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

SEGLUROMET™ (ertugliflozin and metformin hydrochloride) tablets, for oral use
Initial U.S. Approval: 2017

WARNING: LACTIC ACIDOSIS
See full prescribing information for complete boxed warning.

- **Post-marketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. Symptoms included malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Laboratory abnormalities included elevated blood lactate levels, anion gap acidosis, increased lactate/pyruvate ratio, and metformin plasma levels generally >5 mcg/mL. (5.1)**
- **Risk factors include renal impairment, concomitant use of certain drugs, age ≥65 years old, radiological studies with contrast, surgery and other procedures, hypoxic states, excessive alcohol intake, and hepatic impairment. Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high risk groups are provided in the Full Prescribing Information. (5.1)**
- **If lactic acidosis is suspected, discontinue SEGLUROMET and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended. (5.1)**

---------- RECENT MAJOR CHANGES ----------
Warnings and Precautions
Necrotizing Fasciitis of the Perineum (5.8) 10/2018

---------- INDICATIONS AND USAGE ----------
SEGLUROMET is a combination of ertugliflozin, a sodium glucose co-transporter 2 (SGLT2) inhibitor, and metformin, a biguanide, indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are not adequately controlled on a regimen containing ertugliflozin or metformin, or in patients who are already treated with both ertugliflozin and metformin. (1)

Limitations of Use:
- Not for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis. (1)

---------- DOSAGE AND ADMINISTRATION ----------
- Individualize the starting dose based on the patient's current regimen. (2.1)
- Maximum recommended dose is 7.5 mg ertugliflozin/1,000 mg metformin twice daily. (2.1)
- Take twice daily with meals, with gradual dose escalation. (2.1)
- Assess renal function before initiating SEGLUROMET (2.2):
  - Do not use in patients with an estimated glomerular filtration rate (eGFR) below 30 mL/minute/1.73 m^2.
  - Initiation is not recommended in patients with an eGFR of 30 to less than 60 mL/minute/1.73 m^2.
  - Continued use is not recommended in patients with an eGFR persistently between 30 and less than 60 mL/min/1.73 m^2.
- SEGLUROMET may need to be discontinued at time of, or prior to, iodinated contrast imaging procedures. (2.3)

---------- DOSAGE FORMS AND STRENGTHS ----------
Tablets:
- Ertugliflozin 2.5 mg and metformin hydrochloride 500 mg (3)
- Ertugliflozin 2.5 mg and metformin hydrochloride 1,000 mg (3)
- Ertugliflozin 7.5 mg and metformin hydrochloride 500 mg (3)
- Ertugliflozin 7.5 mg and metformin hydrochloride 1,000 mg (3)

---------- CONTRAINDICATIONS ----------
- Severe renal impairment, end stage renal disease, or dialysis. (4, 5.1, 5.4)
- Metabolic acidosis, including diabetic ketoacidosis. (4, 5.1)
- History of serious hypersensitivity reaction to ertugliflozin or metformin. (4)

---------- WARNINGS AND PRECAUTIONS ----------
- *Lactic Acidosis:* See boxed warning. (5.1)
- *Hypotension*: May occur particularly in patients with renal impairment, the elderly, or patients on diuretics. Before initiating, assess and correct volume status. Monitor for signs and symptoms during therapy. (5.2)
- *Ketoacidosis:* Assess patients who present with signs and symptoms of metabolic acidosis for ketoacidosis, regardless of blood glucose level. If suspected, discontinue, evaluate, and treat promptly. Before initiating, consider risk factors for ketoacidosis. Patients may require monitoring and temporary discontinuation of therapy in clinical situations known to predispose to ketoacidosis. (5.3)
- *Acute Kidney Injury and Impairment in Renal Function:* Consider temporarily discontinuing in settings of reduced oral intake or fluid losses. If acute kidney injury occurs, discontinue and promptly treat. Monitor renal function. (5.4)
- *Urosepsis and Pyelonephritis:* Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated. (5.5)
- *Lower Limb Amputation:* Before initiating, consider factors that may increase risk of amputation. Monitor patients for infections or ulcers of lower limbs, and discontinue if these occur. (5.6)
- *Hypoglycemia:* Consider a lower dose of insulin or insulin secretagogue to reduce risk of hypoglycemia when used in combination. (5.7)
- *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. (5.8)
- *Genital Mycotic Infections:* Monitor and treat if indicated. (5.9)
- *Vitamin B_{12}* Deficiency: Metformin may lower vitamin B12 levels. Measure hematological parameters annually. (5.10)
- *Increased LDL-C:* Monitor and treat as appropriate. (5.11)

---------- ADVERSE REACTIONS ----------
- The most common adverse reactions associated with ertugliflozin (incidence ≥5%) were female genital mycotic infections. (6.1)
- Most common adverse reactions associated with metformin (incidence ≥5%): diarrhea, nausea, vomiting, flatulence, abdominal discomfort, indigestion, asthenia, and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS ----------
- Carbonic anhydrase inhibitors may increase risk of lactic acidosis. Consider more frequent monitoring. (7.2)
- Drugs that reduce metformin clearance (such as ranolazine, vandetanib, dolutegravir, and cimetidine) may increase the accumulation of metformin. Consider the benefits and risks of concomitant use. (7.2)
- Alcohol can potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake. (7.2)

---------- 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)
- *Females and Males of Reproductive Potential:* Advise premenopausal females of the potential for an unintended pregnancy. (8.3)
- *Geriatrics:* Higher incidence of adverse reactions related to reduced intravascular volume. (5.2, 8.5)
- *Renal impairment:* Higher incidence of adverse reactions related to reduced intravascular volume and renal function. (5.1, 5.4, 8.6)
- *Hepatic* impairment*:* Avoid use in patients with hepatic impairment. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: LACTIC ACIDOSIS

Post-marketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. The onset of metformin-associated lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Metformin-associated lactic acidosis was characterized by elevated blood lactate levels (>5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), an increased lactate/pyruvate ratio, and metformin plasma levels generally >5 mcg/mL *[see Warnings and Precautions (5.1)]*.

Risk factors for metformin-associated lactic acidosis include renal impairment, concomitant use of certain drugs (e.g., carbonic anhydrase inhibitors such as topiramate), age 65 years old or greater, having a radiological study with contrast, surgery and other procedures, hypoxic states (e.g., acute congestive heart failure), excessive alcohol intake, and hepatic impairment.

Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high risk groups are provided in the Full Prescribing Information *[see Dosage and Administration (2.2), Contraindications (4), Warnings and Precautions (5.1), Drug Interactions (7), and Use in Specific Populations (8.6, 8.7)]*.

If metformin-associated lactic acidosis is suspected, immediately discontinue SEGLUROMET and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

SEGLUROMET™ is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are not adequately controlled on a regimen containing ertugliflozin or metformin, or in patients who are already treated with both ertugliflozin and metformin.

Limitations of Use

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

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

- Individualize the starting dose of SEGLUROMET (ertugliflozin and metformin hydrochloride) based on the patient's current regimen, while not exceeding the maximum recommended daily dose of 15 mg ertugliflozin and 2,000 mg metformin HCl:
  - In patients on metformin, switch to SEGLUROMET tablets containing 2.5 mg ertugliflozin, with a similar total daily dose of metformin.
  - In patients on ertugliflozin, switch to SEGLUROMET tablets containing 500 mg metformin, with a similar total daily dose of ertugliflozin.
  - In patients already treated with ertugliflozin and metformin, switch to SEGLUROMET tablets containing the same total daily dose of ertugliflozin and a similar daily dose of metformin.
- Take SEGLUROMET twice daily with meals, with gradual dose escalation for those initiating metformin to reduce the gastrointestinal side effects due to metformin *[see Adverse Reactions (6.1)]*.
- In patients with volume depletion not previously treated with ertugliflozin, correct this condition prior to initiation of SEGLUROMET *[see Warnings and Precautions (5.2)]*.
- Dosing may be adjusted based on effectiveness and tolerability.

2.2 Patients with Renal Impairment

- Assess renal function prior to initiation of SEGLUROMET and periodically thereafter *[see Warnings and Precautions (5.4)]*.
- Use of SEGLUROMET is contraindicated in patients with an eGFR less than 30 mL/minute/1.73 m^2 *[see Contraindications (4)]*.

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

2.3 Discontinuation for Iodinated Contrast Imaging Procedures

Discontinue SEGLUROMET at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR less than 60 mL/min/1.73 m^2; in patients with a history of liver disease, alcoholism or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart SEGLUROMET if renal function is stable *[see Warnings and Precautions (5.1)]*.

3 DOSAGE FORMS AND STRENGTHS

- Tablets: ertugliflozin 2.5 mg and metformin hydrochloride 500 mg, pink, oval, debossed with "2.5/500" on one side and plain on the other side.
- Tablets: ertugliflozin 2.5 mg and metformin hydrochloride 1000 mg, pink, oval, debossed with "2.5/1000" on one side and plain on the other side.
- Tablets: ertugliflozin 7.5 mg and metformin hydrochloride 500 mg, red, oval, debossed with "7.5/500" on one side and plain on the other side.
- Tablets: ertugliflozin 7.5 mg and metformin hydrochloride 1000 mg, red, oval, debossed with "7.5/1000" on one side and plain on the other side.

4 CONTRAINDICATIONS

- Severe renal impairment, end stage renal disease (ESRD), or patients on dialysis *[see Warnings and Precautions (5.1, 5.4) and Use in Specific Populations (8.6)]*.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma.
- History of a serious hypersensitivity reaction to SEGLUROMET, ertugliflozin, or metformin hydrochloride.

5 WARNINGS AND PRECAUTIONS

5.1 Lactic Acidosis

There have been post-marketing cases of metformin-associated lactic acidosis, including fatal cases. These cases had a subtle onset and were accompanied by nonspecific symptoms such as malaise, myalgias, abdominal pain, respiratory distress, or increased somnolence; however, hypothermia, hypotension and resistant bradyarrhythmias have occurred with severe acidosis. Metformin-associated lactic acidosis was characterized by elevated blood lactate concentrations (>5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), and an increased lactate:pyruvate ratio; metformin plasma levels were generally >5 mcg/mL. Metformin decreases liver uptake of lactate increasing lactate blood levels which may increase the risk of lactic acidosis, especially in patients at risk.

If metformin-associated lactic acidosis is suspected, general supportive measures should be instituted promptly in a hospital setting, along with immediate discontinuation of SEGLUROMET. In SEGLUROMET-treated patients with a diagnosis or strong suspicion of lactic acidosis, prompt hemodialysis is recommended to correct the acidosis and remove accumulated metformin (metformin hydrochloride is dialyzable, with a clearance of up to 170 mL/minute under good hemodynamic conditions). Hemodialysis has often resulted in reversal of symptoms and recovery.

Educate patients and their families about the symptoms of lactic acidosis and if these symptoms occur instruct them to discontinue SEGLUROMET and report these symptoms to their healthcare provider.

For each of the known and possible risk factors for metformin-associated lactic acidosis, recommendations to reduce the risk of and manage metformin-associated lactic acidosis are provided below:

Renal Impairment: The postmarketing metformin-associated lactic acidosis cases primarily occurred in patients with significant renal impairment. The risk of metformin accumulation and metformin-associated lactic acidosis increases with the severity of renal impairment because metformin is substantially excreted by the kidney *[see Warnings and Precautions (5.4) and Clinical Pharmacology (12.3)]*.

- Before initiating SEGLUROMET, obtain an eGFR.
- SEGLUROMET is contraindicated in patients with an eGFR less than 30 mL/minute/1.73 m^2.
- Initiation of SEGLUROMET is not recommended in patients with an eGFR of 30 mL/minute/1.73 m^2 to less than 60 mL/min/1.73 m^2.
- Continued use of SEGLUROMET is not recommended when eGFR is persistently between 30 and less than 60 mL/min/1.73 m^2.
- Renal function should be evaluated prior to initiating SEGLUROMET and periodically thereafter. In patients at increased risk for the development of renal impairment (e.g., the elderly), renal function should be assessed more frequently.

Drug Interactions: The concomitant use of SEGLUROMET with specific drugs may increase the risk of metformin-associated lactic acidosis: those that impair renal function, result in significant hemodynamic change, interfere with acid-base balance or increase metformin accumulation (e.g., cationic drugs) *[see Drug Interactions (7)]*. Therefore, consider more frequent monitoring of patients.

Age 65 or Greater: The risk of metformin-associated lactic acidosis increases with the patient's age because elderly patients have a greater likelihood of having hepatic, renal, or cardiac impairment than younger patients. Assess renal function more frequently in elderly patients *[see Use in Specific Populations (8.5)]*.

Radiological Studies with Contrast: Administration of intravascular iodinated contrast agents in metformin-treated patients has led to an acute decrease in renal function and the occurrence of lactic acidosis. Stop SEGLUROMET at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR less than 60 mL/min/1.73 m^2; in patients with a history of hepatic impairment, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure, and restart SEGLUROMET if renal function is stable.

Surgery and Other Procedures: Withholding of food and fluids during surgical or other procedures may increase the risk for volume depletion, hypotension and renal impairment. SEGLUROMET should be temporarily discontinued while patients have restricted food and fluid intake.

Hypoxic States: Several of the postmarketing cases of metformin-associated lactic acidosis occurred in the setting of acute congestive heart failure (particularly when accompanied by hypoperfusion and hypoxemia). Cardiovascular collapse (shock), acute myocardial infarction, sepsis, and other conditions associated with hypoxemia have been associated with lactic acidosis and may also cause pre-renal azotemia. When such events occur, discontinue SEGLUROMET.

Excessive Alcohol Intake: Alcohol potentiates the effect of metformin on lactate metabolism and this may increase the risk of metformin-associated lactic acidosis. Warn patients against excessive alcohol intake while receiving SEGLUROMET.

Hepatic Impairment: Patients with hepatic impairment have developed metformin-associated lactic acidosis. This may be due to impaired lactate clearance resulting in higher lactate blood levels. Therefore, avoid use of SEGLUROMET in patients with clinical or laboratory evidence of hepatic disease.

5.2 Hypotension

Ertugliflozin, a component of SEGLUROMET, causes intravascular volume contraction. Therefore, symptomatic hypotension may occur after initiating SEGLUROMET *[see Adverse Reactions (6.1)]* particularly in patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2) *[see Use in Specific Populations (8.6)]*, elderly patients (≥65 years), in patients with low systolic blood pressure, and in patients on diuretics. Before initiating SEGLUROMET, volume status should be assessed and corrected if indicated. Monitor for signs and symptoms of hypotension after initiating therapy.

5.3 Ketoacidosis

Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization, have been identified in clinical trials and postmarketing surveillance in patients with type 1 and type 2 diabetes mellitus receiving sodium glucose co-transporter-2 (SGLT2) inhibitors and cases have been reported in ertugliflozin-treated patients in clinical trials. Across the clinical program, ketoacidosis was identified in 3 of 3,409 (0.1%) of ertugliflozin-treated patients and 0% of comparator-treated patients. Fatal cases of ketoacidosis have been reported in patients taking medicines containing SGLT2 inhibitors. SEGLUROMET is not indicated for the treatment of patients with type 1 diabetes mellitus *[see Indications and Usage (1)]*.

Patients treated with SEGLUROMET who present with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of presenting blood glucose levels, as ketoacidosis associated with SEGLUROMET may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, SEGLUROMET should be discontinued, patient should be evaluated, and prompt treatment should be instituted. Treatment of ketoacidosis may require insulin, fluid, and carbohydrate replacement.

In many of the reported cases, and particularly in patients with type 1 diabetes, the presence of ketoacidosis was not immediately recognized and institution of treatment was delayed because presenting blood glucose levels were below those typically expected for diabetic ketoacidosis (often less than 250 mg/dL). Signs and symptoms at presentation were consistent with dehydration and severe metabolic acidosis and included nausea, vomiting, abdominal pain, generalized malaise, and shortness of breath. In some but not all cases, factors predisposing to ketoacidosis such as insulin dose reduction, acute febrile illness, reduced caloric intake due to illness or surgery, pancreatic disorders suggesting insulin deficiency (e.g., type 1 diabetes, history of pancreatitis or pancreatic surgery), and alcohol abuse were identified.

Before initiating SEGLUROMET, consider factors in the patient history that may predispose to ketoacidosis, including pancreatic insulin deficiency from any cause, caloric restriction, and alcohol abuse. In patients treated with SEGLUROMET consider monitoring for ketoacidosis and temporarily discontinuing SEGLUROMET in clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or surgery).

5.4 Acute Kidney Injury and Impairment in Renal Function

SEGLUROMET causes intravascular volume contraction and can cause renal impairment *[see Adverse Reactions (6.1)]*. There have been postmarketing reports of acute kidney injury some requiring hospitalization and dialysis in patients receiving SGLT2 inhibitors.

Before initiating SEGLUROMET, consider factors that may predispose patients to acute kidney injury including hypovolemia, chronic renal insufficiency, congestive heart failure and concomitant medications (diuretics, ACE inhibitors, ARBs, NSAIDs). Consider temporarily discontinuing SEGLUROMET in any setting of reduced oral intake (such as acute illness or fasting) or fluid losses (such as gastrointestinal illness or excessive heat exposure); monitor patients for signs and symptoms of acute kidney injury. If acute kidney injury occurs, discontinue SEGLUROMET promptly and institute treatment.

Ertugliflozin, a component of SEGLUROMET, increases serum creatinine and decreases eGFR. Patients with moderate renal impairment (eGFR 30 to less than 60 mL/min/1.73 m^2) may be more susceptible to these changes. Renal function abnormalities can occur after initiating SEGLUROMET *[see Adverse Reactions (6.1)]*. Renal function should be evaluated prior to initiating SEGLUROMET and periodically thereafter. Use of SEGLUROMET is not recommended when eGFR is persistently between 30 mL/min/1.73 m^2 and less than 60 mL/min/1.73 m^2 and is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m^2 *[see Dosage and Administration (2.2), Contraindications (4), Use in Specific Populations (8.6)]*.

5.5 Urosepsis and Pyelonephritis

There have been postmarketing reports of serious urinary tract infections, including urosepsis and pyelonephritis, requiring hospitalization in patients receiving medicines containing SGLT2 inhibitors. Cases of pyelonephritis also have been reported in ertugliflozin-treated patients in clinical trials. Treatment with medicines containing SGLT2 inhibitors increases the risk for urinary tract infections. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated *[see Adverse Reactions (6.1)]*.

5.6 Lower Limb Amputation

An increased risk for lower limb amputation (primarily of the toe) has been observed in clinical studies with another SGLT2 inhibitor. Across seven Phase 3 clinical trials in the ertugliflozin development program, non-traumatic lower limb amputations were reported in 1 (0.1%) patient in the comparator group, 3 (0.2%) patients in the ertugliflozin 5 mg group, and 8 (0.5%) patients in the ertugliflozin 15 mg group. A causal association between ertugliflozin and lower limb amputation has not been definitively established.

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

5.7 Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues

Ertugliflozin

Insulin and insulin secretagogues (e.g., sulfonylurea) are known to cause hypoglycemia. Ertugliflozin, a component of SEGLUROMET, may increase the risk of hypoglycemia when used in combination with insulin and/or an insulin secretagogue *[see Adverse Reactions (6.1)]*. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with SEGLUROMET.

Metformin

Hypoglycemia does not occur in patients receiving metformin, a component of SEGLUROMET, alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as sulfonylureas and insulin) or ethanol. Elderly, debilitated, or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking β-adrenergic blocking drugs.

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

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

Patients treated with SEGLUROMET 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 SEGLUROMET, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.

5.9 Genital Mycotic Infections

Ertugliflozin, a component of SEGLUROMET, 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.

5.10 Vitamin B_{12} Levels

In controlled clinical trials of metformin, a component of SEGLUROMET, of 29 weeks duration, a decrease to subnormal levels of previously normal serum vitamin B_{12} levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or vitamin B_{12} supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on SEGLUROMET and any apparent abnormalities should be appropriately investigated and managed.

Certain individuals (those with inadequate vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B_{12} levels. In these patients, routine serum vitamin B_{12} measurements at two- to three-year intervals may be useful.

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

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

5.12 Macrovascular Outcomes

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

6 ADVERSE REACTIONS

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

- Lactic Acidosis *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Hypotension *[see Warnings and Precautions (5.2)]*
- Ketoacidosis *[see Warnings and Precautions (5.3)]*
- Acute Kidney Injury and Impairment in Renal Function *[see Warnings and Precautions (5.4)]*
- Urosepsis and Pyelonephritis *[see Warnings and Precautions (5.5)]*
- Lower Limb Amputation *[see Warnings and Precautions (5.6)]*
- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues *[see Warnings and Precautions (5.7)]*
- Necrotizing Fasciitis of the Perineum (Fournier's gangrene) *[see Warnings and Precautions (5.8)]*
- Genital Mycotic Infections *[see Warnings and Precautions (5.9)]*
- Vitamin B_{12} Levels *[see Warnings and Precautions (5.10)]*
- Increases in Low-Density Lipoprotein Cholesterol (LDL-C) *[see Warnings and Precautions (5.11)]*

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 Metformin Hydrochloride

The incidence and type of adverse reactions in the two 26-week, placebo-controlled trials of ertugliflozin 5 mg and 15 mg added to metformin, representing a majority of data from the three 26-week, placebo-controlled trials, were similar to the adverse reactions described in Table 1.

Ertugliflozin

Pool of Placebo-Controlled Trials

The data in Table 1 are derived from a pool of three 26-week, placebo-controlled trials. Ertugliflozin was used as monotherapy in one trial and as add-on therapy in two trials *[see Clinical Studies (14)]*. These data reflect exposure of 1,029 patients to ertugliflozin with a mean exposure duration of

approximately 25 weeks. Patients received ertugliflozin 5 mg (N=519), ertugliflozin 15 mg (N=510), or placebo (N=515) once daily. The mean age of the population was 57 years and 2% were older than 75 years of age. Fifty-three percent (53%) of the population was male and 73% were Caucasian, 15% were Asian, and 7% were Black or African American. At baseline the population had diabetes for an average of 7.5 years, had a mean HbA1c of 8.1%, and 19.4% had established microvascular complications of diabetes. Baseline renal function (mean eGFR 88.9 mL/min/1.73 m^2) was normal or mildly impaired in 97% of patients and moderately impaired in 3% of patients.

Table 1 shows common adverse reactions associated with the use of ertugliflozin. These adverse reactions were not present at baseline, occurred more commonly on ertugliflozin than on placebo, and occurred in at least 2% of patients treated with either ertugliflozin 5 mg or ertugliflozin 15 mg.

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

	Number (%) of Patients		
	Placebo N = 515	**Ertugliflozin 5 mg N = 519**	**Ertugliflozin 15 mg N = 510**
Female genital mycotic infections[†]	3.0%	9.1%	12.2%
Male genital mycotic infections[‡]	0.4%	3.7%	4.2%
Urinary tract infections[§]	3.9%	4.0%	4.1%
Headache	2.3%	3.5%	2.9%
Vaginal pruritus[¶]	0.4%	2.8%	2.4%
Increased urination[#]	1.0%	2.7%	2.4%
Nasopharyngitis	2.3%	2.5%	2.0%
Back pain	2.3%	1.7%	2.5%
Weight decreased	1.0%	1.2%	2.4%
Thirst[Þ]	0.6%	2.7%	1.4%

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

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

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

Volume Depletion

Ertugliflozin causes an osmotic diuresis, which may lead to intravascular volume contraction and adverse reactions related to volume depletion, particularly in patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2). In patients with moderate renal impairment, adverse reactions related to volume depletion (e.g., dehydration, dizziness postural, presyncope, syncope, hypotension, and orthostatic hypotension) were reported in 0%, 4.4%, and 1.9% of patients treated with placebo, ertugliflozin 5 mg, and ertugliflozin 15 mg, respectively. Ertugliflozin may also increase the risk of hypotension in other patients at risk for volume contraction *[see Use in Specific Populations (8.5, 8.6)]*.

Ketoacidosis

Across the clinical program, ketoacidosis was identified in 3 of 3,409 (0.1%) ertugliflozin-treated patients and 0.0% of comparator-treated patients *[see Warnings and Precautions (5.3)]*.

Impairment in Renal Function

Treatment with ertugliflozin was associated with increases in serum creatinine and decreases in eGFR (see Table 2). Patients with moderate renal impairment at baseline had larger mean changes. In a study in patients with moderate renal impairment, these abnormal laboratory findings were observed to reverse after treatment discontinuation *[see Use in Specific Populations (8.5, 8.6)]*.

Table 2: Changes from Baseline in Serum Creatinine and eGFR in the Pool of Three 26-Week Placebo-Controlled Studies and a 26-Week Moderate Renal Impairment Study in Patients with Type 2 Diabetes Mellitus

		Pool of 26-Week Placebo-Controlled Studies		
		Placebo N = 515	**Ertugliflozin 5 mg N = 519**	**Ertugliflozin 15 mg N = 510**
Baseline Mean	Creatinine (mg/dL)	0.83	0.82	0.82
	eGFR (mL/min/1.73 m^2)	89.5	88.2	89.0
Week 6 Change	Creatinine (mg/dL)	0.00	0.03	0.03
	eGFR (mL/min/1.73 m^2)	-0.3	-2.7	-3.1
Week 26 Change	Creatinine (mg/dL)	-0.01	0.00	0.01
	eGFR (mL/min/1.73 m^2)	0.7	0.5	-0.6
		Moderate Renal Impairment Study		
		Placebo N = 154	**Ertugliflozin 5 mg N = 154**	**Ertugliflozin 15 mg N = 154**
Baseline	Creatinine (mg/dL)	1.39	1.38	1.37
	eGFR (mL/min/1.73 m^2)	46.0	46.8	46.9
Week 6 Change	Creatinine (mg/dL)	-0.02	0.11	0.12
	eGFR (mL/min/1.73 m^2)	0.6	-3.2	-4.1
Week 26 Change	Creatinine (mg/dL)	0.02	0.08	0.10
	eGFR (mL/min/1.73 m^2)	0.0	-2.7	-2.6

Renal-related adverse reactions (e.g., acute kidney injury, renal impairment, acute prerenal failure) may occur in patients treated with ertugliflozin, particularly in patients with moderate renal impairment where the incidence of renal-related adverse reactions was 0.6%, 2.5%, and 1.3% in patients treated with placebo, ertugliflozin 5 mg, and ertugliflozin 15 mg, respectively.

Lower Limb Amputation

Across seven Phase 3 clinical trials in which ertugliflozin was studied as monotherapy and in combination with other antihyperglycemic agents, non-traumatic lower limb amputations occurred in 1 of 1,450 (0.1%) in the non-ertugliflozin group, 3 of 1,716 (0.2%) in the ertugliflozin 5 mg group, and 8 of 1,693 (0.5%) in the ertugliflozin 15 mg group.

Hypoglycemia

The incidence of hypoglycemia by study is shown in Table 3.

Table 3: Incidence of Overall* and Severe† Hypoglycemia in Placebo-Controlled Clinical Studies in Patients with Type 2 Diabetes Mellitus

Add-on Combination Therapy with Metformin (26 weeks)	**Placebo (N = 209)**	**Ertugliflozin 5 mg (N = 207)**	**Ertugliflozin 15 mg (N = 205)**
Overall [N (%)]	9 (4.3)	15 (7.2)	16 (7.8)
Severe [N (%)]	1 (0.5)	1 (0.5)	0 (0.0)
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)

* 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, and ertugliflozin 15 mg, respectively. 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.

Metformin

The most common (5% or greater incidence) established adverse reactions due to initiation of metformin therapy are diarrhea, nausea, vomiting, flatulence, abdominal discomfort, indigestion, asthenia, and headache.

Long-term treatment with metformin has been associated with a decrease in vitamin B_{12} absorption, which may very rarely result in clinically significant vitamin B_{12} deficiency (e.g., megaloblastic anemia).

Laboratory Tests

Ertugliflozin

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

In the pool of three placebo-controlled trials, dose-related increases in LDL-C were observed in patients treated with ertugliflozin. Mean percent changes from baseline to Week 26 in LDL-C relative to placebo were 2.6% and 5.4% with ertugliflozin 5 mg and ertugliflozin 15 mg, respectively. The range of mean baseline LDL-C was 96.6 to 97.7 mg/dL across treatment groups *[see Warnings and Precautions (5.11)]*.

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 (mean 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.

Metformin

In controlled clinical trials of metformin of 29 weeks duration, a decrease to subnormal levels of previously normal serum vitamin B_{12} levels, without clinical manifestations, was observed in approximately 7% of patients. Such decreases, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or vitamin B_{12} supplementation *[see Warnings and Precautions (5.10)]*.

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.

- Cases of necrotizing fasciitis of the perineum (Fournier's gangrene) have been seen with SGLT2 inhibitors *[see Warnings and Precautions (5.8)]*

7 DRUG INTERACTIONS

7.1 Drug Interactions with Ertugliflozin

Concomitant Use with Insulin and Insulin Secretagogues

Ertugliflozin may increase the risk of hypoglycemia when used in combination with insulin and/or an insulin secretagogue *[see Adverse Reactions (6.1)]*. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with SEGLUROMET *[see Warnings and Precautions (5.7)]*.

Positive Urine Glucose Test

Monitoring glycemic control with urine glucose tests is not recommended in patients taking medicines containing an SGLT2 inhibitor as SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. Use alternative methods to monitor glycemic control.

Interference with 1,5-anhydroglucitol (1,5-AG) Assay

Monitoring glycemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking medicines containing an SGLT2 inhibitor. Use alternative methods to monitor glycemic control.

7.2 Drug Interactions with Metformin Hydrochloride

Carbonic Anhydrase Inhibitors

Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently cause a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs with SEGLUROMET may increase the risk of lactic acidosis. Consider more frequent monitoring of these patients.

Drugs that Reduce Metformin Clearance

Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter-2 [OCT2] / multidrug and toxin extrusion [MATE] inhibitors such as ranolazine, vandetanib, dolutegravir, and cimetidine) could increase systemic exposure to metformin and may increase the risk for lactic acidosis *[see Clinical Pharmacology (12.3)]*. Consider the benefits and risks of concomitant use.

Alcohol

Alcohol is known to potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake while receiving SEGLUROMET.

Drugs that Affect Glycemic Control

Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving SEGLUROMET the patient should be closely observed to maintain adequate glycemic control.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on animal data showing adverse renal effects, from ertugliflozin, SEGLUROMET is not recommended during the second and third trimesters of pregnancy. Published studies with metformin use during pregnancy have not reported a clear association with metformin and major birth defect or miscarriage risk *(see Data)*.

The limited available data with SEGLUROMET in pregnant women are not sufficient to determine a drug-associated risk for major birth defects or miscarriage. 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)*.

The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with a HbA1c >7 and has been reported to be as high as 20-25% in women with HbA1c >10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Poorly-controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, stillbirth, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Data

Human Data

Published data from post-marketing studies have not reported a clear association with metformin and major birth defects, miscarriage, or adverse maternal or fetal outcomes when metformin was used during pregnancy. However, these studies cannot definitely establish the absence of any metformin-associated risk because of methodological limitations, including small sample size and inconsistent comparator groups.

Animal Data

Ertugliflozin

When ertugliflozin was orally administered to juvenile rats from PND 21 to PND 90, increased kidney weight, renal tubule and renal pelvis dilatation, and renal mineralization occurred at doses greater than or equal to 5 mg/kg (13-fold human exposures, based on AUC). These effects occurred with drug exposure during periods of renal development in rats that correspond to the late second and third trimester of human renal development, and did not fully reverse within a 1-month recovery period.

In embryo-fetal development studies, ertugliflozin (50, 100 and 250 mg/kg/day) was administered orally to rats on gestation days 6 to 17 and to rabbits on gestation days 7 to 19. Ertugliflozin did not adversely affect developmental outcomes in rats and rabbits at maternal exposures that were approximately 300 times the human exposure at the maximum clinical dose of 15 mg/day, based on AUC. A maternally toxic dose (250 mg/kg/day) in rats (707 times the clinical dose) was associated with reduced fetal viability and a higher incidence of a visceral malformation (membranous ventricular septal defect). In the pre- and post-natal development study in pregnant rats, ertugliflozin was administered to the dams from gestation day 6 through lactation day 21 (weaning). Decreased post-natal growth (weight gain) was observed at maternal doses ≥100 mg/kg/day (greater than or equal to 331 times the human exposure at the maximum clinical dose of 15 mg/day, based on AUC).

Metformin hydrochloride

Metformin did not adversely affect development outcomes when administered to rats and rabbits at doses up to 600 mg/kg/day. This represents an exposure of about 2 and 6 times the maximum recommended human dose of 2,000 mg based on body surface area comparisons for rats and rabbits, respectively. Determination of fetal concentrations demonstrated a partial placental barrier to metformin.

8.2 Lactation

Risk Summary

There is no information regarding the presence of SEGLUROMET or ertugliflozin in human milk, the effects on the breastfed infant, or the effects on milk production. Limited published studies report that metformin is present in human milk *(see Data)*. However, there is insufficient information on the effects of metformin on the breastfed infant and no available information on the effects of metformin on milk production. Ertugliflozin *(see Data)* and metformin are present in the milk of lactating rats. 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 SEGLUROMET is not recommended while breastfeeding.

Data

Human Data

There is no information regarding the presence of SEGLUROMET in human milk, the effects on the breastfed infant, or the effects on milk production. Ertugliflozin is 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. Published studies report that metformin is present in human milk which resulted in infant doses approximately 0.11% to 1% of the maternal weight adjusted dosage and a milk/plasma ratio ranging between 0.13 and 1. There are no reports of adverse effects on breastfed infants exposed to metformin. Because of the potential for serious adverse reactions in a breastfed infant, advise women that the use of SEGLUROMET 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).

Metformin hydrochloride

Published clinical lactation studies report that metformin is present in human milk, which resulted in infant doses approximately 0.11% to 1% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 0.13 and 1. However, the studies were not designed to definitely establish the risk of use of metformin during lactation because of small sample size and limited adverse event data collected in infants.

8.3 Females and Males of Reproductive Potential

Discuss the potential for unintended pregnancy with premenopausal women as therapy with metformin may result in ovulation in some anovulatory women.

8.4 Pediatric Use

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

8.5 Geriatric Use

SEGLUROMET

No dosage adjustment of SEGLUROMET 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 metformin is known to be substantially excreted by the kidneys, care should be taken in dose selection in the elderly. Assess renal function in elderly patients prior to initiating dosing and periodically thereafter. *[See Dosage and Administration (2.2) and Warnings and Precautions (5.1, 5.4).]* SEGLUROMET is expected to have diminished efficacy in elderly patients with renal impairment *[see Use in Specific Populations (8.6)]*.

Ertugliflozin

Across the clinical program, a total of 876 (25.7%) patients treated with ertugliflozin were 65 years and older, and 152 (4.5%) patients treated with ertugliflozin were 75 years and older. Patients 65 years and older had a higher incidence of adverse reactions related to volume depletion compared to younger patients; events were reported in 1.1%, 2.2%, and 2.6% of patients treated with comparator, ertugliflozin 5 mg, and ertugliflozin 15 mg, respectively *[see Warnings and Precautions (5.2) and Adverse Reactions (6.1)]*.

Metformin hydrochloride

Controlled clinical studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients, although other reported clinical experience has not identified differences in responses between the elderly and young patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy and the higher risk of lactic acidosis. Assess renal function more frequently in elderly patients. *[See Contraindications (4), Warnings and Precautions (5.1), and Clinical Pharmacology (12.3).]*

8.6 Renal Impairment

The safety and efficacy of ertugliflozin have not been established in patients with type 2 diabetes mellitus and moderate renal impairment. Compared to placebo-treated patients, patients with moderate renal impairment treated with ertugliflozin did not have improvement in glycemic control and had increased risks for renal impairment, renal-related adverse reactions, and volume depletion adverse reactions *[see Dosage and Administration (2.2), Warnings and Precautions (5.4), and Adverse Reactions (6.1)]*. Therefore, SEGLUROMET is not recommended in this population.

SEGLUROMET is contraindicated in patients with severe renal impairment, ESRD, or receiving dialysis. SEGLUROMET is not expected to be effective in these patient populations *[see Contraindications (4)].*

No dosage adjustment or increased monitoring is needed in patients with mild renal impairment.

Metformin is substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment.

8.7 Hepatic Impairment

Use of metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis. SEGLUROMET is not recommended in patients with hepatic impairment *[see Warnings and Precautions (5.1)]*.

10 OVERDOSAGE

SEGLUROMET

In the event of an overdose with SEGLUROMET, 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.

Metformin hydrochloride

Overdose of metformin hydrochloride has occurred, including ingestion of amounts greater than 50 g (25 times the maximum recommended daily dose). Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin hydrochloride has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases *[see Warnings and Precautions (5.1)]*. Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdosage is suspected.

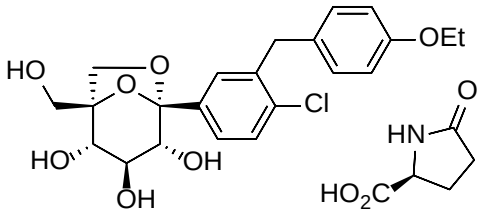
11 DESCRIPTION

SEGLUROMET (ertugliflozin and metformin hydrochloride) tablet for oral use contains ertugliflozin L-pyroglutamic acid, a SGLT2 inhibitor, and metformin hydrochloride, a member of the biguanide class.

Ertugliflozin

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

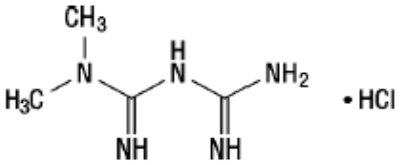
The chemical structure is:



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

Metformin hydrochloride

Metformin hydrochloride (*N*,*N*-dimethylimidodicarbonimidic diamide hydrochloride) is not chemically or pharmacologically related to any other classes of oral antihyperglycemic agents. The structural formula is as shown:



Metformin hydrochloride is a white to off-white crystalline compound with a molecular formula of $C_4H_{11}N_5$•HCl and a molecular weight of 165.63. Metformin hydrochloride is freely soluble in water and is

practically insoluble in acetone, ether and chloroform. The pK_a of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68.

SEGLUROMET is available as film-coated tablets containing:

- 3.24 mg ertugliflozin L-pyroglutamic acid equivalent to 2.5 mg of ertugliflozin and 500 mg metformin hydrochloride (SEGLUROMET 2.5/500)
- 3.24 mg ertugliflozin L-pyroglutamic acid equivalent to 2.5 mg of ertugliflozin and 1,000 mg metformin hydrochloride (SEGLUROMET 2.5/1000)
- 9.71 mg ertugliflozin L-pyroglutamic acid equivalent to 7.5 mg of ertugliflozin and 500 mg metformin hydrochloride (SEGLUROMET 7.5/500)
- 9.71 mg ertugliflozin L-pyroglutamic acid equivalent to 7.5 mg of ertugliflozin and 1,000 mg metformin hydrochloride (SEGLUROMET 7.5/1000)

Inactive ingredients are povidone, microcrystalline cellulose, crospovidone, sodium lauryl sulfate, and magnesium stearate.

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

SEGLUROMET

SEGLUROMET 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 metformin hydrochloride, a member of the biguanide class.

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.

Metformin hydrochloride

Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes mellitus, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Metformin does not produce hypoglycemia in either patients with type 2 diabetes mellitus or normal subjects (except in special circumstances) *[see Warnings and Precautions (5.7)]* and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

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.

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.

Absorption

SEGLUROMET

The effects of a high-fat meal on the pharmacokinetics of ertugliflozin and metformin when administered as SEGLUROMET tablets are comparable to those reported for the individual tablets. Food had no meaningful effect on AUC_{inf} of ertugliflozin and metformin, but reduced mean ertugliflozin C_{max} by approximately 41% and metformin C_{max} by approximately 29% compared to the fasted condition.

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.

Metformin hydrochloride

The absolute bioavailability of a metformin hydrochloride 500-mg tablet given under fasting conditions is approximately 50-60%. Studies using single oral doses of metformin hydrochloride tablets 500 mg to 1,500 mg, and 850 mg to 2,550 mg (approximately 1.3 times the maximum recommended daily dosage), indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alternation in elimination. Food decreases the extent of and slightly delays the absorption of metformin, as shown by approximately a 40% lower mean peak plasma concentration (C_{max}), a 25% lower area under the plasma concentration versus time curve (AUC), and a 35-minute prolongation of time to peak plasma concentration (T_{max}) following administration of a single 850-mg tablet of metformin with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

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.

Metformin hydrochloride

The apparent volume of distribution (V/F) of metformin following single oral doses of metformin hydrochloride tablets 850 mg averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90% protein bound. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of metformin hydrochloride tablets, steady-state plasma concentrations of metformin are reached within 24-48 hours and are generally <1 mcg/mL. During controlled clinical trials of metformin, maximum metformin plasma levels did not exceed 5 mcg/mL, even at maximum doses.

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%).

Metformin hydrochloride

Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion.

Excretion

Ertugliflozin

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

Metformin hydrochloride

Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Specific Populations

Patients with Renal Impairment

SEGLUROMET

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

Ertugliflozin

In a Phase 1 clinical pharmacology study in patients with type 2 diabetes mellitus and mild, moderate, or severe renal impairment (as determined by eGFR), following a single-dose administration of 15 mg ertugliflozin, the mean increases in AUC of ertugliflozin were 1.6-, 1.7-, and 1.6-fold, respectively, for mild, moderate, and severe renally-impaired patients compared to subjects with normal renal function. These increases in ertugliflozin AUC are not considered clinically meaningful. The 24-hour urinary glucose excretion declined with increasing severity of renal impairment *[see Warnings and Precautions (5.4) and Use in Specific Populations (8.6)]*. The plasma protein binding of ertugliflozin was unaffected in patients with renal impairment.

Metformin hydrochloride

In patients with decreased renal function, the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased *[see Contraindications (4) and Warnings and Precautions (5.1)]*.

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)]*.

Metformin hydrochloride

No pharmacokinetic studies of metformin have been conducted in patients with hepatic impairment *[see Use in Specific Populations (8.7)]*.

Pediatric Patients

No studies with SEGLUROMET have been performed in pediatric patients.

Effects of Age, Body Weight, 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.

Metformin hydrochloride

Limited data from controlled pharmacokinetic studies of metformin in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and C_{max} is increased, compared to healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function.

Metformin pharmacokinetic parameters did not differ significantly between normal subjects and patients with type 2 diabetes mellitus when analyzed according to gender. Similarly, in controlled clinical studies in patients with type 2 diabetes mellitus, the antihyperglycemic effect of metformin was comparable in males and females.

No studies of metformin pharmacokinetic parameters according to race have been performed. In controlled clinical studies of metformin in patients with type 2 diabetes mellitus, the antihyperglycemic effect was comparable in Whites (n=249), Blacks (n=51), and Hispanics (n=24).

Drug Interaction Studies

SEGLUROMET

Coadministration of single dose of ertugliflozin (15 mg) and metformin (1,000 mg) did not meaningfully alter the pharmacokinetics of either ertugliflozin or metformin in healthy subjects.

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

Ertugliflozin

In Vitro Assessment of Drug Interactions

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

OATP1B3). Ertugliflozin or ertugliflozin glucuronides do not meaningfully inhibit P-gp, OCT2, OAT1, or OAT3 transporters, or transporting polypeptides OATP1B1 and OATP1B3, at clinically relevant concentrations. Overall, ertugliflozin is unlikely to affect the pharmacokinetics of concurrently administered medications that are substrates of these transporters.

In Vivo Assessment of Drug Interactions

No dose adjustment of SEGLUROMET 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

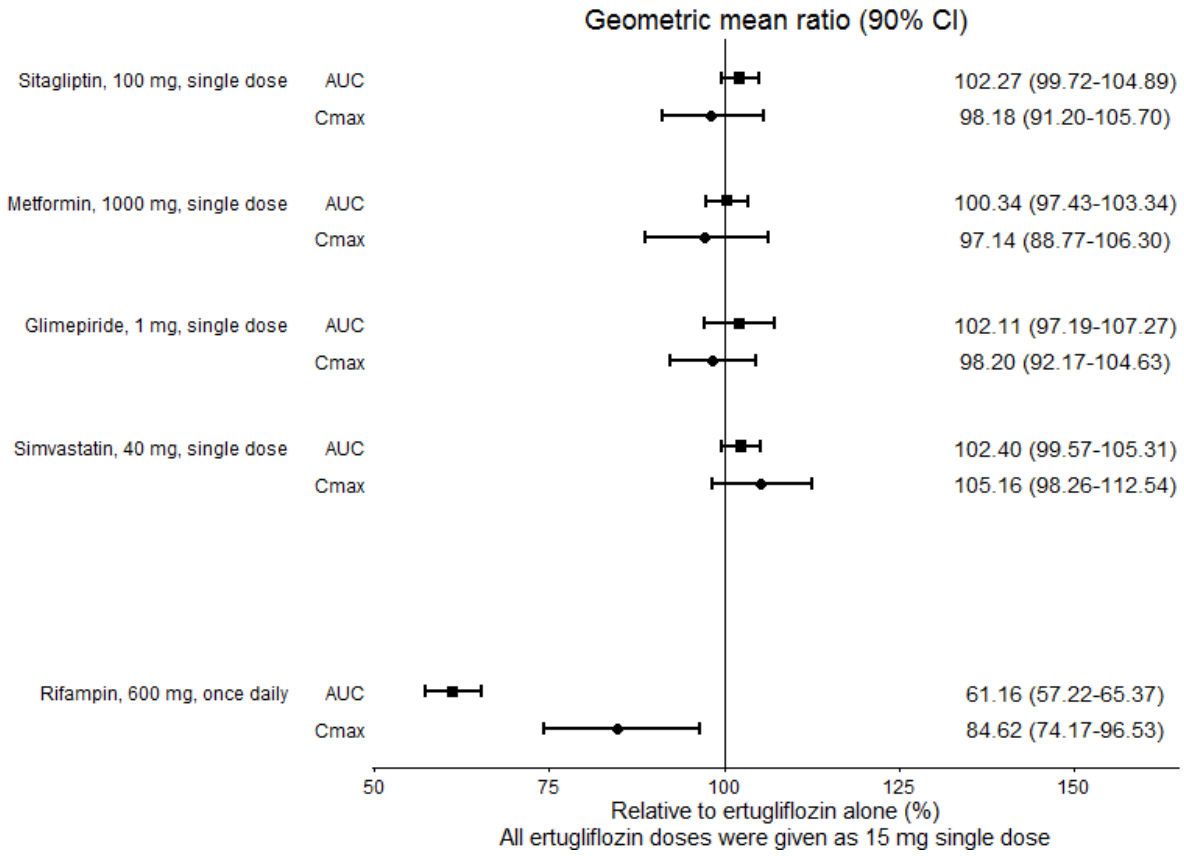
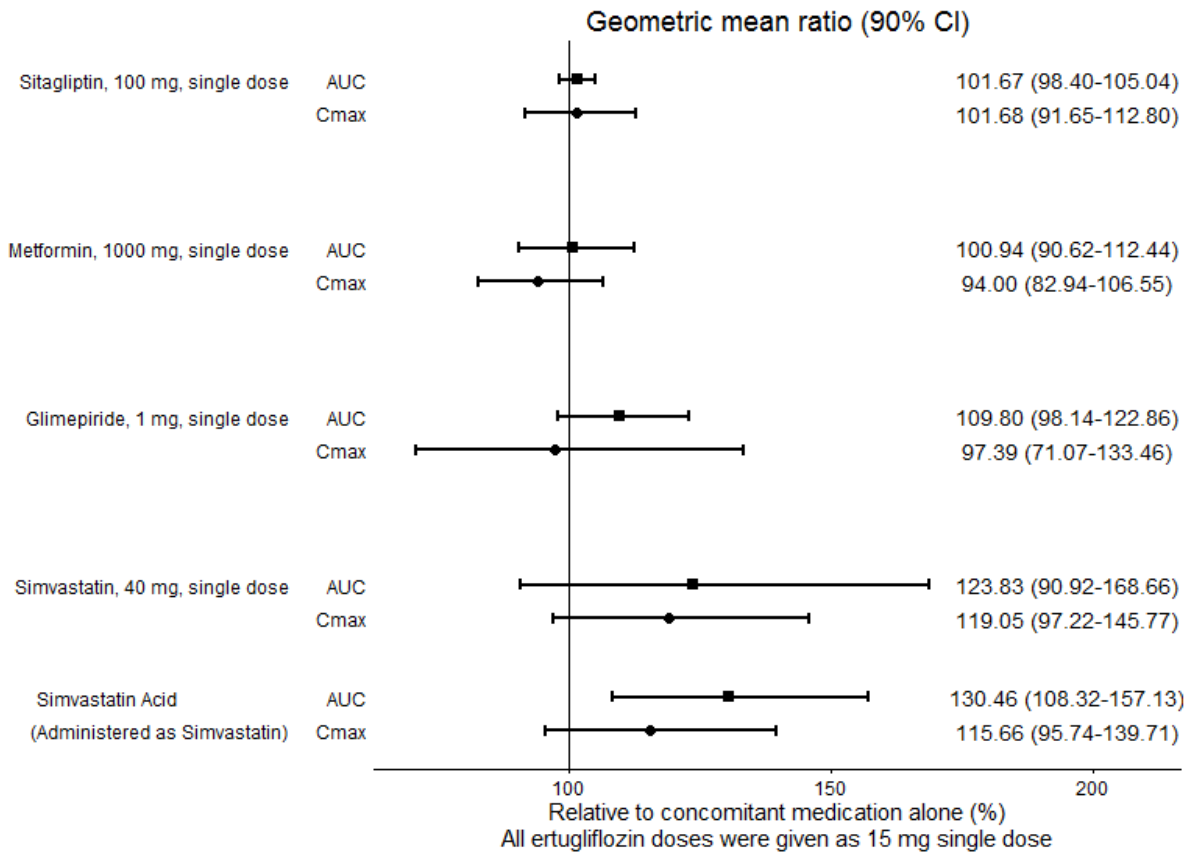


Figure 2: Effects of Ertugliflozin on the Pharmacokinetics of Other Drugs



Metformin hydrochloride

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

Coadministered Drug	**Dose of Coadministered Drug***	**Dose of Metformin***	**Geometric Mean Ratio (ratio with/without metformin) No Effect = 1.00**		
				AUC[†]	C_{max}
No dosing adjustments required for the following:					
Cimetidine	400 mg	850 mg	Cimetidine	0.95[‡]	1.01
Glyburide	5 mg	500 mg[§]	Glyburide	0.78[¶]	0.63[¶]
Furosemide	40 mg	850 mg	Furosemide	0.87[¶]	0.69[¶]
Nifedipine	10 mg	850 mg	Nifedipine	1.10[‡]	1.08
Propranolol	40 mg	850 mg	Propranolol	1.01[‡]	0.94
Ibuprofen	400 mg	850 mg	Ibuprofen	0.97[#]	1.01[#]

* All doses administered as single dose unless otherwise specified.
† AUC is reported as $AUC_{0-\infty}$ unless otherwise specified.
‡ AUC_{0-24hr}.
§ Metformin hydrochloride extended-release tablets 500 mg.
¶ Ratio of arithmetic means, p value of difference <0.05.
# Ratio of arithmetic means.

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

Coadministered Drug	Dose of Coadministered Drug*	Dose of Metformin*	Geometric Mean Ratio (ratio with/without coadministered drug) No Effect = 1.00		
				AUC[†]	C_{max}
No dosing adjustments required for the following:					
Glyburide	5 mg	500 mg[‡]	Metformin[‡]	0.98[§]	0.99[§]
Furosemide	40 mg	850 mg	Metformin	1.09[§]	1.22[§]
Nifedipine	10 mg	850 mg	Metformin	1.16	1.21
Propranolol	40 mg	850 mg	Metformin	0.90	0.94
Ibuprofen	400 mg	850 mg	Metformin	1.05[§]	1.07[§]
Drugs that are eliminated by renal tubular secretion may increase the accumulation of metformin. ***[See Warnings and Precautions (5.1) and Drug Interactions (7.2).]***					
Cimetidine	400 mg	850 mg	Metformin	1.40	1.61
Carbonic anhydrase inhibitors may cause metabolic acidosis. ***[See Warnings and Precautions (5.1) and Drug Interactions (7.2).]***					
Topiramate	100 mg[¶]	500 mg[¶]	Metformin	1.25[¶]	1.17

* All doses administered as single dose unless otherwise specified.
† AUC is reported as $AUC_{0-\infty}$ unless otherwise specified.
‡ Metformin hydrochloride extended-release tablets 500 mg.
§ Ratio of arithmetic means.
¶ Steady-state 100 mg topiramate every 12 hr + metformin 500 mg every 12 hr AUC = 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 relevancy 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).

Metformin hydrochloride

Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1,500 mg/kg/day, respectively. These doses are both approximately four times the maximum recommended human daily dose of 2,000 mg based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day.

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.

Metformin hydrochloride

There was no evidence of a mutagenic potential of metformin in the following *in vitro* tests: Ames test (*S. typhimurium*), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the *in vivo* mouse micronucleus test were also negative.

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).

Metformin hydrochloride

Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately three times the maximum recommended human daily dose based on body surface area comparisons.

14 CLINICAL STUDIES

14.1 Overview of Clinical Studies in Patients with Type 2 Diabetes Mellitus

The efficacy and safety of ertugliflozin in combination with metformin have been studied in 4 multicenter, randomized, double-blind, placebo- and active comparator-controlled, clinical studies involving 3,643 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 86 years.

In patients with type 2 diabetes mellitus, treatment with ertugliflozin in combination with metformin reduced hemoglobin A1c (HbA1c) compared to placebo.

In patients with type 2 diabetes mellitus treated with ertugliflozin in combination with metformin, the reduction in HbA1c was generally similar across subgroups defined by age, sex, race, geographic region, baseline body mass index (BMI), and duration of type 2 diabetes mellitus.

14.2 Ertugliflozin as Add-on Combination Therapy with Metformin

A total of 621 patients with type 2 diabetes mellitus inadequately controlled (HbA1c between 7% and 10.5%) on metformin monotherapy (≥1,500 mg/day for ≥8 weeks) participated in a randomized, double-blind, multi-center, 26-week, placebo-controlled study (NCT02033889) to evaluate the efficacy and safety of ertugliflozin in combination with metformin. Patients entered a 2-week, single-blind, placebo run-in, and were randomized to placebo, ertugliflozin 5 mg, or ertugliflozin 15 mg administered once daily in addition to continuation of background metformin therapy.

At Week 26, statistically significant reductions in HbA1c were observed in the ertugliflozin 5 mg and 15 mg groups compared to placebo. Ertugliflozin also resulted in a greater proportion of patients achieving an HbA1c <7% compared to placebo (see Table 6 and Figure 3).

Table 6: Results at Week 26 from a Placebo-Controlled Study for Ertugliflozin Used in Combination with Metformin in Patients with Type 2 Diabetes Mellitus*

	Placebo	Ertugliflozin 5 mg	Ertugliflozin 15 mg
HbA1c (%)	**N = 207**	**N = 205**	**N = 201**
Baseline (mean)	8.2	8.1	8.1
Change from baseline (LS mean†)	-0.2	-0.7	-0.9
Difference from placebo (LS mean†, 95% CI)		-0.5‡ (-0.7, -0.4)	-0.7‡ (-0.9, -0.5)
Patients [N (%)] with HbA1c <7%	38 (18.4)	74 (36.3)	87 (43.3)
FPG (mg/dL)	**N = 202**	**N = 199**	**N = 201**
Baseline (mean)	169.1	168.1	167.9
Change from baseline (LS mean†)	-8.7	-30.3	-40.9
Difference from placebo (LS mean†, 95% CI)		-21.6‡ (-27.8, -15.5)	-32.3‡ (-38.5, -26.0)

* 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 12%, 6%, and 9% of patients, and during the trial, rescue medication was initiated by 18%, 3%, and 1% 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 include 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%, -0.7%, and -1.0% for placebo, ertugliflozin 5 mg, and ertugliflozin 15 mg, respectively.

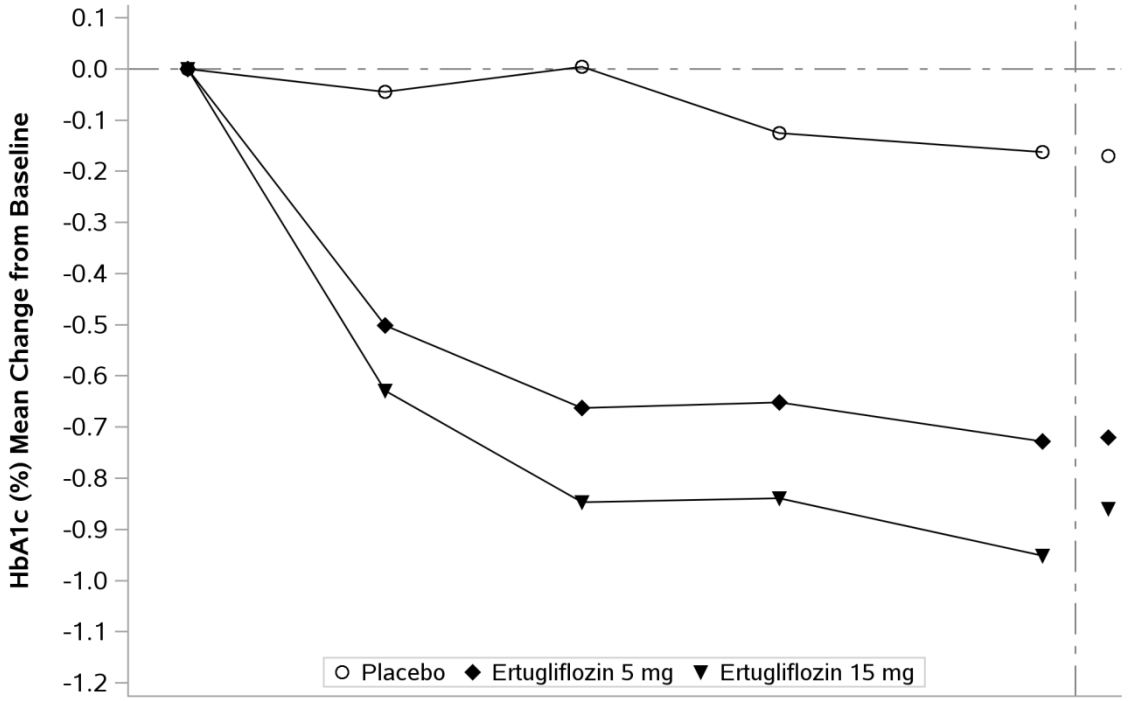
† Intent-to-treat analysis using ANCOVA adjusted for baseline value, prior antihyperglycemic medication, menopausal status and baseline eGFR.

‡ p<0.001 compared to placebo.

The mean baseline body weight was 84.5 kg, 84.9 kg, and 85.3 kg in the placebo, ertugliflozin 5 mg, and ertugliflozin 15 mg groups, respectively. The mean changes from baseline to Week 26 were -1.4 kg, -3.2 kg, and -3.0 kg in the placebo, ertugliflozin 5 mg, and ertugliflozin 15 mg groups, respectively. The difference from placebo (95% CI) for ertugliflozin 5 mg was -1.8 kg (-2.4, -1.2) and for ertugliflozin 15 mg was -1.7 kg (-2.2, -1.1).

The mean baseline systolic blood pressure was 129.3 mmHg, 130.5 mmHg, and 130.2 mmHg in the placebo, ertugliflozin 5 mg, and ertugliflozin 15 mg groups, respectively. The mean changes from baseline to Week 26 were -1.8 mmHg, -5.1 mmHg, and -5.7 mmHg in the placebo, ertugliflozin 5 mg, and ertugliflozin 15 mg groups, respectively. The difference from placebo (95% CI) for ertugliflozin 5 mg was -3.3 mmHg (-5.6, -1.1) and for ertugliflozin 15 mg was -3.8 mmHg (-6.1, -1.5).

Figure 3: HbA1c (%) Change over Time in a 26-Week Placebo-Controlled Study for Ertugliflozin Used in Combination with Metformin in Patients with Type 2 Diabetes Mellitus*



Placebo (N)	207	198	195	174	151
Ertugliflozin 5 mg (N)	205	197	195	193	190
Ertugliflozin 15 mg (N)	201	195	192	189	184

* Data to the left of the vertical line are observed means (non-model-based) excluding values occurring post glycemic rescue. Data to the right of the vertical line represent the final Week 26 data, including all values regardless of use of glycemic rescue medication and use of study drug, with missing Week 26 values imputed using multiple imputation (26-MI) with a mean equal to the baseline value of the patient (see Table 6).

14.3 In Combination with Sitagliptin versus Ertugliflozin Alone and Sitagliptin Alone, as Add-on to Metformin

A total of 1,233 patients with type 2 diabetes mellitus with inadequate glycemic control (HbA1c between 7.5% and 11%) on metformin monotherapy (≥1,500 mg/day for ≥8 weeks) participated in a randomized, double-blind, 26-week, active controlled study (NCT02099110) to evaluate the efficacy and safety of ertugliflozin 5 mg or 15 mg in combination with sitagliptin 100 mg compared to the individual components. Patients were randomized to one of five treatment arms: ertugliflozin 5 mg, ertugliflozin 15 mg, sitagliptin 100 mg, ertugliflozin 5 mg + sitagliptin 100 mg, or ertugliflozin 15 mg + sitagliptin 100 mg.

At Week 26, ertugliflozin 5 mg or 15 mg + sitagliptin 100 mg provided statistically significantly greater reductions in HbA1c compared to ertugliflozin (5 mg or 15 mg) alone or sitagliptin 100 mg alone. The mean change from baseline in HbA1c was -1.4% for ertugliflozin 5 mg or 15 mg + sitagliptin 100 mg versus -1.0%, for ertugliflozin 5 mg, ertugliflozin 15 mg, or sitagliptin 100 mg, respectively. More patients receiving ertugliflozin 5 mg or 15 mg + sitagliptin 100 mg achieved an HbA1c <7% (53.3% and 50.9%, for ertugliflozin 5 mg or 15 mg, respectively, + sitagliptin 100 mg) compared to the individual components (29.3%, 33.7%, and 38.5% for ertugliflozin 5 mg, ertugliflozin 15 mg, or sitagliptin 100 mg, respectively).

14.4 Ertugliflozin as Add-on Combination Therapy with Metformin and Sitagliptin

A total of 463 patients with type 2 diabetes mellitus inadequately controlled (HbA1c between 7% and 10.5%) on metformin (≥1,500 mg/day for ≥8 weeks) and sitagliptin 100 mg once daily participated in a randomized, double-blind, multi-center, 26-week, placebo-controlled study (NCT02036515) to evaluate the efficacy and safety of ertugliflozin. Patients entered a 2-week, single-blind, placebo run-in period and were randomized to placebo, ertugliflozin 5 mg, or ertugliflozin 15 mg.

At Week 26, treatment with ertugliflozin at 5 mg or 15 mg daily provided statistically significant reductions in 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 include measurements collected after initiation of rescue medication. For those patients who did not receive rescue medication and had values measured at 26 weeks, the mean changes from baseline for HbA1c were -0.2%, -0.8%, and -0.9% for placebo, ertugliflozin 5 mg, and ertugliflozin 15 mg, respectively.

† Intent-to-treat analysis using ANCOVA adjusted for baseline value, prior antihyperglycemic medication and baseline eGFR.

‡ p<0.001 compared to placebo.

The mean baseline body weight was 86.5 kg, 87.6 kg, and 86.6 kg in the placebo, ertugliflozin 5 mg, and ertugliflozin 15 mg groups, respectively. The mean changes from baseline to Week 26 were -1.0 kg, -3.0 kg, and -2.8 kg in the placebo, ertugliflozin 5 mg, and ertugliflozin 15 mg groups, respectively. The difference from placebo (95% CI) for ertugliflozin 5 mg was -1.9 kg (-2.6, -1.3) and for ertugliflozin 15 mg was -1.8 kg (-2.4, -1.2).

The mean baseline systolic blood pressure was 130.2 mmHg, 132.1 mmHg, and 131.6 mmHg in the placebo, ertugliflozin 5 mg, and ertugliflozin 15 mg groups, respectively. The mean changes from baseline to Week 26 were -0.2 mmHg, -3.8 mmHg, and -4.5 mmHg in the placebo, ertugliflozin 5 mg, and ertugliflozin 15 mg groups, respectively. The difference from placebo (95% CI) for ertugliflozin 5 mg was -3.7 mmHg (-6.1, -1.2) and for ertugliflozin 15 mg was -4.3 mmHg (-6.7, -1.9).

14.5 Active Controlled Study of Ertugliflozin Versus Glimepiride as Add-on Combination Therapy with Metformin

A total of 1,326 patients with type 2 diabetes mellitus inadequately controlled (HbA1c between 7% and 9%) on metformin monotherapy participated in a randomized, double-blind, multi-center, 52-week, active comparator-controlled study (NCT01999218) to evaluate the efficacy and safety of ertugliflozin in combination with metformin. These patients, who were receiving metformin monotherapy (≥1,500 mg/day for ≥8 weeks), entered a 2-week, single-blind, placebo run-in period and were randomized to glimepiride, ertugliflozin 5 mg, or ertugliflozin 15 mg administered once daily in addition to continuation of background metformin therapy. Glimepiride was initiated at 1 mg/day and titrated up to a maximum dose of 6 or

8 mg/day (depending on maximum approved dose in each country) or a maximum tolerated dose or down-titrated to avoid or manage hypoglycemia. The mean daily dose of glimepiride was 3.0 mg.

Ertugliflozin 15 mg was non-inferior to glimepiride after 52 weeks of treatment. (See Table 8.)

Table 8: Results at Week 52 from an Active-Controlled Study Comparing Ertugliflozin to Glimepiride as Add-on Therapy in Patients with Type 2 Diabetes Mellitus Inadequately Controlled on Metformin*

	Glimepiride	Ertugliflozin 5 mg	Ertugliflozin 15 mg
HbA1c (%)	**N = 437**	**N = 447**	**N = 440**
Baseline (mean)	7.8	7.8	7.8
Change from baseline (LS mean†)	-0.6	-0.5	-0.5
Difference from glimepiride (LS mean†, 95% CI)		0.2‡ (0.0, 0.3)	0.1‡ (-0.0, 0.2)
Patients [N (%)] with HbA1c <7%	208 (47.7)	177 (39.5)	186 (42.2)

* N includes all randomized and treated patients with a baseline measurement of the outcome variable. At Week 52, the primary HbA1c endpoint was missing for 15%, 20%, and 16% of patients and during the trial, rescue medication was initiated by 3%, 6%, and 4% of patients randomized to glimepiride, ertugliflozin 5 mg, and ertugliflozin 15 mg, respectively. Missing Week 52 measurements were imputed using multiple imputation with a mean equal to the baseline value of the patient. Results include measurements collected after initiation of rescue medication. For those patients who did not receive rescue medication and had values measured at 52 weeks, the mean changes from baseline for HbA1c were -0.8%, -0.6%, and -0.7% for glimepiride, ertugliflozin 5 mg, and ertugliflozin 15 mg, respectively.

† Intent-to-treat analysis using ANCOVA adjusted for baseline value, prior antihyperglycemic medication and baseline eGFR.

‡ Non-inferiority is declared when the upper bound of the two-sided 95% confidence interval (CI) for the mean difference is less than 0.3%.

The mean baseline body weight was 86.8 kg, 87.9 kg, and 85.6 kg in the glimepiride, ertugliflozin 5 mg, and ertugliflozin 15 mg groups, respectively. The mean changes from baseline to Week 52 were 0.6 kg, -2.6 kg, and -3.0 kg in the glimepiride, ertugliflozin 5 mg, and ertugliflozin 15 mg groups, respectively. The difference from glimepiride (95% CI) for ertugliflozin 5 mg was -3.2 kg (-3.7, -2.7) and for ertugliflozin 15 mg was -3.6 kg (-4.1, -3.1).

16 HOW SUPPLIED/STORAGE AND HANDLING

SEGLUROMET (ertugliflozin and metformin hydrochloride) tablets are available in the strengths listed below:

ertugliflozin 2.5 mg and metformin hydrochloride 500 mg tablets are pink, oval, debossed with “2.5/500” on one side and plain on the other side. They are supplied as follows:

NDC 0006-5369-03 unit-of-use bottles of 60
NDC 0006-5369-06 unit-of-use bottles of 180
NDC 0006-5369-07 bulk bottles of 500

ertugliflozin 2.5 mg and metformin hydrochloride 1000 mg tablets are pink, oval, debossed with “2.5/1000” on one side and plain on the other side. They are supplied as follows:

NDC 0006-5373-03 unit-of-use bottles of 60
NDC 0006-5373-06 unit-of-use bottles of 180
NDC 0006-5373-07 bulk bottles of 500

ertugliflozin 7.5 mg and metformin hydrochloride 500 mg tablets are red, oval, debossed with “7.5/500” on one side and plain on the other side. They are supplied as follows:

NDC 0006-5370-03 unit-of-use bottles of 60
NDC 0006-5370-06 unit-of-use bottles of 180
NDC 0006-5370-07 bulk bottles of 500

ertugliflozin 7.5 mg and metformin hydrochloride 1000 mg tablets are red, oval, debossed with “7.5/1000” on one side and plain on the other side. They are supplied as follows:

NDC 0006-5374-03 unit-of-use bottles of 60

NDC 0006-5374-06 unit-of-use bottles of 180
NDC 0006-5374-07 bulk bottles of 500

Storage of Bottles

Store at 20°C-25°C (68°F-77°F), excursions permitted between 15°C-30°C (between 59°F-86°F) [see USP Controlled Room Temperature]. Protect from moisture. Store in a dry place.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Instructions

Instruct patients to read the Medication Guide before starting SEGLUROMET (ertugliflozin and metformin) and to reread it each time the prescription is renewed.

Inform patients of the potential risks and benefits of SEGLUROMET and of alternative modes of therapy. Also inform patients about the importance of adherence to dietary instructions, regular physical activity, periodic blood glucose monitoring and HbA1c testing, recognition and management of hypoglycemia and hyperglycemia, and assessment for diabetes complications. Advise patients to seek medical advice promptly during periods of stress such as fever, trauma, infection, or surgery, as medication requirements may change.

Instruct patients to take SEGLUROMET only as prescribed. If a dose is missed, advise patients to take it as soon as it is remembered unless it is almost time for the next dose, in which case patients should skip the missed dose and take the medicine at the next regularly scheduled time. Advise patients not to take two doses of SEGLUROMET at the same time.

Hypoglycemia with Concomitant Use of Insulin and/or Insulin Secretagogue

Inform patients that the incidence of hypoglycemia may increase when SEGLUROMET is added to insulin and/or an insulin secretagogue and that a lower dose of insulin or insulin secretagogue may be required to reduce the risk of hypoglycemia *[see Warnings and Precautions (5.7)]*.

Fetal Toxicity

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

Pregnancy

Inform female patients that treatment with metformin may result in an unintended pregnancy in some premenopausal anovulatory females due to its effect on ovulation *[see Use in Specific Populations (8.3)].*

Lactic Acidosis

Inform patients of the risks of lactic acidosis due to the metformin component, its symptoms, and conditions that predispose to its development *[see Warnings and Precautions (5.1)]*. Advise patients to discontinue SEGLUROMET immediately and to notify their doctor promptly if unexplained hyperventilation, malaise, myalgia, unusual somnolence, slow or irregular heartbeat, sensation of feeling cold (especially in the extremities), or other nonspecific symptoms occur. GI symptoms are common during initiation of metformin treatment and may occur during initiation of SEGLUROMET therapy; however, advise patients to consult their doctor if they develop unexplained symptoms. Although GI symptoms that occur after stabilization are unlikely to be drug related, such an occurrence of symptoms should be evaluated to determine if it may be due to metformin-induced lactic acidosis or other serious disease.

Hypotension

Inform patients that symptomatic hypotension may occur with SEGLUROMET and advise them to contact their doctor if they experience such symptoms *[see Warnings and Precautions (5.2)]*. Inform patients that dehydration may increase the risk for hypotension, and to have adequate fluid intake.

Ketoacidosis

Inform patients that ketoacidosis is a serious life-threatening condition. Inform patients that ketoacidosis has been reported during use of medicines containing SGLT2 inhibitors, including ertugliflozin. Instruct patients to check ketones (when possible) if symptoms consistent with ketoacidosis occur even if blood glucose is not elevated. If symptoms of ketoacidosis (including nausea, vomiting, abdominal pain, tiredness, and labored breathing) occur, instruct patients to discontinue SEGLUROMET and seek medical advice immediately *[see Warnings and Precautions (5.3)]*.

Acute Kidney Injury

Inform patients that acute kidney injury has been reported during use of SEGLUROMET. Advise patients to seek medical advice immediately if they have reduced oral intake (due to acute illness or fasting) or increased fluid losses (due to vomiting, diarrhea, or excessive heat exposure), as it may be appropriate to temporarily discontinue SEGLUROMET use in those settings *[see Warnings and Precautions (5.4)]*.

Monitoring of Renal Function

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

Serious Urinary Tract Infections

Inform patients of the potential for urinary tract infections, which may be serious. Provide them with information on the symptoms of urinary tract infections. Advise them to seek medical advice if such symptoms occur *[see Warnings and Precautions (5.5)]*.

Amputation

Inform patients of the potential for an increased risk of amputations. Counsel patients about the importance of routine preventative foot care. Instruct patients to monitor for new pain or tenderness, sores or ulcers, or infections involving the leg or foot and to seek medical advice immediately if such signs or symptoms develop *[see Warnings and Precautions (5.6)]*.

Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)

Inform patients that necrotizing infections of the perineum (Fournier's gangrene) have occurred with SGLT2 inhibitors. Counsel patients to promptly seek medical attention if they develop pain or tenderness, redness, or swelling of the genitals or the area from the genitals back to the rectum, along with a fever above 100.4°F or malaise *[see Warnings and Precautions (5.8)].*

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 (5.9)]*.

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 (5.9)]*.

Laboratory Tests

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

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

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

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Medication Guide
SEGLUROMET™ (seg-LUR-oh-met)
(ertugliflozin and metformin hydrochloride)
tablets, for oral use

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

What is the most important information I should know about SEGLUROMET?

SEGLUROMET may cause serious side effects, including:

Lactic Acidosis. Metformin, one of the medicines in SEGLUROMET, can cause a rare but serious condition called lactic acidosis (a buildup of an acid in the blood) that can cause death. Lactic acidosis is a medical emergency and must be treated in the hospital.

Call your doctor right away if you have any of the following symptoms, which could be signs of lactic acidosis:

- you feel cold in your hands or feet
- you feel very weak or tired
- you have trouble breathing
- you have stomach pains, nausea or vomiting
- you have a slow or irregular heartbeat
- you have unusual (not normal) muscle pain
- you have unusual sleepiness or sleep longer than usual
- you feel dizzy or lightheaded

Most people who have had lactic acidosis had other conditions that, in combination with metformin use, led to the lactic acidosis. Tell your doctor if you have any of the following, because you have a higher chance for getting lactic acidosis with SEGLUROMET if you:

- have severe kidney problems or your kidneys are affected by certain x-ray tests that use injectable dye.
- have liver problems.
- drink alcohol very often, or drink a lot of alcohol in the short term “binge” drinking.
- get dehydrated (lose a large amount of body fluids). This can happen if you are sick with a fever, vomiting, or diarrhea. Dehydration can also happen when you sweat a lot with activity or exercise and do not drink enough fluids.
- have surgery.
- have a heart attack, severe infection, or stroke.

The best way to keep from having a problem with lactic acidosis from metformin is to tell your doctor if you have any of the problems in the list above. Your doctor may decide to stop your SEGLUROMET for a while if you have any of these things.

SEGLUROMET can have other serious side effects. See “What are the possible side effects of SEGLUROMET?”

What is SEGLUROMET?

- SEGLUROMET contains 2 prescription medicines called ertugliflozin (STEGLATRO™) and metformin hydrochloride. SEGLUROMET can be used along with diet and exercise to lower blood sugar (glucose) in adults with type 2 diabetes who are already using ertugliflozin and metformin for treatment or who do not have control of their blood sugar on ertugliflozin or metformin alone.
- SEGLUROMET is not for people with type 1 diabetes.
- SEGLUROMET is not for people with diabetic ketoacidosis (increased ketones in your blood or urine).
- It is not known if SEGLUROMET is safe and effective in children under 18 years of age.

Do not take SEGLUROMET if you:

- have severe kidney problems or are on dialysis.
- have a condition called metabolic acidosis or diabetic ketoacidosis (increased ketones in the blood or urine).
- are allergic to ertugliflozin, metformin, or any of the ingredients in SEGLUROMET. See the end of this Medication Guide for a list of ingredients in SEGLUROMET. Symptoms of a **serious** allergic reaction to SEGLUROMET may include skin rash, raised red patches on your skin (hives), swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing.

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

- have type 1 diabetes or have had diabetic ketoacidosis.
- have kidney problems.
- have liver problems.
- have or have had problems with your pancreas, including pancreatitis or surgery on your pancreas.
- have heart problems, including congestive heart failure.
- have a history of urinary tract infections or problems with urination.
- are going to get an injection of dye or contrast agents for an x-ray procedure. SEGLUROMET may need to be stopped for a short time. Talk to your doctor about when you should stop SEGLUROMET and when you should start SEGLUROMET again. See **"What is the most important information I should know about SEGLUROMET?".**
- are eating less due to illness, surgery, or a change in your diet.
- have a history of amputation.
- have had blocked or narrowed blood vessels, usually in the leg.
- have damage to the nerves (neuropathy) in your leg.
- have had diabetic foot ulcers or sores.
- are going to have surgery.
- drink alcohol very often, or drink a lot of alcohol in the short term ("binge" drinking).
- are pregnant or plan to become pregnant. SEGLUROMET may harm your unborn baby. If you become pregnant while taking SEGLUROMET, your doctor may switch you to a different medicine to control your blood sugar. Talk to your doctor about the best way to control your blood sugar if you plan to become pregnant or while you are pregnant.
- are a premenopausal woman (before the "change of life"), who does not have periods regularly or at all. Talk to your doctor about birth control choices while taking SEGLUROMET if you are not planning to become pregnant since SEGLUROMET may increase your chance of becoming pregnant. Tell your doctor right away if you become pregnant while taking SEGLUROMET.
- are breastfeeding or plan to breastfeed. It is not known if SEGLUROMET passes into your breast milk. You should not breastfeed if you take SEGLUROMET.

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

How should I take SEGLUROMET?

- Take SEGLUROMET exactly as your doctor tells you to take it.
- Your doctor may do certain blood tests before you start SEGLUROMET.
- Take SEGLUROMET by mouth 2 times a day with meals. Taking SEGLUROMET with meals may lower your chance of having an upset stomach.
- Your doctor may change your dose if needed.
- If you miss a dose, take it as soon as you remember. If it is almost time for your next dose, skip

the missed dose and take the medicine at the next regularly scheduled time. **Do not** take 2 doses of SEGLUROMET at the same time.

- Your doctor may tell you to take SEGLUROMET along with other diabetes medicines. Low blood sugar can happen more often when SEGLUROMET is taken with certain other diabetes medicines. See "What are the possible side effects of SEGLUROMET?".
- Stay on your prescribed diet and exercise program while taking SEGLUROMET.
- Check your blood sugar as your doctor tells you to.
- Your doctor will check your diabetes with regular blood tests, including your blood sugar levels and your HbA1c.
- Talk to your doctor about how to prevent, recognize, and manage low blood sugar (hypoglycemia), high blood sugar (hyperglycemia), complications of diabetes.
- Your doctor will do blood tests to check how well your kidneys are working before and during your treatment with SEGLUROMET.
- When your body is under some types of stress, such as fever, trauma (such as a car accident), infection, or surgery, the amount of diabetes medicine you need may change. Tell your doctor right away if you have any of these conditions and follow your doctor's instructions.
- When taking SEGLUROMET, you may have sugar in your urine, which will show up on a urine test.
- If you take too much SEGLUROMET, call your doctor or go to the nearest hospital emergency room right away.

What should I avoid while taking SEGLUROMET?

- Avoid drinking alcohol very often, or drinking a lot of alcohol in a short period of time ("binge" drinking). It can increase your chances of getting serious side effects.

What are the possible side effects of SEGLUROMET?

SEGLUROMET may cause serious side effects, including:

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

- **dehydration.** SEGLUROMET can cause some people to become dehydrated (the loss of body water and salt). Dehydration may cause you to feel dizzy, faint, lightheaded, or weak, especially when you stand up (orthostatic hypotension).

You may be at risk of dehydration if you:

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

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

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

If you get any of these symptoms during treatment with SEGLUROMET, if possible check for

ketones in your urine, even if your blood sugar is less than 250 mg/dL.

- **kidney problems.** Sudden kidney injury has happened to people treated with SEGLUROMET. Talk to your doctor right away if you:
  - reduce the amount of food or liquid you drink, for example, if you are sick or cannot eat or
  - you start to lose liquids from your body, for example, from vomiting, diarrhea, or being in the sun too long
- **serious urinary tract infections.** Serious urinary tract infections that may lead to hospitalization have happened in people who are taking SEGLUROMET. Tell your doctor if you have any signs or symptoms of a urinary tract infection such as a burning feeling when passing urine, a need to urinate often, the need to urinate right away, pain in the lower part of your stomach (pelvis), or blood in the urine. Sometimes people may also have a fever, back pain, nausea, or vomiting.
- **amputations. SEGLUROMET may increase your risk of lower limb amputations. Amputations mainly involve removal of the toe.**
  You may be at a higher risk of lower limb amputation if you:
  - have a history of amputation
  - have had blocked or narrowed blood vessels, usually in your leg
  - have damage to the nerves (neuropathy) in your leg
  - have had diabetic foot ulcers or sores

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

- **low blood sugar (hypoglycemia).** If you take SEGLUROMET with another medicine that can cause low blood sugar such as a sulfonylurea or insulin, your risk of getting low blood sugar is higher. The dose of your sulfonylurea or insulin may need to be lowered while you take SEGLUROMET. Signs and symptoms of low blood sugar may include:
  - headache
  - drowsiness
  - hunger
  - irritability
  - dizziness
  - confusion
  - sweating
  - feeling jittery or shaky
  - weakness
  - fast heartbeat
- **a rare but serious bacterial infection that causes damage to the tissue under the skin (necrotizing fasciitis) in the area between and around the anus and genitals (perineum).** Necrotizing fasciitis of the perineum has happened in women and men who take medicines that lower blood sugar in the same way as one of the medicines in SEGLUROMET. Necrotizing fasciitis of the perineum may lead to hospitalization, may require multiple surgeries, and may lead to death. **Seek medical attention immediately if you have fever or you are feeling very weak, tired or uncomfortable (malaise) and you develop any of the following symptoms in the area between and around your anus and genitals:**
  - pain or tenderness
  - swelling
  - redness of skin (erythema)
- **vaginal yeast infection.** Women who take SEGLUROMET may get vaginal yeast infections. Symptoms of a vaginal yeast infection include:
  - vaginal odor
  - white or yellowish vaginal discharge (discharge may be lumpy or look like cottage cheese)
  - vaginal itching
- **yeast infection of the penis (balanitis or balanoposthitis)**. Men who take SEGLUROMET may get a yeast infection of the skin around the penis. Certain men who are not circumcised may have swelling of the penis that makes it difficult to pull back the skin around the tip of your penis. Other symptoms of yeast infection of the penis include:
  - redness, itching, or swelling of the penis
  - foul smelling discharge from the penis
  - rash of the penis
  - pain in the skin around your penis

Talk to your doctor about what to do if you get symptoms of a yeast infection of the vagina or penis. Your doctor may suggest you use an over-the-counter antifungal medicine. Talk to your doctor

right away if you use an over-the-counter antifungal medicine and your symptoms do not go away.

- **low vitamin B_{12} (vitamin B_{12} deficiency).** Using metformin for long periods of time may cause a decrease in the amount of vitamin B_{12} in your blood, especially if you have had low vitamin B_{12} blood levels before. Your doctor may do blood tests to check your vitamin B_{12} levels.
- **increased fats in your blood (bad cholesterol or LDL).**

The most common side effects of ertugliflozin include:

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

The most common side effects of metformin hydrochloride include:

- o diarrhea
- o nausea
- o vomiting
- o gas
- o stomach discomfort
- o indigestion
- o weakness
- o headache

These are not all the possible side effects of SEGLUROMET.
Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088.

How should I store SEGLUROMET?

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

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

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

What are the ingredients in SEGLUROMET?
Active ingredients: ertugliflozin and metformin hydrochloride.
Inactive ingredients: povidone, microcrystalline cellulose, crospovidone, sodium lauryl sulfate, and magnesium stearate.
The tablet film coating contains the following inactive ingredients: hydroxypropyl methylcellulose, hydroxypropyl cellulose, titanium dioxide, iron oxide red, and carnauba wax.

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

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

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