PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

ℙ SEGLUROMET®

ertugliflozin and metformin hydrochloride tablets
2.5 mg/500 mg, 2.5 mg/1000 mg, 7.5 mg/500 mg, and 7.5 mg/1000 mg
ertugliflozin/metformin hydrochloride, tablets, oral

ATC Code: A10BD23
Combinations of oral blood glucose lowering drugs

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RECENT MAJOR LABEL CHANGES:

INDICATION, Geriatrics (1.2)	**10-2019**
CONTRAINDICATION (2)	**10-2019**
DOSAGE AND ADMINISTRATION (4)	**10-2019**
WARNINGS AND PRECAUTIONS (7)	**10-2019**
WARNING AND PRECAUTIONS, Geriatrics (7.1.4)	**10-2019**
DRUG INTERACTIONS, Drug-Drug Interactions (9.2)	**10-2019**
ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics (10.3)	**10-2019**
NON-CLINICAL TOXICOLOGY (16)	**10-2019**
PATIENT MEDICATION INFORMATION	**10-2019**

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PART I: HEALTH PROFESSIONAL INFORMATION

Note: for additional information on ertugliflozin and metformin hydrochloride, consult the individual Product Monographs.

1 INDICATIONS

SEGLUROMET® (ertugliflozin and metformin hydrochloride tablets) is indicated as an adjunct to diet and exercise, to improve glycemic control in adult patients with type 2 diabetes mellitus (T2DM) who are:

- inadequately controlled on metformin, or
- already controlled with metformin and ertugliflozin as individual components.

SEGLUROMET® (ertugliflozin and metformin hydrochloride tablets) is indicated for use in combination with sitagliptin as an adjunct to diet and exercise, to improve glycemic control in adult patients with type 2 diabetes mellitus who are:

- inadequately controlled on metformin and sitagliptin, or
- already controlled with metformin, sitagliptin and ertugliflozin, as individual components.

See CLINICAL TRIALS section

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (≥65 years of age): SEGLUROMET® should be used with caution in geriatric patients. Evidence from clinical studies suggests that ertugliflozin use in the geriatric population is associated with an increase in risk of adverse reactions related to volume depletion in this population (see DOSAGE AND ADMINISTRATION, WARNINGS AND PRECAUTIONS, and ACTION AND CLINICAL PHARMACOLOGY).

Metformin is substantially excreted by the kidney and the risk of serious adverse reactions to the drug is greater in patients with impaired renal function. Because aging is associated with reduced renal function, SEGLUROMET® should be used with caution in geriatric patients (see DOSAGE AND ADMINISTRATION and WARNINGS AND PRECAUTIONS).

2 CONTRAINDICATIONS

- Unstable and/or insulin-dependent (type 1) diabetes mellitus.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma, history of ketoacidosis with or without coma.
- In patients with a history of lactic acidosis, irrespective or precipitating factors (see WARNINGS AND PRECAUTIONS).
- In renally impaired patients with an estimated glomerular filtration rate (eGFR) less than 45 mL/min/1.73 m^2, severe renal impairment, end-stage renal disease (ESRD), or patients on dialysis (see WARNINGS AND PRECAUTIONS).
- In excessive alcohol intake, acute or chronic.
- In patients suffering from severe hepatic dysfunction, since severe hepatic dysfunction has been associated with some cases of lactic acidosis, SEGLUROMET® should not be used in patients with clinical or laboratory evidence of hepatic disease.
- In cases of cardiovascular collapse and in disease states associated with hypoxemia such as cardiorespiratory insufficiency, which are often associated with hyperlactacidemia.
- During stress conditions, such as severe infections, trauma or surgery and the recovery phase thereafter.
- In patients suffering from severe dehydration or shock.
- Known hypersensitivity to ertugliflozin, metformin or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container (see WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS). For a complete listing, see DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING section.
- During pregnancy and breastfeeding (see WARNINGS AND PRECAUTIONS).
- During period around administration of iodinated contrast materials, because the use of such products may result in acute alteration of renal function (see WARNINGS AND PRECAUTIONS).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Lactic Acidosis

- Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with SEGLUROMET® (ertugliflozin and metformin hydrochloride tablets) (see WARNINGS AND PRECAUTIONS).

- Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking SEGLUROMET®, since alcohol intake potentiates the effect of metformin on lactate metabolism (see WARNINGS AND PRECAUTIONS).

Diabetic Ketoacidosis

- Clinical trial and post-market cases of diabetic ketoacidosis (DKA), a serious life-threatening condition requiring urgent hospitalization, have been reported in patients with type 2 diabetes mellitus (T2DM) treated with sodium-glucose co-transporter 2 (SGLT2) inhibitors and cases have been reported in clinical trials with ertugliflozin (see ADVERSE REACTIONS). Fatal cases of ketoacidosis have been reported in patients taking SGLT2 inhibitors. A number of these cases have been atypical with blood glucose values below 13.9 mmol/L (250 mg/dL).

- Patients should be assessed for diabetic ketoacidosis immediately if non-specific symptoms such as difficulty breathing, nausea, vomiting, abdominal pain, confusion, anorexia, excessive thirst and unusual fatigue or sleepiness occur, regardless of blood glucose level, and SEGLUROMET® should be **discontinued immediately**.

- SEGLUROMET® should not be used for the treatment of DKA or in patients with a history of DKA.

- SEGLUROMET® is not indicated, and should not be used, in patients with type 1 diabetes.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- **Diuretics:** SEGLUROMET® should be used with caution in patients taking diuretics, particularly loop diuretics, due to the increased risk of adverse events of volume depletion during co-administration (see WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS, and DRUG INTERACTIONS).

- **Concomitant Use with Medication(s) that May Decrease Renal Function:** Caution should be exercised when using concomitant medication(s) that may decrease renal function (like diuretics, particularly loop diuretics) or may interfere with the disposition of metformin, such

as cationic drugs, that are eliminated by renal tubular secretion, due to the increased risk of developing lactic acidosis during co-administration (see DRUG INTERACTIONS).

4.2 Recommended Dose and Dosage Adjustment

- The recommended dose of SEGLUROMET® is one tablet twice daily with meals. Each tablet is a fixed dose of ertugliflozin and metformin. In patients on metformin, switch to SEGLUROMET® tablets containing 2.5 mg ertugliflozin and the nearest therapeutically appropriate dose of metformin. Patients switching from separate tablets of ertugliflozin and metformin to SEGLUROMET® should receive the same daily dose of ertugliflozin and metformin already being taken or at the nearest therapeutically appropriate dose of metformin. The maximum daily dose is 15 mg ertugliflozin and 2000 mg metformin.

- In patients with evidence of volume depletion, correct this condition prior to initiation of SEGLUROMET® (see WARNINGS AND PRECAUTIONS).

- Factors that may increase the risk of lactic acidosis should be reviewed before considering initiation of metformin-containing products in patients with renal impairment.

Pediatrics (<18 years of age): Safety and effectiveness of SEGLUROMET® or its individual components in pediatric and adolescent patients have not been established; therefore, Health Canada has not authorized an indication for pediatric use (see INDICATIONS).

Geriatrics (≥65 years of age): No dose adjustment of SEGLUROMET® is required based on age; however, elderly patients may have reduced renal function and be at greater risk for adverse reactions related to volume depletion. Because renal function abnormalities can occur after initiating ertugliflozin, SEGLUROMET® should be used with caution in patients 65 years and older. Metformin is substantially excreted by the kidneys, and elderly patients are more likely to have decreased renal function associated with aging and be at risk of developing lactic acidosis (see WARNINGS AND PRECAUTIONS). Regular assessment of renal function is necessary.

Renal Impairment: The efficacy of SEGLUROMET® declines with decreasing renal function (see CLINICAL TRIALS). Renal function must be assessed prior to initiation of SEGLUROMET® therapy and periodically thereafter, with more intensive monitoring of glycemic and renal biomarkers, and signs and symptoms of renal dysfunction in patients whose eGFR decreases <60 mL/min/1.73 m^2 (see WARNINGS AND PRECAUTIONS).

SEGLUROMET® is contraindicated in renally impaired patients with an eGFR less than 45 mL/min/1.73 m^2, severe renal impairment, end-stage renal disease or patients on dialysis (see CONTRAINDICATIONS).

SEGLUROMET® should not be initiated in patients with an eGFR <60 mL/min/1.73 m^2. Use of SEGLUROMET® is not recommended in patients with an eGFR persistently between 45 to <60 mL/min/1.73 m^2. SEGLUROMET® should be discontinued if eGFR falls below 45 mL/min/1.73

m^2 (see WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS and ACTION AND CLINICAL PHARMACOLOGY).

No dose adjustment for SEGLUROMET® is indicated in patients with mild renal impairment (eGFR ≥60 mL/min/1.73 m^2).

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 acceptable and found to be stable (see WARNINGS AND PRECAUTIONS).

Hepatic Impairment: SEGLUROMET® is contraindicated in patients with severe hepatic impairment and should not be used in patients with clinical or laboratory evidence of hepatic disease (see CONTRAINDICATIONS). Metformin use in patients with impaired hepatic function has been associated with some cases of lactic acidosis (see WARNINGS AND PRECAUTIONS).

4.3 Administration

Take SEGLUROMET® twice daily with meals.

4.4 Reconstitution

Not applicable.

4.5 Missed Dose

If a dose of SEGLUROMET® is missed, it should be taken as soon as the patient remembers. A double dose of SEGLUROMET® should not be taken at the same time.

5 OVERDOSAGE

In the event of an overdose, employ the usual supportive measures (e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment) as dictated by the patient's clinical status.

There is no information available on overdose with SEGLUROMET® (ertugliflozin and metformin hydrochloride tablets).

Ertugliflozin
Removal of ertugliflozin by hemodialysis has not been studied.

Metformin hydrochloride

Available information concerning treatment of a massive overdosage of metformin hydrochloride is very limited. It would be expected that adverse reactions of a more intense character including epigastric discomfort, nausea and vomiting followed by diarrhea, drowsiness, weakness, dizziness, malaise and headache might be seen. Should those symptoms persist, lactic acidosis should be excluded. The drug should be discontinued, and proper supportive therapy should be instituted.

Overdose of metformin hydrochloride has occurred, including ingestion of amounts greater than 50 grams. 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). 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.

Pancreatitis may occur in the context of a metformin overdose (see WARNINGS AND PRECAUTIONS).

For management of a suspected drug overdose, contact your regional Poison Control Centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form/ Strength/Composition	Non-medicinal Ingredients
Oral	Tablets 2.5 mg/500 mg* 2.5 mg/1000 mg* 7.5 mg/500 mg* 7.5 mg/1000 mg*	Carnauba wax, crospovidone, hydroxypropyl cellulose, hypromellose, iron oxide red, magnesium stearate, microcrystalline cellulose, povidone, sodium lauryl sulfate and titanium dioxide.

* Ertugliflozin (as ertugliflozin L-pyroglutamic acid) and metformin hydrochloride

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

SEGLUROMET® tablets, 2.5 mg/500 mg, are pink, oval, film-coated tablets debossed with "2.5/500" on one side and plain on the other side. They are supplied as bottles of 60 tablets.

SEGLUROMET® tablets, 2.5 mg/1000 mg, are pink, oval, film-coated tablets debossed with "2.5/1000" on one side and plain on the other side. They are supplied as bottles of 60 tablets.

SEGLUROMET® tablets, 7.5 mg/500 mg, are red, oval, film-coated tablets debossed with "7.5/500" on one side and plain on the other side. They are supplied as bottles of 60 tablets.

SEGLUROMET® tablets, 7.5 mg/1000 mg, are red, oval, film-coated tablets debossed with "7.5/1000" on one side and plain on the other side. They are supplied as bottles of 60 tablets.

7 WARNINGS AND PRECAUTIONS

Please see the Serious Warnings and Precautions Box at the beginning of Part I: Health Professional Information.

General

SEGLUROMET® is not indicated for use in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

Cardiovascular

Patients at Risk for Volume Depletion, Hypotension and/or Electrolyte Imbalances:

Ertugliflozin

SEGLUROMET® is not recommended for use in patients who are volume-depleted. Due to its mechanism of action, ertugliflozin, a component of SEGLUROMET®, causes diuresis that can result in intravascular volume contraction. Therefore, symptomatic hypotension, including postural dizziness can occur after initiating SEGLUROMET® (see ADVERSE REACTIONS).

Caution should be exercised in patients for whom an ertugliflozin-induced decrease in blood pressure could pose a risk. This includes patients who have known cardiovascular disease, patients on anti-hypertensive therapy or on diuretics, who are elderly (≥65 years), patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2), patients with low systolic blood pressure, or patients with intercurrent conditions that may lead to volume depletion (such as gastrointestinal illness).

Before initiating SEGLUROMET®, careful monitoring of volume status is recommended (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, and ADVERSE REACTIONS).

Temporary interruption of treatment with SEGLUROMET® is recommended for patients who develop volume depletion until the fluid loss is corrected.

Hypoxic States:

Metformin hydrochloride

Cardiovascular collapse (shock) from whatever cause (e.g., acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia) have been associated with lactic acidosis (see WARNINGS AND PRECAUTIONS, Endocrine and Metabolism) and may also cause prerenal azotemia. When such events occur in patients on SEGLUROMET® therapy, the drug should be promptly discontinued.

Endocrine and Metabolism

Diabetic Ketoacidosis (DKA):

Ertugliflozin

SEGLUROMET® is not indicated, and should not be used, in patients with type 1 diabetes mellitus. The diagnosis of T2DM should therefore be confirmed before initiating SEGLUROMET®.

Clinical trial and post-market cases of DKA, a serious life-threatening condition requiring urgent hospitalization, have been reported in patients with T2DM treated with SGLT2 inhibitors and cases have been reported in clinical trials with ertugliflozin, a component of SEGLUROMET® (see ADVERSE REACTIONS). Fatal cases of ketoacidosis have been reported in patients taking SGLT2 inhibitors. In a number of reported cases, the presentation of the condition was atypical with only moderately increased blood glucose values, below 13.9 mmol/L (250 mg/dL).

DKA must be considered in the event of non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness.

If these symptoms occur, regardless of blood glucose level, patients should discontinue SEGLUROMET® treatment and be assessed for diabetic ketoacidosis immediately.

Consider interrupting treatment with SEGLUROMET® in T2DM patients who are hospitalized for major surgical procedures, serious infections or acute serious medical illnesses.

SGLT2 inhibitors have been shown to increase blood ketones in clinical trial subjects. Conditions that can precipitate DKA while taking SEGLUROMET® include a very low carbohydrate diet (as the combination may further increase ketone body production), dehydration, high alcohol consumption, and a low beta-cell function reserve. SEGLUROMET® should be used with caution in these patients and these patients should be monitored closely.

Hypoglycemia:

Ertugliflozin

SEGLUROMET® is not indicated in combination with insulin or insulin secretagogues, such as sulfonylurea (see INDICATIONS). The use of SGLT2 inhibitors in combination with these drugs has been shown to increase the risk of hypoglycemia.

Metformin hydrochloride

Hypoglycemia does not occur in patients receiving metformin 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 or ethanol.

Elderly, debilitated, or malnourished patients and patients with adrenal, pituitary, or hepatic 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.

Hypothyroidism:
Metformin hydrochloride
Metformin induces a reduction in thyrotropin (thyroid stimulating hormone (TSH)) levels in patients with treated or untreated hypothyroidism (see ADVERSE REACTIONS). Regular monitoring of TSH levels is recommended in patients with hypothyroidism (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

Studies have shown that metformin reduces plasma TSH levels, often to subnormal levels, when it is administered to patients with untreated hypothyroidism or to hypothyroid patients effectively treated with Levothyroxine. The metformin-induced reduction of plasma TSH levels is not observed when metformin is administered to patients with normal thyroid function. Metformin has been suggested to enhance the inhibitory modulation of thyroid hormones on TSH secretion.

Levothyroxine can reduce the hypoglycemic effect of metformin. Careful monitoring of blood glucose levels is recommended in patients with hypothyroidism treated with levothyroxine, especially when thyroid hormone therapy is initiated, changed, or stopped (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests and DRUG INTERACTIONS).

Increases in Low-Density Lipoprotein Cholesterol (LDL-C):
Ertugliflozin
Dose-related increases in LDL-C are seen with ertugliflozin (see ADVERSE REACTIONS). LDL-C levels should be monitored in patients treated with SEGLUROMET® and treated as appropriate (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

Lactic Acidosis:
Metformin hydrochloride
Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with SEGLUROMET®; when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels (>5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 µg/mL are generally found.

The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient-years). Reported cases have occurred primarily in diabetic patients with significant renal impairment, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications (see DOSAGE AND ADMINISTRATION).

Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. The risk of lactic acidosis increases with

the degree of renal dysfunction and the patient's age (see WARNINGS AND PRECAUTIONS, Special Populations). The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking metformin and by use of the minimum effective dose of metformin.

In addition, SEGLUROMET® should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, metformin should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking SEGLUROMET®, since alcohol potentiates the effects of metformin hydrochloride on lactate metabolism. In addition, SEGLUROMET® should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure.

The onset of lactic acidosis often is subtle, and accompanied only by nonspecific symptoms such as malaise, myalgia, respiratory distress, increasing somnolence, and nonspecific abdominal distress. There may be associated hypothermia, hypotension, and resistant bradyarrhythmias with more marked acidosis. The patient and the patient's physician must be aware of the possible importance of such symptoms and the patient should be instructed to notify the physician immediately if they occur. SEGLUROMET® should be withdrawn until the situation is clarified. Serum electrolytes, ketones, blood glucose, and if indicated, blood pH, lactate levels, and even blood metformin levels may be useful. Once a patient is stabilized on any dose level of metformin, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

Levels of fasting venous plasma lactate above the upper limit of normal but less than 5 mmol/L in patients taking metformin do not necessarily indicate impending lactic acidosis and may be explainable by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity, or technical problems in sample handling.

Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia).

Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking SEGLUROMET®, the drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable (with a clearance of up to 170 mL/min under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS, Cardiovascular, Hepatic/Biliary/Pancreatic, and Renal).

Physicians should instruct their patients to recognize the symptoms which could be a signal of the onset of lactic acidosis. If acidosis of any kind develops, SEGLUROMET® should be discontinued immediately and the patient should be immediately hospitalized.

Change in Clinical Status of Previously Controlled Diabetes Patients:
Metformin hydrochloride
A diabetic patient previously well controlled on SEGLUROMET® who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate and metformin levels. If acidosis of either form occurs, SEGLUROMET® must be stopped immediately and appropriate corrective measures initiated.

Loss of Control of Blood Glucose:
Metformin hydrochloride
When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of glycemic control may occur. At such times, it may be necessary to withhold SEGLUROMET® and temporarily administer insulin. SEGLUROMET® may be reinstituted after the acute episode is resolved.

The effectiveness of oral antidiabetic drugs in lowering blood glucose to a targeted level decreases in many patients over a period of time. This phenomenon, which may be due to progression of the underlying disease or to diminished responsiveness to the drug, is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective during initial therapy. Should secondary failure occur with SEGLUROMET®, therapeutic alternatives should be considered.

Vitamin B_{12} Levels:
Metformin hydrochloride
Impairment of vitamin B_{12} absorption has been reported in some patients treated with metformin. Therefore, measurements of serum vitamin B_{12} are advisable at least every one to two years in patients on long-term treatment with SEGLUROMET®.

A decrease to subnormal levels of previously normal serum vitamin B_{12} levels, without clinical manifestations, is observed in approximately 7% of patients receiving metformin in controlled clinical trials of 28 weeks duration. 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 with 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 (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests). Certain individuals (those with inadequate vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B_{12} levels.

Long-term treatment with metformin has been associated with a decrease in serum vitamin B_{12} levels which may cause peripheral neuropathy. Serious cases of peripheral neuropathy have been reported with metformin treatment, one of the components of SEGLUROMET®, in the context of vitamin B_{12} deficiency (see ADVERSE REACTIONS). Monitoring of serum vitamin B_{12}

levels is recommended (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

Genitourinary

Genital Mycotic Infections:

Ertugliflozin

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). Monitor and treat as appropriate.

Urinary Tract Infections (including urosepsis and pyelonephritis):

Ertugliflozin

Cases of pyelonephritis have been reported in ertugliflozin-treated patients in clinical trials (see ADVERSE REACTIONS). There have also been post-marketing reports of serious urinary tract infections including urosepsis and pyelonephritis, some of them requiring hospitalization, in patients receiving SGLT2 inhibitors. Treatment with SGLT2 inhibitors increases the risk of urinary tract infections. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated.

Hematologic

Elevated Hemoglobin:

Ertugliflozin

Mean hemoglobin increased in patients administered ertugliflozin, a component of SEGLUROMET®, as did the frequency of patients with abnormally elevated values for hemoglobin (see ADVERSE REACTIONS). SEGLUROMET® should be used with caution in patients with elevated hemoglobin.

Metformin hydrochloride

Serious cases of metformin-induced hemolytic anemia, some with fatal outcome, have been reported (see ADVERSE REACTIONS). Two mechanisms were described for the metformin-induced immune hemolytic anemia; formation of an antibody against the erythrocyte-metformin complex and autoantibody formation. Monitoring of hematologic parameters is recommended (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

Hepatic/Biliary/Pancreatic

Hepatic Impairment: SEGLUROMET® is contraindicated in patients with severe hepatic impairment and should not be used in patients with clinical or laboratory evidence of hepatic disease (see CONTRAINDICATIONS).

Ertugliflozin

Ertugliflozin, a component of SEGLUROMET®, has not been studied in patients with severe hepatic impairment (see ACTION AND CLINICAL PHARMACOLOGY).

Metformin hydrochloride

Impaired hepatic function has been associated with some cases of lactic acidosis.

Pancreatitis:
Metformin hydrochloride
Serious cases of pancreatitis have been reported in patients receiving metformin (see ADVERSE REACTIONS). The reported pancreatitis cases occurred either in the context of an acute metformin overdose (see OVERDOSAGE) or in patients receiving therapeutic doses of metformin with concurrent renal failure and/or lactic acidosis, indicating metformin accumulation.

Lower Limb Amputation
Ertugliflozin
An increased risk for lower limb amputation (primarily of the toe) has been observed in clinical studies with another SGLT2 inhibitor. A numerical imbalance in non-traumatic lower limb amputations is reported in trials with ertugliflozin, a component of SEGLUROMET® (see ADVERSE REACTIONS). Based on the current data and the presence of confounding factors, a causal association between ertugliflozin and lower limb amputation remains uncertain. It is anticipated that completion of the ongoing long-term clinical study will further inform on this risk with ertugliflozin.

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 and adequate hydration. 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.

Monitoring and Laboratory Tests
Blood Glucose and HbA1c: Response to SEGLUROMET® treatment should be monitored by periodic measurements of blood glucose and HbA1c levels.

Hematology: Initial and periodic monitoring of hematologic parameters (e.g., hemoglobin/hematocrit and red blood cell indices) should be performed regularly. While megaloblastic anemia has rarely been seen with metformin therapy, if this is suspected, vitamin B_{12} deficiency should be excluded. Periodic measurements of serum vitamin B_{12} levels should be performed in patients on long-term treatment with SEGLUROMET®, especially in patients with anemia or neuropathy (see WARNINGS AND PRECAUTIONS, Endocrine and Metabolism).

A close monitoring of the International Normalized Ratio (INR) is recommended in patients concurrently administering metformin and phenprocoumon or other antivitamin K anticoagulants (see DRUG INTERACTIONS).

Hypothyroidism: Regular monitoring of thyroid-stimulating hormone (TSH) levels is recommended in patients with hypothyroidism.

For hypothyroid patients treated with levothyroxine, careful monitoring of blood glucose levels is recommended, especially when thyroid hormone therapy is initiated, changed, or stopped (see WARNINGS AND PRECAUTIONS, Endocrine and Metabolism and DRUG INTERACTIONS).

LDL-Cholesterol: LDL-C levels should be measured at baseline and at regular intervals during treatment with SEGLUROMET® due to dose-dependent increases in LDL-C seen with SEGLUROMET® therapy (see ADVERSE REACTIONS).

Reduced Intravascular Volume: SEGLUROMET® is not recommended for use in patients who are volume depleted (see DOSAGE AND ADMINISTRATION). Before initiating SEGLUROMET®, assess volume status, particularly in patients at risk such as patients with known cardiovascular disease, patients on anti-hypertensive therapy or on diuretics, elderly patients (≥65 years), patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2), or patients with low systolic blood pressure (see WARNINGS AND PRECAUTIONS, Cardiovascular and DOSAGE AND ADMINISTRATION). In patients with volume depletion, the condition should be corrected prior to initiation of SEGLUROMET® (see DOSAGE AND ADMINISTRATION).

Volume status should also be assessed in cases of intercurrent conditions that may lead to fluid loss (such as a gastrointestinal illness) for patients already taking SEGLUROMET®. In these patients, careful monitoring of volume status (e.g., physical examination, blood pressure measurements, laboratory tests, including hematocrit, serum electrolytes and renal function tests) is recommended. Temporary interruption of treatment with SEGLUROMET® should be considered until fluid loss is corrected.

Renal Function: Renal function must be assessed prior to initiation of SEGLUROMET® and periodically thereafter, with more frequent monitoring in patients whose eGFR decreases to <60 mL/min/1.73 m^2. SEGLUROMET® is contraindicated in patients with renal impairment with an eGFR less than 45 mL/min/1.73 m^2 (see CONTRAINDICATIONS). SEGLUROMET® must be discontinued if eGFR falls below 45 mL/min/1.73 m^2 (see DOSAGE AND ADMINISTRATION).

Monitoring of renal function is recommended prior to and following initiation of any concomitant drug which might have an impact on renal function (see DOSAGE AND ADMINISTRATION and DRUG INTERACTIONS).

Neurologic

Metformin hydrochloride

Serious cases of metformin-induced encephalopathy have been reported (see ADVERSE REACTIONS). Some of these cases were reported without association with lactic acidosis, hypoglycemia, or renal impairment.

Peri-Operative Consideration

Metformin hydrochloride

SEGLUROMET® therapy should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids). SEGLUROMET® should be discontinued 2 days before surgical intervention and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as acceptable and found to be stable (see DOSAGE AND ADMINISTRATION).

Renal

SEGLUROMET® is contraindicated in renally impaired patients with an eGFR less than 45 mL/min/1.73 m^2, severe renal impairment, end-stage renal disease (ESRD), or on dialysis (see CONTRAINDICATIONS).

Renal function must be assessed prior to initiation of SEGLUROMET® and periodically thereafter. In patients whose eGFR decreases to <60 mL/min/1.73 m^2, close monitoring of renal function is recommended (see DOSAGE AND ADMINISTRATION and WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

SEGLUROMET® should not be initiated in patients with an eGFR <60 mL/min/1.73 m^2 and must be discontinued if eGFR falls below 45 mL/min/1.73 m^2 (see DOSAGE AND ADMINISTRATION).

Special caution should be exercised in situations where renal function may become impaired, for example in the elderly, the case of dehydration when initiating antihypertensive therapy or diuretic therapy, or when starting therapy with a non-steroidal anti-inflammatory drug (NSAID). Therefore, consider more frequent monitoring of patients.

Ertugliflozin

Ertugliflozin may cause intravascular volume contraction and increases serum creatinine and decreases eGFR. Renal-related adverse reactions can occur after initiating SEGLUROMET® and the risk is increased in patients with moderate renal impairment (eGFR 30 to less than 60 mL/min/1.73 m^2) (see ADVERSE REACTIONS).

The glucose-lowering benefit of ertugliflozin, which decreases with declining renal function, was not demonstrated to be statistically significant in subjects with eGFR less than 60 mL/min/1.73m^2, and adverse reactions are more frequent (see ADVERSE REACTIONS).

Cases of acute kidney injury have been observed in clinical trials with ertugliflozin, a component of SEGLUROMET® (see ADVERSE REACTIONS). There have also been post-marketing reports of acute kidney injury some requiring hospitalization and dialysis in patients receiving SGLT2 inhibitors. Patients with moderate renal impairment are more susceptible to these changes (see ADVERSE REACTIONS).

Before initiating SEGLUROMET®, consider factors that may predispose patients to acute kidney injury including hypovolemia, chronic renal impairment, congestive heart failure and concomitant medications (diuretics, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (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.

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

Use of concomitant medications that may affect renal function or metformin disposition:
Concomitant medication(s) that may affect renal function or result in significant hemodynamic change or may interfere with the disposition of metformin, such as cationic drugs, that are eliminated by renal tubular secretion (see DRUG INTERACTIONS), should be used with caution. The concomitant use of SEGLUROMET® with these specific drugs may increase the risk of metformin-associated lactic acidosis and therefore, consider more frequent monitoring of patients.

Radiologic studies involving the use of intravascular iodinated contrast materials (for example, intravenous urogram, intravenous cholangiography, angiography, and computed tomography (CT) scans with intravascular contrast materials): Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin (see CONTRAINDICATIONS). Therefore, 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, SEGLUROMET® should be discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been re-evaluated and found to be acceptable and stable (see DOSAGE AND ADMINISTRATION).

7.1 Special Populations

7.1.1 Pregnant Women

SEGLUROMET® (ertugliflozin and metformin hydrochloride tablets) is contraindicated in pregnancy (see CONTRAINDICATIONS). There are very limited data for the use of ertugliflozin in pregnant women in clinical studies, including no adequate and well-controlled studies in this population with SEGLUROMET® or its individual components; therefore, the safety of SEGLUROMET® in pregnant women is not known. When pregnancy is detected, SEGLUROMET® should be discontinued.

Ertugliflozin
Based on results from animal studies, ertugliflozin may affect renal development and maturation (see NON-CLINICAL TOXICOLOGY).

Metformin hydrochloride
Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day, or about two and six times the maximum recommended human daily dose on a body surface area basis. Determination of fetal concentrations demonstrated a partial placental barrier to metformin. Because animal reproduction studies are not always predictive of human response, SEGLUROMET™ is contraindicated during pregnancy (see CONTRAINDICATIONS).

7.1.2 Breast-feeding

SEGLUROMET® is contraindicated during breast-feeding (see CONTRAINDICATIONS). No studies in lactating animals have been conducted with the combined components of SEGLUROMET®.

Ertugliflozin
There is no information regarding the presence of ertugliflozin in human milk, the effects on the breastfed infant, or the effects on milk production. Ertugliflozin is 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 if SEGLUROMET® is used during breastfeeding.

Metformin hydrochloride
Studies in lactating rats show that metformin is excreted into milk and reaches levels comparable to those in plasma. Metformin hydrochloride is also excreted into human breast milk in very small amounts.

7.1.3 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Geriatrics (≥65 years of age): Because aging is associated with reduced renal function and the risk of serious adverse reactions to the drug is greater in patients with impaired renal function, SEGLUROMET® should be used with caution in geriatric patients (see INDICATIONS, DOSAGE AND ADMINISTRATION, and WARNINGS AND PRECAUTIONS, Renal).

Ertugliflozin
A total of 876 (25.7%) patients of 65 years and older, and 152 (4.5%) patients of 75 years and older were exposed to ertugliflozin across the clinical program (see CLINICAL TRIALS). An increased risk of adverse reactions related to volume depletion was seen with ertugliflozin in patients ≥65 years of age (see ADVERSE REACTIONS). Therapeutic experience in patients aged ≥75 years is limited. SEGLUROMET® is expected to have diminished antihyperglycemic efficacy in elderly patients who have impaired renal function (see DOSAGE AND ADMINISTRATION, WARNINGS AND PRECAUTIONS, Renal, and ACTION AND CLINICAL PHARMACOLOGY).

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. 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 CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS, Renal).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

There have been no clinical studies conducted with SEGLUROMET® (ertugliflozin and metformin hydrochloride tablets). SEGLUROMET® tablets demonstrated comparable bioavailability of ertugliflozin and metformin with co-administered tablets of ertugliflozin and metformin in comparative bioavailability studies (see ACTION AND CLINICAL PHARMACOLOGY).

Ertugliflozin
A total of 3409 subjects with type 2 diabetes mellitus were exposed to ertugliflozin in seven Phase 3 clinical trials to evaluate the safety of ertugliflozin alone or in combination with other antidiabetic agents.

The primary assessment of safety and tolerability was conducted in a pooled analysis of three Phase 3 placebo-controlled clinical trials where 1544 subjects were randomized and received at least 1 dose of study medication.

In this data pool, the most frequently (≥10%) adverse reactions reported was female genital mycotic infections. The most common (>1%) adverse reactions were male genital mycotic infections and increased urination. The incidences of serious adverse events and adverse events resulting in discontinuation were similar across groups.

Metformin hydrochloride
Lactic Acidosis: very rare (<1/10,000 and isolated reports) (see WARNINGS AND PRECAUTIONS and OVERDOSAGE). Lactic acidosis is a serious side effect and is fatal in approximately 50% of cases.

Gastrointestinal Reactions: very common (>1/10): Gastrointestinal symptoms (diarrhea, nausea, vomiting, abdominal bloating, flatulence, and anorexia) are the most common reactions to metformin and are approximately 30% more frequent in patients on metformin monotherapy than in placebo-treated patients, particularly during initiation of metformin therapy. These symptoms are generally transient and resolve spontaneously during continued treatment.

Because significant diarrhea and/or vomiting can cause dehydration and prerenal azotemia, SEGLUROMET® should be temporarily discontinued, under such circumstances.

For patients who have been stabilized on metformin, nonspecific gastrointestinal symptoms should not be attributed to therapy unless intercurrent illness or lactic acidosis have been excluded.

Special Senses: common (≥1/100): Taste disturbance, i.e., metallic taste.

Dermatologic Reactions: very rare (<1/10,000 and isolated reports): Reports of skin reactions such as erythema, pruritus, and urticaria are very rare.

Hematologic: Decrease of vitamin B_{12} absorption with decrease of serum levels during long-term use of metformin is rare (≥1/10,000 and <1/1,000). Consideration of such etiology is recommended if a patient presents with megaloblastic anemia.

Hepatic: very rare (<1/10,000 and isolated reports): Liver function tests abnormalities or hepatitis resolving upon metformin discontinuation has been documented in isolated reports.

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Ertugliflozin and Metformin
In a pooled dataset of two 26 weeks placebo-controlled trials, the safety of concomitantly administered ertugliflozin and metformin has been evaluated in 1,083 patients with type 2 diabetes mellitus treated with ertugliflozin as add-on therapy to metformin and as add-on therapy to sitagliptin and metformin (see CLINICAL TRIALS). The incidence and type of adverse reactions in these two trials were similar to the adverse reactions seen with ertugliflozin used in monotherapy. There were no additional adverse reactions identified in the pooling of these two

placebo-controlled trials that included metformin relative to the three placebo-controlled studies with ertugliflozin (see Table 2).

Ertugliflozin

Pool of Placebo-Controlled Trials

In a pooled dataset of the three 26-week, placebo-controlled trials, ertugliflozin was used as monotherapy in one trial and as add-on therapy in two trials (see CLINICAL TRIALS). These data reflect exposure of 1,029 patients to ertugliflozin. Patients received ertugliflozin 5 mg (N=519), ertugliflozin 15 mg (N=510), or placebo (N=515) once daily. Across the treatment arms, the mean age of patients was 57.3 years, 2.1% were 75 years or older and 52.6% of the population was male. The population in these studies was 73.4% White, 6.6% Black or African American, 15.1% Asian; 18.7% were of Hispanic or Latino ethnicity. At baseline, the population had diabetes for an average of 7.5 years and had a mean HbA1c of 8.1%, and 19.4% had established microvascular complications of diabetes. Baseline estimated renal function was normal or mildly impaired in 97% of patients and moderately impaired in 3% of patients (overall mean eGFR 88.9 mL/min/1.73 m^2).

Table 2 summarizes adverse events regardless of causality, excluding hypoglycemia, that occurred in ≥2% of patients receiving ertugliflozin and more commonly than in patients given placebo.

Table 2 – Adverse Events Reported in ≥2% Patients with Type 2 Diabetes Mellitus Treated with Ertugliflozin* and More Frequently than in Patients Treated with Placebo Group

System Organ Class Preferred Term	Number (%) of Patients		
	Ertugliflozin 5 mg N = 519	Ertugliflozin 15 mg N = 510	Placebo N = 515
Infections and Infestations			
Female genital mycotic infections†	9.1%	12.2%	3.0%
Male genital mycotic infections‡	3.7%	4.2%	0.4%
Urinary tract infections§	4.0%	4.1%	3.9%
Nasopharyngitis	2.5%	2.0%	2.3%
Nervous system disorders			
Headache	3.5%	2.9%	2.3%
Musculoskeletal and connective tissue disorders			
Back pain	1.7%	2.5%	2.3%
Renal and urinary disorders			
Increased urination¶	2.7%	2.4%	1.0%
Investigations			
Weight decreased	1.2%	2.4%	1.0%

* 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: pollakiuria, micturition urgency, polyuria, urine output increased, and nocturia.

Description of selected adverse reactions

Ertugliflozin

Diabetic Ketoacidosis: Cases of diabetic ketoacidosis, a serious life-threatening condition requiring urgent hospitalization, have been reported in 3 of 3409 (0.1%) of ertugliflozin-treated patients with T2DM and 0% of comparator-treated patients across the clinical program. SEGLUROMET® is not indicated, and should not be used, in patients with type 1 diabetes. Fatal cases of ketoacidosis have been reported in patients taking SGLT2 inhibitors. In some cases, the presentation of the condition was atypical, with blood glucose levels only moderately elevated (<13.9 mmol/L (250 mg/dL)) (see WARNINGS AND PRECAUTIONS).

Genital Mycotic Infections: In the pool of three placebo-controlled clinical trials, female genital mycotic infections (e.g., genital candidiasis, genital infection fungal, vaginal infection, vulvitis, vulvovaginal candidiasis, vulvovaginal mycotic infection, vulvovaginitis) occurred in 9.1%, 12.2%, and 3.0% of females treated with ertugliflozin 5 mg, ertugliflozin 15 mg, and placebo, respectively. In females, discontinuation due to genital mycotic infections occurred in 0.6% and 0% of patients treated with ertugliflozin and placebo, respectively.

In the same pool, male genital mycotic infections (e.g., balanitis candida, balanoposthitis, genital infection, genital infection fungal) occurred in 3.7%, 4.2%, and 0.4% of males treated with ertugliflozin 5 mg, ertugliflozin 15 mg, and placebo, respectively. Male genital mycotic infections occurred more commonly in uncircumcised males. In males, discontinuations due to genital mycotic infections occurred in 0.2% and 0% of patients treated with ertugliflozin and placebo, respectively. Across the clinical program, phimosis was reported at an incidence of 0.5% in ertugliflozin treated patients, 50% of these male ertugliflozin-treated patients required circumcision.

Hypoglycemia: The incidence of hypoglycemia depended on the type of background therapy used in each study and is shown in Table 3.

Table 3 – Incidence of Overall* and Severe† Hypoglycemia in Placebo-Controlled Clinical Studies

Monotherapy (26 weeks)			
	Ertugliflozin 5 mg (N = 156)	**Ertugliflozin 15 mg (N = 152)**	**Placebo (N = 153)**
Overall [N (%)]	4 (2.6)	4 (2.6)	1 (0.7)
Severe [N (%)]	0 (0.0)	2 (1.3)	0 (0.0)
In Combination with Metformin (26 weeks)			
	Ertugliflozin 5 mg (N = 207)	**Ertugliflozin 15 mg (N = 205)**	**Placebo (N = 209)**
Overall [N (%)]	15 (7.2)	16 (7.8)	9 (4.3)
Severe [N (%)]	1 (0.5)	0 (0.0)	1 (0.5)
In Combination with Metformin and Sitagliptin (26 weeks)			
	Ertugliflozin 5 mg (N = 156)	**Ertugliflozin 15 mg (N = 153)**	**Placebo (N = 153)**
Overall [N (%)]	7 (4.5)	3 (2.0)	5 (3.3)
Severe [N (%)]	1 (0.6)	0 (0.0)	1 (0.7)

* Overall hypoglycemic events: plasma or capillary glucose of less than or equal to 3.89 mmol/L.

† Severe hypoglycemic events: required assistance, lost consciousness, or experienced a seizure regardless of blood glucose.

In a 52-week study comparing the efficacy and safety of ertugliflozin 5 mg or 15 mg versus glimepiride in patients with inadequate glycemic control on metformin alone, treatment with ertugliflozin resulted in a lower proportion of patients with hypoglycemic events compared to glimepiride (5.6% for ertugliflozin 5 mg, 8.2% for ertugliflozin 15 mg, 27.2% for glimepiride). Ertugliflozin treatment also resulted in a lower proportion of severe hypoglycemic events

compared to glimepiride (0.2% for ertugliflozin 5 mg, 0.2% for ertugliflozin 15 mg, 2.3% for glimepiride).

Impairment of Renal Function: Use of ertugliflozin was associated with increases in serum creatinine and decreases in eGFR. Patients with moderate renal impairment at baseline (eGFR 30 to <60 mL/min/1.73m^2) displayed larger mean changes (see ADVERSE REACTIONS, Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data).

Renal-related adverse reactions (e.g., acute kidney injury, renal impairment, acute prerenal failure) may occur in patients treated with ertugliflozin. A higher incidence of renal-related adverse reactions was seen in a study of patients with moderate renal impairment; events were reported by 2.5%, 1.3%, and 0.6% of patients treated with ertugliflozin 5 mg, ertugliflozin 15 mg, and placebo, respectively.

Lower Limb Amputation: Across seven Phase 3 clinical studies in which ertugliflozin was studied as monotherapy and in combination with other antihyperglycemic agents, non-traumatic lower limb amputations occurred 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 remains uncertain (see WARNINGS AND PRECAUTIONS).

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), elderly patients (≥65 years) or patients on diuretics (see WARNINGS AND PRECAUTIONS). In the pool of three placebo-controlled clinical trials, adverse reactions related to volume depletion (e.g., dehydration, dizziness postural, presyncope, syncope, hypotension, and orthostatic hypotension) were reported by 0.8%, 1.0%, and 1.7% of patients treated with ertugliflozin 5 mg, ertugliflozin 15 mg, and placebo, respectively. A higher incidence was seen in a study of patients with moderate renal impairment (eGFR <60 mL/min/1.73 m^2); events were reported by 4.4%, 1.9%, and 0% of patients treated with ertugliflozin 5 mg, ertugliflozin 15 mg, and placebo, respectively. The incidence of volume depletion was increased in patients ≥65 years of age across the clinical trial program, with adverse events reported for 2.2%, 2.6%, and 1.1% of patients treated with ertugliflozin 5 mg, 15 mg, and placebo/comparator, respectively.

8.3 Less Common Clinical Trial Adverse Reactions (<2%)[1]

Ertugliflozin
General disorders and administration site conditions: thirst[2]
Reproductive system and breast disorders: pruritus genital, vulvovaginal pruritus

1 Based on medical assessment (including biological plausibility/mechanism of action/dose response) of adverse events reported in <2% of subjects in the 3-study placebo-controlled pool.
2 Includes thirst and polydipsia

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Ertugliflozin

Increases in Hemoglobin: In the pool of three placebo-controlled trials, hemoglobin increases with ertugliflozin were observed. Mean changes (percent changes) from baseline in hemoglobin were 3.5%, 3.5% and -1.4% for ertugliflozin 5 mg, ertugliflozin 15 mg, and placebo, respectively. Elevations of hemoglobin above the upper limit of normal occurred more frequently in patients receiving ertugliflozin than in those receiving placebo (1.5%, 0.7% and 0.0% for ertugliflozin 5 mg, 15 mg, and placebo, respectively).

Increases in Lipids: In the pool of three placebo-controlled trials, dose-related increases in LDL-C and total cholesterol were observed in patients treated with ertugliflozin. Mean percent changes from baseline in LDL-C relative to placebo were 2.6% and 5.4% with ertugliflozin 5 mg and ertugliflozin 15 mg, respectively. Increases in total cholesterol of 1.5% and 4.0% were seen, relative to placebo, for ertugliflozin 5 mg and ertugliflozin 15 mg, respectively. Small non-dose dependent increases were also seen in HDL-C and small decreases were seen in triglyceride levels for both ertugliflozin groups relative to placebo group.

Increases in Serum Creatinine, Decreases in eGFR and Increases in Blood Urea Nitrogen (BUN): In the pool of three placebo-controlled clinical trials, mean changes from baseline for creatinine (μmol/L) at 6 weeks were 2.41 and 2.76 for ertugliflozin 5 mg and 15 mg, respectively, compared to 0.24 for placebo. At 26 weeks, mean changes from baseline for creatinine were -0.08 and 0.80 for ertugliflozin 5 mg and 15 mg, respectively, compared to -0.57 for placebo.

At 6 weeks, mean changes from baseline for eGFR (mL/min/1.73 m^2) were -2.7 and -3.1 for ertugliflozin 5 mg and 15 mg, respectively, compared to -0.3 for placebo. Mean changes from baseline for eGFR at 26 weeks were 0.5 and -0.6 for ertugliflozin 5 mg and 15 mg, respectively, compared to 0.7 for placebo.

Patients with moderate renal impairment at baseline had larger mean changes in both serum creatinine and eGFR. At 6 weeks, mean changes from baseline for creatinine (μmol/L) were 9.4 and 10.2 for ertugliflozin 5 mg and 15 mg, respectively, compared to -1.4 for placebo. At 26 weeks, mean changes from baseline for creatinine were 7.2 and 9.0 for ertugliflozin 5 mg and 15 mg, respectively, compared to 1.8 for placebo.

At 6 weeks, mean changes from baseline for eGFR (mL/min/1.73 m^2) were -3.2 and -4.1 for ertugliflozin 5 mg and 15 mg, respectively, compared to 0.6 for placebo. Mean changes from baseline for eGFR at 26 weeks were -2.7 and -2.6 for ertugliflozin 5 mg and 15 mg, respectively, compared to 0.0 for placebo.

These changes were observed to reverse after treatment discontinuation.

In the pool of three placebo-controlled trials, mean percent increases from baseline in BUN were 13.2% and 17.0% for ertugliflozin 5 mg and ertugliflozin 15 mg, respectively, compared to 5.9%

for placebo. The proportion of subjects having any occurrence of BUN values ≥50% increase and value >ULN was numerically higher in the ertugliflozin groups (8.8%) relative to the placebo group (5.1%).

Increases in Serum Phosphate: In the pool of three placebo-controlled trials, percent changes from baseline in serum phosphate were 6.8%, 8.5%, and 1.9% with ertugliflozin 5 mg, ertugliflozin 15 mg, and placebo. Elevations of serum phosphate above the upper limit of normal and greater than 0.5 mg/dL occurred more frequently in patients receiving ertugliflozin than in those receiving placebo (5.1%, 5.3% and 1.6% for ertugliflozin 5 mg, 15 mg, and placebo, respectively). In a clinical trial of patients with moderate renal impairment, percent changes from baseline at Week 26 in serum phosphate were 9.7% with ertugliflozin 5 mg, 7.8% with ertugliflozin 15 mg, and 0.8% with placebo.

Metformin hydrochloride
During controlled clinical trials of 29 weeks duration, approximately 9% of patients on metformin monotherapy developed asymptomatic subnormal serum vitamin B_{12} levels; serum folic acid levels did not decrease significantly. Five cases of megaloblastic anemia have been reported with metformin administration and no increased incidence of neuropathy has been observed. However, serious cases of peripheral neuropathy have been reported with metformin treatment in the post-marketing experience in patients with vitamin B_{12} deficiency (see WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS, Post-Market Adverse Reactions).

8.5 Clinical Trial Adverse Reactions (Pediatrics)

Not applicable.

8.6 Post-Market Adverse Reactions

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.

Ertugliflozin
Not applicable

Metformin hydrochloride
Blood and Lymphatic System Disorders: hemolytic anemia, some with a fatal outcome (see WARNINGS AND PRECAUTIONS)
Gastrointestinal Disorders: abdominal discomfort, abdominal distension, abdominal pain, abdominal pain upper, constipation, diarrhea, dry mouth, dyspepsia, flatulence, gastric disorder, gastric ulcer, gastrointestinal disorder, nausea, vomiting
Hepatobiliary Disorders: liver function tests abnormalities or hepatitis resolving upon metformin discontinuation, autoimmune hepatitis, drug-induced liver injury, hepatitis, pancreatitis (see WARNINGS AND PRECAUTIONS)

Investigations: blood lactic acid increased; reduction of thyrotropin level in patients with treated or untreated hypothyroidism (see WARNINGS AND PRECAUTIONS)
Metabolism and Nutrition Disorders: lactic acidosis, decrease of vitamin B_{12} absorption with decrease of serum levels during long-term use of metformin, weight decreased, decreased appetite; peripheral neuropathy in patients with vitamin B_{12} deficiency (see WARNINGS AND PRECAUTIONS); hypomagnesemia in the context of diarrhea
Nervous System Disorders: encephalopathy (see WARNINGS AND PRECAUTIONS)
Skin and Subcutaneous Tissue Disorders: photosensitivity, erythema, pruritus, rash, skin lesion, urticaria

9 DRUG INTERACTIONS

9.1 Overview

Ertugliflozin and metformin hydrochloride
Specific pharmacokinetic drug interaction studies with SEGLUROMET® have not been performed; however, such studies have been conducted with the individual ertugliflozin and metformin components of SEGLUROMET®.

***In Vitro* Assessment of Drug Interactions:**
Ertugliflozin
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 (IC50 >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:**
Metformin hydrochloride
In healthy volunteers, the pharmacokinetics of propranolol and ibuprofen were not affected by metformin when co-administered in single-dose interaction studies.

Metformin is negligibly bound to plasma proteins and is, therefore, less likely to interact with highly protein-bound drugs such as salicylates, sulfonamides, chloramphenicol, and probenecid, as compared to sulfonylureas, which are extensively bound to serum proteins.

9.2 Drug-Drug Interactions

Ertugliflozin
No clinically significant pharmacokinetic interaction was seen when ertugliflozin was co-administered with metformin (OCT2), sitagliptin (OAT3), glimepiride (CYP2C9), or simvastatin (CYP3A4, OATP1B1, OATP1B3 substrate).

Pharmacokinetic interactions
Effects of other co-administered drugs on ertugliflozin
The effects of co-administered drugs on the pharmacokinetics of ertugliflozin have been assessed in drug-drug interaction studies. Ertugliflozin pharmacokinetics were similar with and without co-administration of metformin, glimepiride, sitagliptin, and simvastatin in healthy subjects (see Table 4).

Co-administration 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.

Table 4 – Effects of Other Drugs on the Pharmacokinetics of Ertugliflozin

Co-administered drug	Dose of co-administered drug	Dose of ertugliflozin	Geometric mean ratio (ratio with/without co-administered drug); No effect=100%		Clinical comment
			AUC (90% CI)	C_{max} (90% CI)	
Metformin	1000 mg, single dose	15 mg, single dose	100.34% (97.43%, 103.34%)	97.14% (88.77%, 106.30%)	No dosage adjustment needed
Sitagliptin	100 mg, single dose	15 mg, single dose	102.27% (99.72%, 104.89%)	98.18% (91.20%, 105.70%)	No dosage adjustment needed
Glimepiride	1 mg, single dose	15 mg, single dose	102.11% (97.19%, 107.27%)	98.20% (92.17%, 104.63%)	No dosage adjustment needed
Simvastatin	40 mg, single dose	15 mg, single dose	102.40% (99.57%, 105.31%)	105.16% (98.26%, 112.54%)	No dosage adjustment needed
Rifampin	600 mg q.d. x 10 days	15 mg, single (dosed on Day 8)	61.16% (57.22%, 65.37%)	84.62% (74.17%, 96.53%)	No dosage adjustment needed

Effects of ertugliflozin on other co-administered drugs
The effects of ertugliflozin on the pharmacokinetics of co-administered drugs have been assessed in drug-drug interaction studies. Ertugliflozin had no clinically relevant effect on the pharmacokinetics of metformin, glimepiride, sitagliptin, and simvastatin when co-administered in healthy subjects (see Table 5)

Physiologically-based PK (PBPK) modeling suggests that co-administration 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 of ertugliflozin are not expected to be clinically relevant.

Table 5 – Effects of Ertugliflozin on the Pharmacokinetics of Other Drugs

Co-administered drug	Dose of co-administered drug	Dose of ertugliflozin	Geometric mean ratio (ratio with/without co-administered drug); No effect=100%		Clinical comment
			AUC (90% CI)	C_{max} (90% CI)	
Metformin	1000 mg, single dose	15 mg, single dose	100.94% (90.62%, 112.44%)	94.00% (82.94%, 106.55%)	No dosage adjustment needed
Sitagliptin	100 mg, single dose	15 mg, single dose	101.67% (98.40%, 105.04%)	101.68% (91.65%, 112.80%)	No dosage adjustment needed
Glimepiride	1 mg, single dose	15 mg, single dose	109.80% (98.14%, 122.86%)	97.39% (71.07%, 133.46%)	No dosage adjustment needed
Simvastatin	40 mg, single dose	15 mg, single dose	123.83% (90.92%, 168.66%)	119.05% (97.22%, 145.77%)	No dosage adjustment needed
			Simvastatin acid: 130.46% (108.32%, 157.13%)	Simvastatin acid: 115.66% (95.74%, 139.71%)	

Pharmacodynamic interactions

Diuretics: Ertugliflozin may add to the diuretic effect of diuretics and may increase the risk of dehydration and hypotension. Caution is recommended when SEGLUROMET® is co-administered with diuretics; particularly loop diuretics (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION).

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.

Glyburide: In a single-dose interaction study in type 2 diabetes patients, co-administration of metformin and glyburide did not result in any changes in either metformin pharmacokinetics or pharmacodynamics. Decreases in glyburide AUC and C_{max} were observed, but were highly variable. The single-dose nature of this study and the lack of correlation between glyburide blood levels and pharmacodynamic effects make the clinical significance of this interaction uncertain.

Furosemide: A single-dose, metformin-furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by co-administration. Furosemide increased the metformin plasma and blood C_{max} by 22% and blood AUC by 15%, without any significant change in metformin renal clearance. When administered with metformin, the C_{max} and AUC of furosemide were 31% and 12% smaller, respectively, than when administered alone, and the terminal half-life was decreased by 32%, without any

significant change in furosemide renal clearance. No information is available about the interaction of metformin and furosemide when co-administered chronically.

Nifedipine: A single-dose, metformin-nifedipine drug interaction study in normal healthy volunteers demonstrated that co-administration of nifedipine increased plasma metformin C_{max} and AUC by 20% and 9%, respectively, and increased the amount excreted in the urine. T_{max} and half-life were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine.

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 WARNINGS AND PRECAUTIONS). In both single- and multiple-dose metformin-cimetidine drug interaction studies, there was a 60% increase in peak metformin plasma and whole blood concentrations and a 40% increase in plasma and whole blood metformin AUC. There was no change in elimination half-life in the single-dose study. Metformin had no effect on cimetidine pharmacokinetics. Close monitoring of glycemic control, dose adjustment within the recommended posology and changes in diabetic treatment should be considered when such products are co-administered.

Levothyroxine: Levothyroxine can reduce the hypoglycemic effect of metformin. Monitoring of blood glucose levels is recommended, especially when thyroid hormone therapy is initiated, changed, or stopped (see WARNINGS AND PRECAUTIONS), and SEGLUROMET™ dosage adjusted as necessary.

Anticoagulant: Elimination rate of the anticoagulant phenprocoumon has been reported to be increased by 20% when used concurrently with metformin. Therefore, a close monitoring of the International Normalized Ratio (INR) is recommended in patients concurrently administering metformin and phenprocoumon or other antivitamin K anticoagulants (see WARNINGS AND PRECAUTIONS). In such cases, an important increase of prothrombin time may occur upon cessation of SEGLUROMET® therapy, with an increased risk of hemorrhage.

Other: Other drugs tend to produce hyperglycemia and may lead to a loss of blood sugar control. These include thiazide and other diuretics, corticosteroids, phenothiazines, thyroid hormone replacement drugs e.g. levothyroxine, estrogens, estrogen plus progestogen, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, isoniazid, and beta-2-agonists.

ACE-inhibitors may decrease the blood glucose levels. When such drugs are administered to patients receiving SEGLUROMET®, the patient should be closely observed to maintain adequate glycemic control.

Diuretics, especially loop diuretics, may increase the risk of lactic acidosis due to their potential to decrease renal function (see DOSAGE AND ADMINISTRATION).

9.3 Drug-Food Interactions

Administration of SEGLUROMET® with a high-fat and high-calorie meal decreases ertugliflozin C_{max} by 41% and prolongs T_{max} by 1 hour. Food reduced mean metformin C_{max} by 29% but had no meaningful effect on AUC_{inf} of ertugliflozin and metformin compared to the fasted condition. The observed effect of food on ertugliflozin and metformin pharmacokinetics is not considered clinically relevant.

9.4 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.5 Drug-Laboratory Test Interactions

Ertugliflozin
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 SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

Metformin hydrochloride
Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

9.6 Drug-Lifestyle Interactions

Effects of Smoking, Alcohol, and Diet
The effects of smoking, diet, and alcohol use on the pharmacokinetics of SEGLUROMET® have not been specifically studied.

Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking SEGLUROMET®, since alcohol intake potentiates the effect of metformin on lactate metabolism (see CONTRAINDICATIONS). The risk of lactic acidosis is increased in acute alcohol intoxication, particularly in case of fasting or malnutrition or hepatic insufficiency. It is recommended that consumption of alcohol and alcohol-containing medicinal product be avoided.

Effects on Ability to Drive and Use Machines
No formal studies have been conducted with SEGLUROMET® on the effects on the ability to drive and use machines. However, patients should be alerted to the elevated risk of adverse

reactions related to reduced intravascular volume, such as postural dizziness (see DOSAGE AND ADMINISTRATION, WARNINGS AND PRECAUTIONS, and ADVERSE REACTIONS).

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Ertugliflozin and metformin hydrochloride
SEGLUROMET® combines two antihyperglycemic agents with complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes: ertugliflozin, a sodium-glucose co-transporter (SGLT2) inhibitor, and metformin hydrochloride, a member of the biguanide class.

Ertugliflozin
Sodium-glucose co-transporter 2 (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 a biguanide derivative producing an antihyperglycemic effect which can only be observed in man or in the diabetic animal and only when there is insulin secretion. Metformin, at therapeutic doses, does not cause hypoglycemia when used alone in man or in the non-diabetic animal, except when using a near lethal dose. Metformin has no effects on the pancreatic beta cells. The mode of action of metformin is not fully understood. It has been postulated that metformin might potentiate the effect of insulin or that it might enhance the effect of insulin on the peripheral receptor site. This increased sensitivity seems to follow an increase in the number of insulin receptors on cell surface membranes.

10.2 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 T2DM 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
In a randomized, placebo- and positive-controlled, crossover study in 42 healthy subjects, there was no evidence of a treatment-related effect on the QTcF interval, the QRS duration, the PR interval, or ventricular heart rate with a single supratherapeutic oral dose of ertugliflozin 100 mg (6.7 times the maximum recommended dose).

Metformin hydrochloride
Few data are available on the relationship between pharmacodynamics and pharmacokinetics, and therefore the effect of metformin on glucose control cannot be predicted from pharmacokinetic data alone. Tissue concentrations of metformin in the dual target sites of the liver and muscle appear to be more informative, and the deep metformin compartment supplying these tissues is critical and related to plasma concentrations. This view substantiates the clinical observation that the glucose-lowering action of metformin takes time to be fully expressed and also that activity is not lost immediately on drug withdrawal.

10.3 Pharmacokinetics

Ertugliflozin and metformin hydrochloride
SEGLUROMET® has been shown to be bioequivalent to co-administration of corresponding doses of ertugliflozin and metformin tablets.

Ertugliflozin
The pharmacokinetics of ertugliflozin are similar in healthy subjects and patients with T2DM. Based on the population PK analysis, a T2DM patient had ~9% lower CL/F relative to a healthy subject, which is not considered clinically meaningful. 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 1193 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.

Table 6 – Summary of Ertugliflozin Pharmacokinetic Parameters in Healthy Subjects at Steady State

Ertugliflozin Dose	C_{max}[1]	AUC_{τ}[1]	T_{max}[1]
5 mg, multiple dose	81.3 ng/mL	398 ng·hr/mL	1 hour
15 mg, multiple dose	268 ng/mL	1,193 ng·hr/mL	

[1] Steady state with once daily dosing, healthy subjects

The 24-hour UGE values at steady state were similar between the 7.5 mg twice daily and 15 mg once daily dose, 2.5 mg twice daily and 5 mg once daily dose, suggesting no meaningful pharmacodynamics differences for the twice daily vs corresponding once daily doses. The mean systemic exposure (AUC) at steady state was similar following once daily and twice daily dosing regimens at the same total daily dose of 5 mg or 15 mg.

Absorption:
Ertugliflozin and metformin hydrochloride
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. Food delayed the ertugliflozin T_{max} from 1.5 to 2.5 hours and also, the metformin T_{max} from 2.25 to 4.0 hours.

Ertugliflozin
Following single-dose oral administration of 5 mg and 15 mg of ertugliflozin, peak plasma concentrations (median T_{max}) of ertugliflozin occur at 1 hour post-dose under fasted conditions. Plasma C_{max} and AUC of ertugliflozin increase in a dose-proportional manner following single doses from 0.5 mg to 300 mg and following multiple doses from 1 mg to 100 mg. The absolute oral bioavailability of ertugliflozin following administration of a 15 mg dose is approximately 100%.

Metformin hydrochloride
Metformin absorption is relatively slow and may extend over about 6 hours.

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
Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean volume of distribution (Vd) ranged between 63-276 L.

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
Metformin is not metabolized. Its main sites of concentration are the intestinal mucosa and the salivary glands. The plasma concentration at steady state ranges about 1 to 2 mcg/mL. Certain drugs may potentiate the effects of metformin (see WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS).

Elimination:
Ertugliflozin
The mean systemic plasma clearance following an intravenous 100 µg dose was 11.2 L/hr. The mean elimination half-life in T2DM 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
The drug is excreted in urine at high renal clearance rate of about 450 mL/min. The initial elimination of metformin is rapid with a half-life varying between 1.7 and 3 hours. The terminal elimination phase accounting for about 4 to 5% of the absorbed dose is slow with a half-life between 9 and 17 hours.

Special Populations and Conditions

Pediatrics: No studies with SEGLUROMET® have been performed in pediatric patients.

Geriatrics:
Ertugliflozin
Based on a population pharmacokinetic analysis, age does not have a clinically meaningful effect on the pharmacokinetics of ertugliflozin. Relative to the ≥45 and <55 ages for the ertugliflozin 5 and 15 mg once-daily doses, median AUCτ changed by <14% across all other ages (<45 and >55 years). However, across clinical studies, patients 65 years and older had a higher incidence of adverse reactions related to volume depletion compared to younger patients treated with SEGLUROMET® (see DOSAGE AND ADMINISTRATION, WARNINGS AND PRECAUTIONS, and ADVERSE REACTIONS).

Metformin hydrochloride
Controlled clinical studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients.

Gender:
Ertugliflozin
Based on a population pharmacokinetic analysis, gender does not have a clinically meaningful effect on the pharmacokinetics of ertugliflozin. The geometric mean exposure in females was 4% higher compared to males and is not considered clinically meaningful.

Ethnic Origin:
Ertugliflozin
Based on a population pharmacokinetic analysis, race does not have a clinically meaningful effect on the pharmacokinetics of ertugliflozin. The geometric mean exposure in African American patients was comparable to Caucasian patients. The geometric mean exposure in Asian patients was 7% lower compared to Caucasian patients when matched with covariates such as baseline body weight, baseline eGFR and is not considered clinically meaningful.

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.

Metformin hydrochloride
No pharmacokinetic studies of metformin have been conducted in patients with hepatic insufficiency.

Renal Impairment:
Ertugliflozin and metformin hydrochloride
Studies characterizing the pharmacokinetics of ertugliflozin and metformin after administration of SEGLUROMET® in renally impaired patients have not been performed (see DOSAGE AND ADMINISTRATION).

Ertugliflozin
In a Phase 1 clinical pharmacology study in patients with T2DM 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 for mild, moderate and severe renally impaired patients respectively, compared to subjects with normal renal function. The C_{max} increased by 1.4-fold in mild and moderate renally impaired subjects and decreased by 0.1-fold in severe renally impaired subjects. These increases in ertugliflozin AUC and changes in C_{max} are not considered clinically relevant. The 24-hour urinary glucose excretion declined with increasing severity of renal impairment (see WARNINGS AND PRECAUTIONS). 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 and WARNINGS AND PRECAUTIONS).

Obesity:
Ertugliflozin
Based on a population pharmacokinetic analysis body weight does not have a clinically meaningful effect on the pharmacokinetics of ertugliflozin. Relative to the approximate median weight (85 kg), body weight over a range of 59.5 kg to 123 kg (representing 5th and 95th percentiles of the observed weights), was estimated to be associated with ≤31% change in AUC_{tau}, which is not considered clinically relevant.

Genetic Polymorphism:
Ertugliflozin
Based on the results of a pooled analysis of AUC values from 20 Phase 1 studies evaluating the impact of UGT1A9 genotype on the pharmacokinetics of ertugliflozin, the effect of the UGT1A9 allelic variants on ertugliflozin AUC was within ±10% of the wild type and is not considered clinically meaningful.

11 STORAGE, STABILITY AND DISPOSAL

Store at 15°C to 30°C. Protect from moisture.

12 SPECIAL HANDLING INSTRUCTIONS

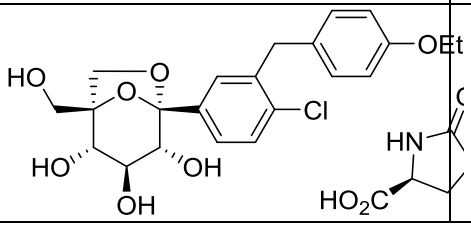
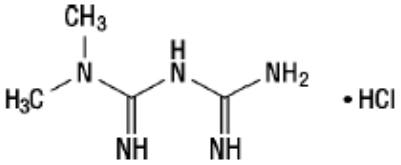
Not applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

SEGLUROMET® contains ertugliflozin (in the form of ertugliflozin co-crystallized with L-pyroglutamic acid), a SGLT2 inhibitor, and metformin hydrochloride, a member of the biguanide class.

	ertugliflozin	metformin
Proper/common name	Ertugliflozin L-pyroglutamic acid	Metformin hydrochloride*
Chemical name	(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	*N*,*N*-dimethylimidodicarbonimidic diamide hydrochloride
Molecular formula	$C_{22}H_{25}ClO_7$ (Ertugliflozin) / $C_{22}H_{25}ClO_7$ with $C_5H_7NO_3$ (Ertugliflozin L-PGA)	$C_4H_{11}N_5$•HCl
Molecular mass	436.88 Daltons (Ertugliflozin) / 566.00 Daltons (Ertugliflozin L-PGA)	165.63**
Structural formula		

Physicochemical properties	Ertugliflozin is co-crystallized with L-pyroglutamic acid (L-PGA) to form a crystalline, white to off-white powder. Due to rapid dissociation of ertugliflozin L-PGA in aqueous media, the thermodynamic aqueous solubility of ertugliflozin L-PGA cannot be determined. However, using ertugliflozin L-PGA as a source of ertugliflozin, the solubility of ertugliflozin in unbuffered water at pH 5.5, simulated gastric fluid without enzyme at pH 1.2 and phosphate buffered saline at pH 6.5 was found to be 0.76, 0.74 and 0.64 mg/mL respectively.	Metformin hydrochloride is a white to off-white crystalline compound. It is freely soluble in water and is practically insoluble in acetone, ether and chloroform. The pKa of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68.

* Metformin hydrochloride is not chemically or pharmacologically related to any other classes of oral antihyperglycemic agents.

** Molecular weight

14 CLINICAL TRIALS

The clinical efficacy studies described below were conducted with individual ertugliflozin and metformin hydrochloride tablets administered together and not with SEGLUROMET® (ertugliflozin and metformin hydrochloride tablets). However, the bioavailability of SEGLUROMET® (ertugliflozin and metformin hydrochloride tablets) is comparable to individual ertugliflozin and metformin hydrochloride tablets administered together at the same respective doses (see ACTION AND CLINICAL PHARMACOLOGY).

Treatment with ertugliflozin in combination with metformin or metformin with sitagliptin produced clinically and statistically significant improvements in HbA1c compared to placebo after 26 weeks of treatment. In a 52 week study, reductions of HbA1c were sustained. In patients with T2DM treated with ertugliflozin, the reduction in HbA1c was generally similar across subgroups defined by age, sex, race, geographic region, baseline body mass index, and duration of disease.

14.1 Trial Design and Study Demographics

Table 7 – Summary of Patient Demographics for Clinical Trials in Specific Indication

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age years (Range)	Gender (%M/F)
Add-on Therapy with Metformin					
P007/1017	Randomised, double-blind, placebo-controlled, multicentre	Ertugliflozin 5 mg or 15 mg vs. placebo Tablets, orally, once daily Main treatment period: 26 weeks	Ertugliflozin 5 mg: 207 Ertugliflozin 15 mg: 205 Placebo: 209	56.6 (24-79)	46.4/53.6
P002/1013	Randomized, double-blind, active-controlled, multicentre	Ertugliflozin 5 mg or 15 mg or Glimepiride titrated up to a maximum dose of 6 or 8 mg/day Tablets, orally, once daily Main treatment period: 52 weeks	Ertugliflozin 5 mg: 448 Ertugliflozin 15 mg: 441 Glimepiride: 437	58.2 (22-86)	48.551.5
Add-on Therapy with Metformin and Sitagliptin					
P006/1015	Randomised, double-blind, placebo-controlled, multicentre	Ertugliflozin 5 mg or 15 mg vs. placebo Tablets, orally, once daily Main treatment period: 26 weeks	Ertugliflozin 5 mg: 156 Ertugliflozin 15 mg: 154 Placebo: 153	59.1 (34-84)	56.9/43.1

14.2 Study Results

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 (≥1500 mg/day for ≥8 weeks) was evaluated for efficacy of ertugliflozin in combination with metformin.

In Study P007/1017, patients were randomized (1:1:1) to receive ertugliflozin 5 mg, ertugliflozin 15 mg or placebo administered once daily in addition to continuation of background metformin therapy. Of the randomized and treated patients, 15% were aged ≥65 to <75 years, and 0.6% were aged ≥75 years. Mean BMI was 30.9 kg/m^2, 66.2% of patients were Caucasian/White, with lesser representation of Asian (16.1%), Black (10.3%), and other races (7.4%). In the study, mean duration of diabetes at screening was 8.0 years.

For the primary endpoint, treatment of ertugliflozin provided statistically significant improvements in HbA1c after 26 weeks of treatment compared to placebo (see Table 8).

Table 8 – Results at Week 26 (cLDA*) from a Placebo-Controlled Study of Ertugliflozin in Add-on Combination with Metformin

Efficacy Parameter	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Placebo + Metformin
N (FAS)	207	205	209
HbA1c (%)			
Baseline (mean)	8.1	8.1	8.2
Change from baseline (LS mean†)	-0.73	-0.91	-0.03
Difference from placebo (LS mean†, 95% CI)	-0.7‡ (-0.87, -0.53)	-0.88‡ (-1.05, -0.71)	
Patients (%) with HbA1c <7%	35.3§	40.0§	15.8
N (FAS)	207	205	209
FPG (mmol/L)			
Baseline (mean)	9.3	9.3	9.4
Change from baseline (LS mean†)	-1.53	-2.17	-0.05
Difference from placebo (LS mean†, 95% CI)	-1.48‡ (-1.83, -1.14)	-2.12 ‡ (-2.47, -1.78)	
N (FAS)	207	205	209
Body Weight (kg)			
Baseline (mean)	84.9	85.3	84.5
Change from baseline (LS mean†)	-3.01	-2.93	-1.3
Difference from placebo (LS mean†, 95% CI)	-1.67‡ (-2.24, -1.11)	-1.60‡ (-2.16, -1.03)	

* cLDA = constrained longitudinal data analysis; FAS = full analysis set; N = includes all randomized, treated patients who had at least one measurement of the outcome variable.

† Least squares means adjusted for treatment, time, prior antihyperglycemic medication (metformin monotherapy or metformin + another AHA), baseline eGFR (continuous), menopausal status randomization stratum (men, premenopausal women, women who are perimenopausal or <3 years postmenopausal, women who are ≥3 years postmenopausal) and the interaction of time by treatment.

‡ p<0.001 compared to placebo.

§ p<0.001 compared to placebo (based on adjusted odds ratio comparisons from a logistic regression model using multiple imputation for missing data values).

Statistically significant (p<0.001) reductions in systolic blood pressure were observed with ertugliflozin 5 mg and 15 mg, -3.3 mmHg and -3.8 mmHg, respectively, relative to placebo.

Add-on Combination Therapy with Metformin -
Active-Controlled Study of Ertugliflozin versus Glimepiride

A total of 1326 patients with type 2 diabetes mellitus inadequately controlled (HbA1c between 7% and 9%) on metformin monotherapy was evaluated for efficacy of ertugliflozin in combination with metformin.

In Study P002/1013, these patients, who were receiving metformin monotherapy (≥1500 mg/day for ≥8 weeks), were randomized (1:1:1) to receive ertugliflozin 5 mg, ertugliflozin 15 mg or glimepiride 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 or a maximum tolerated dose or down-titrated to avoid or manage hypoglycemia. The mean daily dose of glimepiride was 3 mg. Of randomized and treated patients 21.6% were aged ≥65 to <75 years, and 3.8% were aged ≥75 years. Mean BMI was 31.4 kg/m^2, 72.9% of patients were Caucasian/White, with lesser representation of Asian (18.0%), Black (4.6%), and other races (4.5%). In the study, mean duration of diabetes at screening was 7.5 years.

For the primary endpoint, only treatment with ertugliflozin at 15 mg daily was non-inferior to glimepiride after 52 weeks of treatment (see Table 9).

Table 9 – Results at Week 52 (cLDA)* from an Active-Controlled Study Comparing Ertugliflozin to Glimepiride as Add-on Therapy to Metformin

Efficacy Parameter	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Glimepiride + Metformin
N (FAS)	448	440	437
HbA1c (%)			
Baseline (mean)	7.8	7.8	7.8
Change from baseline (LS mean†)	-0.56	-0.64	-0.74
Difference from glimepiride (LS mean†, 95% CI)	0.18 (0.06, 0.30)	0.10‡ (-0.02, 0.22)	
Patients (%) with HbA1c <7%**	34.4	38.0	43.5
N (FAS)	448	440	437
Body Weight (kg)			
Baseline (mean)	87.9	85.6	86.8
Change from baseline (LS mean†)	-2.96	-3.38	0.91
Difference from glimepiride (LS mean†, 95% CI)	3.87 (-4.36, -3.38)	4.29§ (-4.77, -3.80)	

* cLDA = constrained longitudinal data analysis; FAS = full analysis set; N = includes all randomized, treated patients who had at least one measurement of the outcome variable.

** Statistical tests for this endpoint were not included in the multiplicity scheme.

† Least squares means adjusted for treatment, time, prior antihyperglycemic medication (monotherapy or dual therapy), baseline eGFR (continuous) and the interaction of time by treatment. Time was treated as a categorical variable.

‡ 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%.

§ p<0.001 compared to glimepiride.

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 (≥1500 mg/day for ≥8 weeks) and sitagliptin 100 mg once daily was evaluated for efficacy of ertugliflozin in combination with metformin and sitagliptin.

In Study P006/1015, patients were randomized (1:1:1) to receive ertugliflozin 5 mg, ertugliflozin 15 mg, or placebo administered once daily in addition to continuation of background metformin and sitagliptin therapy. Of randomized and treated patients, 27.1% were aged ≥65 to <75 years, and 2.8% were aged ≥75 years. Mean BMI was 30.8 kg/m^2, 72.9% of patients were Caucasian/White, with lesser representation of Asian (20.3%), Black (1.9%), and other races (4.8%). In the study, mean duration of diabetes at screening was 9.5 years.

For the primary endpoint, treatment of ertugliflozin provided statistically significant improvements in HbA1c after 26 weeks of treatment compared to placebo (see Table 10).

Table 10 – Results of a 26-Week (cLDA)* Placebo-Controlled Study of Ertugliflozin in Add-on Combination Therapy to Metformin and Sitagliptin

Efficacy Parameter	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Placebo + Metformin/ Sitagliptin
N (FAS)	156	153	153
HbA1c (%)			
Baseline (mean)	8.1	8.0	8.0
Change from baseline (LS mean†)	-0.78	-0.86	-0.09
Difference from placebo (LS mean†, 95% CI)	-0.69‡ (-0.87, -0.5)	-0.76‡ (-0.95, -0.58)	
Patients (%) with HbA1c <7%	32.1§	39.9§	17.0
N (FAS)	156	153	156
FPG (mmol/mL)			
Baseline (mean)	9.3	9.5	9.4
Change from baseline (LS mean†)	-1.49	-1.83	-0.10
Difference from placebo (LS mean†, 95% CI)	-1.40‡ (-1.82, -0.97)	-1.74‡ (-2.16, -1.31)	
N (FAS)	156	153	156
Body Weight (kg)			
Baseline (mean)	87.6	86.6	86.5
Change from baseline (LS mean†)	-3.35	-3.04	-1.32
Difference from placebo (LS mean†, 95% CI)	-2.03‡ (-2.65, -1.40)	-1.72‡ (-2.35, -1.09)	

* cLDA = constrained longitudinal data analysis; FAS = full analysis set; N = includes all randomized, treated patients who had at least one measurement of the outcome variable.

† Least squares means adjusted for treatment, time, prior antihyperglycemic medication.

‡ p<0.001 compared to placebo.

§ p<0.001 compared to placebo (based on adjusted odds ratio comparisons from a logistic regression model using multiple imputation for missing data values).

Statistically significant (p<0.001) reductions in systolic blood pressure were observed with ertugliflozin 5 mg and 15 mg, -3.7 mmHg and -4.3 mmHg, respectively, relative to placebo.

15 MICROBIOLOGY

Not applicable.

16 NON-CLINICAL TOXICOLOGY

General Toxicology
No animal studies have been conducted with the combined products in SEGLUROMET® to evaluate carcinogenesis, mutagenesis, or impairment of fertility.

Acute Toxicity
Ertugliflozin
Single doses of ertugliflozin were well tolerated in male and female Beagle dogs at 5 or 50 mg/kg (approximately 180 times human exposure at the maximum recommended human dose (MRHD) of 15 mg/day based on AUC comparisons). However, the dose of 500 mg/kg resulted in emesis.

Chronic Toxicity
Ertugliflozin
Repeat-dose oral toxicity studies were conducted in mice, rats, and dogs for up to 13, 26, and 39 weeks, respectively. Signs of toxicity that were considered adverse were generally observed at exposures greater than or equal to 47 times the human exposure (AUC) at the MRHD of 15 mg/day. Most toxicity was consistent with pharmacology related to urinary glucose loss and included decreased body weight and body fat, increased food consumption, diarrhea, dehydration, decreased serum glucose and increases in other serum parameters reflective of increased protein metabolism, gluconeogenesis and electrolyte imbalances, and urinary changes such as polyuria, glucosuria, and calciuria. Microscopic changes related to glucosuria and/or calciuria observed only in rodents included, dilatation of renal tubules, hypertrophy of zona glomerulosa in adrenal glands (rats), renal tubular mineralization (rats) and increased trabecular bone (rats). Most of these changes resolved or showed signs of on-going recovery following the 8-week non-dosing recovery period; however, incidences of tubular mineralization remained high in males at the end of the recovery period. There were no adverse toxicity findings in dogs at 379 times the human exposure (AUC) at the MRHD of 15 mg/day.

Carcinogenesis
Ertugliflozin
In the 2-year mouse carcinogenicity study, ertugliflozin was administered by oral gavage at doses of 5, 15, and 40 mg/kg/day. There were no ertugliflozin-related neoplastic findings at doses up to 40 mg/kg/day (approximately 41 times human exposure at the MRHD of 15 mg/day based on AUC). In the 2-year rat carcinogenicity study, ertugliflozin was administered by oral gavage at doses of 1.5, 5, and 15 mg/kg/day. Ertugliflozin-related neoplastic findings included an increased incidence of benign adrenal medullary pheochromocytoma in male rats at 15 mg/kg/day. This finding may be related to carbohydrate malabsorption leading to altered calcium homeostasis, which has been associated with pheochromocytoma 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).

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 1500 mg/kg/day, respectively. These doses are both approximately 4 times the maximum recommended human daily dose of 2000 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.

Reproductive and Developmental Toxicology

Reproduction
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 386 times human exposure at the MRHD of 15 mg/day based on AUC comparisons).

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.

Development
Ertugliflozin
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 239 and 1069 times, respectively, the human exposure at the maximum clinical dose of 15 mg/day, based on AUC. At a maternally toxic dose in rats (250 mg/kg/day), lower fetal viability, lower maternal body weight, a higher incidence of a visceral malformation (membranous ventricular septal defect) and skeletal variations were observed at maternal exposure that was 510 times the human exposure at the 15 mg/day maximum clinical dose. In the

pre- and post-natal development study, decreased post-natal growth and development were observed in rats administered ertugliflozin gestation day 6 through lactation day 21 at ≥100 mg/kg/day (estimated 239 times the human exposure at the maximum clinical dose of 15 mg/day, based on AUC).

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 the human exposure at the maximum clinical dose of 15 mg/day, based on AUC). These effects did not fully reverse within the 1 month recovery period. Following the 4-week non-dosing recovery period, there was no recovery of kidney mineralization. These effects occurred with drug exposure during periods in rats that correspond to the late second and third trimester of human renal development. Similar effects were seen in adult mice and rats.

Metformin hydrochloride
Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day. This represents an exposure of about 2 times the maximum recommended human daily dose of 2000 mg based on body surface area comparisons for rats and rabbits, respectively. Determination of fetal concentrations demonstrated a partial placental barrier to metformin.

17 SUPPORTING PRODUCT MONOGRAPHS

1. GLUCOPHAGE* tablets 500 mg, 850 mg, Submission Control No. 211582, Product Monograph, Sanofi-Aventis Canada Inc. (Mar 2, 2018)

2. JANUMET® tablets 50 mg/500 mg, 50 mg/850 mg and 50 mg/1000 mg tablets and JANUMET® XR 50 mg/500 mg, 50 mg/1000 mg, and 100 mg/1000 mg tablets, Submission Control No. 211798, Product Monograph, Merck Canada Inc. (Nov 2, 2018)

* All other trademarks are the property of their respective owner(s).

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

Segluromet®

ertugliflozin and metformin hydrochloride tablets

Read this carefully before you start taking **Segluromet®** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Segluromet®**.

Serious Warnings and Precautions

Lactic Acidosis

Lactic acidosis is a rare but serious buildup of acid in the blood. It can cause death. It must be treated in the hospital. Segluromet® contains a drug called metformin hydrochloride. If you build up too much metformin in your blood you are at risk for lactic acidosis.

Alcohol increases the risk of lactic acidosis caused by metformin. Do not "binge" drink or drink alcohol often when you are taking Segluromet®.

Diabetic Ketoacidosis

Diabetic ketoacidosis (DKA) can happen while you are taking Segluromet®. It is a serious and life-threatening condition. Some cases of **DKA** can lead to death. It needs urgent hospital care. **DKA** can happen to diabetic patients with normal or high blood sugar levels. In **DKA** your body produces high levels of blood acids called ketones. It occurs when your body can not produce enough insulin.

Seek medical attention and **stop taking Segluromet® right away** if you have any of the **DKA** symptoms. Do this even if your blood sugar levels are normal. The symptoms of **DKA** are: difficult breathing, nausea, vomiting, stomach pain, and loss of appetite. Confusion, thirst, unusual fatigue, sleepiness or tiredness, along with a sweet or metallic taste in the mouth or sweet smelling breath can be noticed. You may have a different odour to your urine or sweat.

Do not use Segluromet® if you have type 1diabetes. It is a disease where your body does not produce any insulin.

Do not use Segluromet® if you have a history of **DKA**.

What is Segluromet® used for?
Segluromet® is used with diet and exercise. It is used to improve blood sugar (glucose) levels in adults with type 2 diabetes.

Segluromet® can be used:
- when blood sugar is not controlled on metformin, or
- when blood sugar is already controlled on ertugliflozin and metformin, as individual drugs, or
- with sitagliptin, when blood sugar is not controlled on metformin and sitagliptin, or
- when blood sugar is already controlled on ertugliflozin, metformin and sitagliptin, as individual drugs.

How does Segluromet® work?
Segluromet® is a tablet. It contains two medicines. They are ertugliflozin and metformin hydrochloride. They work together to reduce the amount of sugar in your blood:
- ertugliflozin helps remove sugar from the body through the urine
- metformin helps to lower the amount of sugar made by the liver

What are the ingredients in Segluromet®?
- Medicinal ingredients: **ertugliflozin** (in the form of ertugliflozin co-crystallized with L-pyroglutamic acid) and **metformin hydrochloride**.
- Non-medicinal ingredients: carnauba wax, crospovidone, hydroxypropyl cellulose, hypromellose, iron oxide red, magnesium stearate, microcrystalline cellulose, povidone, sodium lauryl sulfate and titanium dioxide.

Segluromet® comes in the following dosage forms:
Tablets: 2.5 mg/500 mg, 2.5 mg/1000 mg, 7.5 mg/500 mg, 7.5 mg/1000 mg of ertugliflozin/metformin hydrochloride.

Do not use Segluromet® if you:
- are allergic to any of its ingredients;
- have severe kidney disease. Have end-stage kidney disease or are on dialysis. If you have moderate kidney problems, talk to your health care professional before you take Segluromet®;
- have liver problems;
- are experiencing a loss of fluids from the body for any reason (severe dehydration). This could be due to excess heat exposure, vomiting or diarrhea. It can be due to reduced drinking with illness or fasting;
- drink alcohol very often, or drink a lot of alcohol in the short term ("binge" drinking);
- have severe heart problems or heart failure;
- have a lack of oxygen in the blood. This is called hypoxemia. This can happen when you have conditions that affect your heart or breathing;
- have a severe infection, are experiencing trauma, are about to have surgery, or are recovering from surgery;
- have severe **dehydration** or shock;

- are pregnant or planning to become pregnant. It is not known if Segluromet® may harm your unborn baby. If you are pregnant, talk with your doctor about the best way to control your blood sugar while you are pregnant;
- are breast-feeding or plan to breast-feed. It is not known if Segluromet® passes into breast milk. Talk with your doctor if you would like to breast-feed;
- are going to receive an injection of dye or a contrast agent for an x-ray procedure. Talk to your physician or pharmacist about when to stop Segluromet® and when to start again.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Segluromet®. Talk about any health conditions or problems you may have, including if you:

- are older than 65 years of age;
- have kidney problems;
  You have a higher chance of having **Kidney problems**, if you:
  - are dehydrated or suffer from excessive vomiting, diarrhea, or sweating;
  - are not eating and drinking as per your normal diet. For example, you are fasting or ill.
  - have existing kidney issues;
  - have heart failure;
  - take or change other medications such as a diuretic, blood pressure pill or an NSAID (nonsteroidal anti-inflammatory drug);
  - are over 65 years old.
- have heart failure or heart disease;
- have low blood pressure;
- are taking a high blood pressure medicine;
- are taking a diuretic medicine also known as water pills. They are used to remove excess water from the body;
- often get urinary tract infections;
- have an increased chance of developing **DKA**, if you:
  - are dehydrated or suffer from excessive vomiting, diarrhea, or sweating;
  - are on a very low carbohydrate diet;
  - drink a lot of alcohol;
  - have/have had problems with your pancreas. This includes pancreatitis or surgery on your pancreas;
  - are hospitalized for major surgery, serious infection, or sudden serious medical illness;
  - have a history of **DKA**.
- have vitamin B_{12} deficiency or anemia;
- have hypothyroidism (low levels of thyroid hormones);
- are at increased risk for a possible **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. This feels like tingling or numb hands and feet;
  - have had diabetic foot ulcers or sores;
  - have a lower limb infection;

- are dehydrated. Staying well hydrated and doing regular foot care may help you avoid amputations. Ask your doctor for advice on these topics.

Other warnings you should know about:

- You have a higher chance of getting **lactic acidosis** if you:
  - have severe kidney problems;
    Your kidneys can be affected by certain x-ray tests that use injected dye. Segluromet® is usually stopped before and for 2 days after such a test. Your doctor should discuss this with you;
  - have liver problems;
  - have congestive heart failure that requires treatment with medicines;
  - drink a lot of alcohol (very often or short-term "binge" drinking);
  - get **dehydration** (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 don't drink enough fluids;
  - have surgery. Talk with your doctor before any surgery if you must restrict what you eat and drink. In these cases, Segluromet® should be stopped for 2 days before the surgery. Wait until you are eating and drinking again before you restart Segluromet®. You doctor should discuss this with you;
  - have certain x-ray tests with dyes or contrast agents that are injected into your body;
  - have a heart attack, severe infection, or stroke;
  - are older. This is because older people tend to have more liver, kidney and heart issues;
  - take other medications.
- Segluromet® is not recommended for use in patients under 18 years of age.
- Segluromet® may cause higher levels of bad cholesterol, called LDL. This is a type of fat in your blood.
- Segluromet® increases the chance of getting a yeast infection of the penis or vagina. This is more likely in people who have had yeast infections in the past. It is also more common in uncircumcised men. In rare instances, phimosis (when the foreskin of the penis cannot be pulled back past the glans) was reported and sometimes circumcision was performed.
- Segluromet® may cause abnormal kidney function or kidney problems.

Driving and using machines: Segluromet® may cause you to feel dizzy, weak or lightheaded. Do not drive or use machines until you know how the medicine affects you.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements, or alternative medicines.

If you start any new medicine, tell your healthcare professional.

The following may interact with Segluromet®:

- Nifedipine (used to treat high blood pressure and chest pain).
- Drugs that decrease the rate of elimination of metformin from your body (e.g., ranolazine, vandetanib, dolutegravir and cimetidine).
- Certain "blood thinners" (phenprocoumon or other antivitamin K anticoagulants).
- Diuretics, known as water pills. They are used to remove excess water from the body.

- Medicines to lower your blood pressure.
- Other drugs that tend to produce high blood sugar (hyperglycemia) and may lead to a loss of blood sugar control. Some example of drugs that can increase the blood sugar include:
  - Thiazide and other diuretics (water pills)
  - Corticosteroids (used to treat joint pain and swelling)
  - Phenothiazines (used to treat schizophrenia)
  - Thyroid products
  - Estrogens or estrogens plus progestogen
  - Oral contraceptives (birth control pills)
  - Phenytoin (used to treat epilepsy)
  - Nicotinic Acid
  - Sympathomimetics (used for heart problems)
  - Calcium channel blocking drugs (used for high blood pressure)
  - Isoniazid (used to treat tuberculosis)
  - Beta-2-agonists (used to treat breathing problems)
  - Carbonic anhydrase inhibitors
- ACE inhibitors drugs may lower blood glucose and the combination with Segluromet® should be carefully monitored.

Tell your healthcare professional if you take medicines to lower your blood sugar. Examples are glyburide, gliclazide, glimepiride (sulfonylureas) or insulin. If you take Segluromet® with any of these drugs it can increase the risk of low blood sugar. This is called **hypoglycemia**. Segluromet® is not approved for use with these drugs.

How to take Segluromet®:
- 2 times a day
- by mouth
- with a meal to lower your chance of an upset stomach

Follow the directions given to you by your doctor.

Usual adult dose: 1 tablet twice a day.

Your doctor will individualize your starting dose of Segluromet® based on your current treatment regimen. Take Segluromet® exactly as your physician has prescribed.

Your doctor may adjust your dose, if needed to further control your blood sugar level.

Overdose:

If you think you have taken too much Segluromet®, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed dose:

- If you miss a dose, take it as soon as you remember. If you do not remember until it is time for your next dose, skip the missed dose and go back to your regular schedule.
- Do not take 2 doses of Segluromet® at the same time.

What are possible side effects from using Segluromet®?
These are not all the possible side effects you may have when taking Segluromet®. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:
- Unusual thirst
- Vaginal itching
- You feel generally well and have changes in your urination. These include the need to urinate more often, in larger amounts, or at night
- Headache
- **Gastrointestinal symptoms:** Diarrhea, nausea, vomiting. Abdominal bloating, gas and loss of appetite. Severe vomiting and diarrhea can lead to **dehydration**.
- Change in taste or a metallic taste
- Skin reactions such as redness, itching, and hives

Segluromet® will cause your urine to test positive for sugar (glucose). You should use a different way to monitor your diabetes.

Segluromet® can cause abnormal blood test results. Your doctor may do blood tests before you start Segluromet® and while you take it. They may check your blood sugar, blood fat levels, liver and thyroid function, amount of vitamin B_{12} and red blood cells in your blood and how well your kidneys are working. Your doctor will decide when to perform blood tests and will interpret the results.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Genital infections –Vaginal yeast infection: severe itching, burning, soreness, irritation and a whitish-grey cottage cheese-like discharge.	X		
COMMON			
Volume depletion (dehydration, loss of fluids from your body): dry or sticky mouth, headache, dizziness, urinating less often than normal, thirst.		X	
Low blood sugar (hypoglycemia): shaking, sweating, rapid heartbeat, change in vision, hunger, headache and change in mood.		X	
Genital infections – Yeast infection of the penis: red, swollen, itchy head of the penis; thick, lumpy discharge under foreskin with an unpleasant odour;	X		

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
difficulty retracting foreskin, pain when passing urine or during sex.			
UNCOMMON			
Urinary tract infection: burning sensation when passing urine, pain in the pelvis or mid-back pain, increased need to urinate.		X	
Acute kidney infection: painful, urgent or frequent urination, lower back (flank) pain, fever or chills, cloudy or foul smelling urine, blood in your urine.			X
Kidney problems: you feel unwell and you have any change in the amount, frequency or colour (pale or dark) of your urine.		X	
Low blood pressure: dizziness, fainting, lightheadedness, which may occur when you go from lying to sitting to standing up and when you start on Segluromet®.		X	
Possible need for lower limb amputation: on the feet, toes or legs, new pain or tenderness in a specific bone with redness; non-healing sores or ulcers; brownish/black cold skin.		X	
RARE			
Diabetic ketoacidosis (DKA): difficulty breathing, nausea, vomiting, stomach pain, loss of appetite, confusion, thirst, unusual fatigue, sleepiness or tiredness, a sweet or metallic taste in the mouth, sweet smelling breath, or different odour to urine or sweat.			X
Encephalopathy (disease of the brain that severely alters thinking): muscle weakness in one area, poor decision-making or concentration, involuntary twitching, trembling, difficulty speaking or swallowing, seizures.			X
Lowering of thyroid stimulating hormone level in patients with low thyroid function: fatigue, feeling cold, dry skin, poor memory and concentration, weight gain.		X	
Hemolytic anemia (when red blood cells are destroyed faster than bone marrow can replace them): fatigue, pale color, rapid heartbeat, shortness of breath, dark urine, chills, and backache.			X
Peripheral neuropathy (a result of damage to your peripheral nerves): gradual onset of numbness, prickling or tingling in your feet or hands, which can spread upward into your legs and arms, sharp, jabbing, throbbing, freezing or burning pain, extreme sensitivity to touch, lack of coordination and falling, muscle weakness or paralysis if motor nerves are affected.			X

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Pancreatitis (inflammation of the pancreas): prolonged severe stomach pain and possible vomiting			X
Lactic acidosis (buildup of lactic acid in the blood): malaise or a feeling of general discomfort, uneasiness or pain; feeling very weak or tired; sleepiness, drowsiness or an increasing strong desire for sleep; low blood pressure, dizziness, lightheadedness; cold hands or feet; slow or irregular heartbeat, trouble breathing; unusual muscle pain; stomach pain with nausea, vomiting, or diarrhea.			X
VERY RARE			
Vitamin B_{12} deficiency (decreased vitamin B_{12} levels in the blood): fatigue, shortness of breath, tingling or numbness of the fingers or toes, difficulty walking properly, irritability, confusion, tender calves.		X	
Hepatitis (inflammation of the liver) or Liver disorder: yellow of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite.		X	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Store at 15°C to 30°C. Protect from moisture.

Keep out of reach and sight of children.

If you want more information about Segluromet®:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html) or the Merck Canada website www.merck.ca or by calling Merck Canada at 1-800-567-2594.

To report an adverse event related to Segluromet®, please contact 1-800-567-2594.

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