1.11)

N=Number of patients, CI=Confidence interval, CV=Cardiovascular, MI=Myocardial infarction.

* Intent-to-treat analysis set.

† MACE was evaluated in subjects who took at least one dose of study medication and, for subjects who discontinued study medication prior to the end of the study, censored events that occurred more than 365 days after the last dose of study medication. Other endpoints were evaluated using all randomized subjects and events that occurred any time after the first dose of study medication until the last contact date. The total number of first events was analyzed for each endpoint.

‡ HR and CI are based on Cox proportional hazards regression model, stratified by cohorts.

16 HOW SUPPLIED/STORAGE AND HANDLING

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

Strength	Description	How Supplied	NDC
5 mg/100 mg tablets	beige, almond-shaped, debossed with "554" on one side and plain on the other side.	unit-of-use bottles of 30	0006-5367-03
		unit-of-use bottles of 90	0006-5367-06
15 mg/100 mg tablets	brown, almond-shaped, debossed with "555" on one side and plain on the other side.	unit-of-use bottles of 30	0006-5368-03
		unit-of-use bottles of 90	0006-5368-06

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).

Diabetic Ketoacidosis in Patients with Type 1 Diabetes Mellitus and Other Ketoacidosis

Inform patients that STEGLUJAN can cause potentially fatal ketoacidosis and that type 2 diabetes mellitus and pancreatic disorders (e.g., history of pancreatitis or pancreatic surgery) are risk factors.

Educate all patients on precipitating factors (such as insulin dose reduction or missed insulin doses, infection, reduced caloric intake, ketogenic diet, surgery, dehydration, and alcohol abuse) and symptoms of ketoacidosis (including nausea, vomiting, abdominal pain, tiredness, and labored breathing). Inform patients that blood glucose may be normal even in the presence of ketoacidosis.

Advise patients that they may be asked to monitor ketones. If symptoms of ketoacidosis occur, instruct patients to discontinue STEGLUJAN and seek medical attention immediately [see *Warnings and Precautions* (5.1)].

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* (5.2)].

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* (5.3)].

Volume Depletion

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

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* (5.6)].

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)].

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. Educate patients or caregivers on the signs and symptoms of hypoglycemia [see *Warnings and Precautions* (5.8)].

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)].

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* (5.12)].

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* (5.13)].

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)].

Laboratory Tests

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

Missed Dose

Instruct patients to take STEGLUJAN only as prescribed. If a dose is missed, it should be taken as soon as the patient remembers. Advise patients not to double their next dose.

Manufactured for: Merck Sharp & Dohme LLC
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For patent information: www.msd.com/research/patent

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