CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209806Orig1s000

LABELING

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

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

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

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

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

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

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

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

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

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

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

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

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

---------- USE IN SPECIFIC POPULATIONS ----------
- *Pregnancy:* Advise females of the potential risk to a fetus, especially during the second and third trimesters. (8.1)
- *Lactation:* Breastfeeding not recommended. (8.2)
- *Females and Males of Reproductive Potential:* Advise premenopausal females of the potential for an unintended pregnancy. (8.3)
- *Geriatrics:* Higher incidence of adverse reactions related to reduced intravascular volume. (5.2, 8.5)
- *Renal impairment:* Higher incidence of adverse reactions related to reduced intravascular volume and renal function. (5.1, 5.4, 8.6)
- *Hepatic* impairment*:* Avoid use in patients with hepatic impairment. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: LACTIC ACIDOSIS

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

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

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

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

1 INDICATIONS AND USAGE

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

Limitations of Use

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

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

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

2.2 Patients with Renal Impairment

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

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

2.3 Discontinuation for Iodinated Contrast Imaging Procedures

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

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Lactic Acidosis

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

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

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

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

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.