Ertugliflozin (Steglatro™), Ertugliflozin/Metformin (Segluromet™),
and Ertugliflozin/Sitagliptin (Steglujan™) New Drug Update

January 2018

<table>
<thead>
<tr>
<th>Drug Name:</th>
<th>ertugliflozin</th>
<th>ertugliflozin/metformin</th>
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<tr>
<td>Trade Name (Manufacturer):</td>
<td>Steglatro™ (Merck)</td>
<td>Segluromet™ (Merck)</td>
<td>Steglujan™ (Merck)</td>
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<td>Form:</td>
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<td>2.5 mg/500 mg, 2.5 mg/1,000 mg, 7.5 mg/500 mg, and 7.5 mg/1,000 mg</td>
<td>5 mg/100 mg and 15 mg/100 mg</td>
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<td>Market Availability:</td>
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<td>Antihyperglycemics – sodium glucose cotransporter 2 (SGLT2) inhibitors (C4D)</td>
<td>Specific Therapeutic Class (HIC3): TBD</td>
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INDICATION\(^1,2,3\)

Ertugliflozin (Steglatro), a sodium-glucose co-transporter 2 (SGLT2) inhibitor, is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM).

Its fixed-ratio combination with the biguanide metformin (Segluromet) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM who are not adequately controlled on a regimen containing ertugliflozin or metformin, or in patients who are already treated with both ertugliflozin and metformin.

Its fixed-ratio combination with the dipeptidyl peptidase-4 (DPP-4) inhibitor sitagliptin (Steglujan) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both ertugliflozin and sitagliptin is appropriate.

None of these agents is indicated for type 1 diabetes (T1DM) or diabetic ketoacidosis.

Ertugliflozin/sitagliptin has not been studied in patients with a history of pancreatitis.

PHARMACOKINETICS

In healthy patients and those with T2DM, the pharmacokinetics of ertugliflozin are similar. Ertugliflozin reaches a peak plasma concentration (C\(_{\text{max}}\)) in approximately 1 hour (T\(_{\text{max}}\)) after oral administration on an empty stomach. Ertugliflozin exhibits linear pharmacokinetics at routinely used doses. Administration
with a high-fat meal decreases $C_{\text{max}}$ by 29%, delays the $T_{\text{max}}$ by 1 hour, and does not change the AUC; however, ertugliflozin can be given without regard to food. Ertugliflozin is 93.6% bound to plasma proteins. Ertugliflozin is primarily metabolized by UGT1A9 and UGT2B7 to metabolites that are inactive at clinically relevant concentrations. The half-life of ertugliflozin is 16.6 hours. Ertugliflozin is excreted in the urine (50.2%) and feces (40.9%) as the parent molecule. Only 1.5% of the given dose is eliminated unchanged in the urine and 33.8% in the feces.

**CONTRAINDICATIONS/WARNINGS**

Ertugliflozin, ertugliflozin/metformin, and ertugliflozin/sitagliptin are contraindicated in patients with severe renal impairment (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m$^2$), end stage renal disease (ESRD), and patients on dialysis. Use of these medications in patients with a history of serious hypersensitivity reactions to any component of the product is contraindicated.

There is a boxed warning for lactic acidosis associated with ertugliflozin/metformin due to the metformin component; use of this medication in patients with metabolic acidosis, including ketoacidosis, is contraindicated.

Symptomatic hypotension can occur after starting ertugliflozin as it causes intravascular volume contraction. Symptomatic hypotension occurs particularly in patients with impaired renal function (eGFR < 60 mL/min/1.73 m$^2$), elderly patients, patients with low systolic blood pressure, and patients on a diuretic. The patient’s volume status should be assessed and corrected prior to starting ertugliflozin and monitored thereafter.

Ertugliflozin can cause ketoacidosis. Consider risk factors for ketoacidosis before initiating ertugliflozin and discontinue ertugliflozin promptly if ketoacidosis is suspected.

Ertugliflozin can cause renal impairment. Renal function should be evaluated prior to initiating ertugliflozin and thereafter. Consider predisposing factors of acute kidney injury before initiation including hypovolemia, chronic renal insufficiency, congestive heart failure, and concomitant medications. Regularly assess patient’s renal function and monitor for signs and symptoms of acute kidney injury. If acute kidney injury occurs, discontinue ertugliflozin.

Ertugliflozin use is associated with an increased risk of urosepsis and pyelonephritis. Monitor patients for signs and symptoms of urinary tract infections and treat if indicated.

An increased risk of lower limb amputation has been reported with another SGLT2 inhibitor. Before initiating, consider predisposing factors of amputations such as smoking, prior amputation, and peripheral artery disease. Discontinue ertugliflozin if patients develop infections or ulcers of lower limbs.

A lower dose of insulin or insulin secretagogue may be needed to reduce the risk of hypoglycemia when used with ertugliflozin.

Patients with a history of genital mycotic infections and uncircumcised males are more likely to develop mycotic infections when using ertugliflozin and should be monitored closely, as ertugliflozin can increase the risk of genital mycotic infections

Ertugliflozin may cause dose-related increases in low-density-lipoprotein cholesterol (LDL-C); therefore, monitoring is warranted.

No clinical studies have established a benefit of ertugliflozin on macrovascular risk.
Metformin is associated with lowering vitamin B12 levels. It is recommended to check hematological parameters annually in patients taking ertugliflozin/metformin.

Select other DPP-4 inhibitors have been associated with an increased risk of heart failure. Evaluate the risks and benefits in patients taking ertugliflozin/sitagliptin with known risk factors for heart failure and monitor for signs and symptoms. DPP-4 inhibitors may cause bullous pemphigoid requiring hospitalization, monitor for development of blisters or erosions and discontinue ertugliflozin/sitagliptin if bullous pemphigoid is suspected.

**DRUG INTERACTIONS**

Ertugliflozin is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) and is a weak inhibitor of UGT1A1 and UGT1A4. No dose adjustments are necessary with concomitant medications because ertugliflozin is unlikely to affect their pharmacokinetics. Coadministration with other blood sugar lowering medications may increase the risk of hypoglycemia. SGLT-2 inhibitors increase urinary glucose excretion, it is not recommended to monitor glycemic control with urine glucose tests because there is potential for a false positive result.

Patients taking ertugliflozin/metformin may be at an increased risk for lactic acidosis if they are concomitantly consuming alcohol, taking a carbonic anhydrase inhibitor (e.g., topiramate, zonisamide, acetazolamide) or taking a medication that reduces clearance of metformin (e.g., organic cationic transporter-2/multidrug and toxin extrusion inhibitors such as ranolazine, dolutegravir, and cimetidine).

Coadministration of ertugliflozin/sitagliptin and digoxin may increase the area under the curve and mean drug concentration of sitagliptin. However, no dose adjustment of digoxin or ertugliflozin/sitagliptin is recommended.

**COMMON ADVERSE EFFECTS**

In three 26-week placebo controlled trials (1 monotherapy trial and 2 add-on therapy trials) ertugliflozin was used to treat 1,029 patients with uncontrolled T2DM Patients received ertugliflozin 5 mg, ertugliflozin 15 mg, or placebo once daily. The most common adverse reactions reported in ≥ 3% of patients associated with ertugliflozin were female genital mycotic infections (9.1% to 12.2%), male genital mycotic infections (3.7% to 4.2%), urinary tract infections (4% to 4.1%), and headache (2.9% to 3.5%). Within these 3 trials, renal-related adverse reactions (e.g., acute kidney injury, renal impairment, acute pre-renal failure) occurred in numerically more patients taking ertugliflozin 5 mg (2.5%) and patients taking ertugliflozin 15 mg (1.3%) compared to those taking placebo (0.6%). Within all phase 3 clinical trials in which ertugliflozin was studied as monotherapy and in conjunction with other antihyperglycemic agents, non-traumatic lower limb amputations occurred in 0.1% in the non-ertugliflozin group, 0.2% in the ertugliflozin 5 mg group, and 0.5% in the ertugliflozin 15 mg group. Across the clinical program, ketoacidosis occurred in 0.1% of ertugliflozin-treated patients and 0% of comparator-treated patients. The most common adverse reactions reported in ≥ 5% of patients associated with metformin were diarrhea, nausea, vomiting, flatulence, abdominal discomfort, indigestion, asthenia, and headache. The most common adverse reactions reported in ≥ 5% of patients associated with sitagliptin were upper respiratory tract infection, nasopharyngitis, and headache. Additionally, hypoglycemia was more commonly reported in patients treated with sitagliptin than placebo in the add-on to sulfonylurea and add-on to insulin studies.
SPECIAL POPULATIONS

Pregnancy

The use of ertugliflozin, ertugliflozin/metformin, and ertugliflozin/sitagliptin is not recommended for use in pregnancy during the second and third trimesters. Data on the use of ertugliflozin in pregnant women are not sufficient to determine a drug-associated risk of adverse developmental outcomes.

Pediatrics

No information is available regarding the efficacy or safety of any of these ertugliflozin-containing products in patients under 18 years old.

Geriatrics

Patients 65 years and older experienced a higher incidence adverse reactions pertaining to volume depletion than younger patients. Events were reported in 1.1% of patients less than 65 years, 2.2% of patients 65 years and older taking ertugliflozin 5 mg, and 2.6% of patients 65 years and older taking ertugliflozin 15 mg.

Hepatic Impairment

There are no dosage adjustments recommended for patients with mild or moderate hepatic impairment (Child-Pugh classes A and B). There are no data for using ertugliflozin in patients with severe hepatic impairment (Child-Pugh Class C); the manufacturer recommends avoiding ertugliflozin in these patients. Ertugliflozin/metformin is not recommended in patients with hepatic impairment due to cases of lactic acidosis associated with metformin.

Renal Impairment

Ertugliflozin is not recommended in patients with moderate renal impairment (eGFR, 30 to 59 mL/min/1.73 m²). Patients with moderate renal impairment had less glycemic efficacy and higher occurrence of volume depletion adverse reactions, renal-related adverse reactions, and renal impairment compared to patients with mild renal impairment (eGFR 60, to 89 mL/min/1.73 m²) or normal renal function (eGFR ≥ 90 mL/min/1.73 m²). Ertugliflozin is not expected to be effective in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m²), ESRD, or those receiving dialysis; it is contraindicated in these patients.

DOSAGES

The starting dosage for ertugliflozin is 5 mg by mouth daily, given without regard to food. The dose may be increased to the maximum recommended dose (15 mg) if the patient is tolerating the current dose. The dosage of ertugliflozin/sitagliptin is also once daily. The dose of sitagliptin is not variable (100 mg), but the dosing of ertugliflozin is the same as listed above and it is available as 5 mg/100 mg or 15 mg/100mg.

Ertugliflozin/metformin is available as 4 different combination tablets: 2.5 mg/500 mg, 2.5 mg/1,000 mg, 7.5 mg/500 mg, and 7.5 mg/1,000 mg. The starting dose should be individualized based on the patient’s current regimen. This product should be taken twice daily with meals and gradually titrated to the maximum recommended dose of 7.5 mg/1,000 mg twice daily.
Patients with volume depletion should have their volume condition corrected prior to initiating ertugliflozin.

**CLINICAL TRIALS**

*A literature search was performed using “ertugliflozin,” “ertugliflozin + metformin,” and “ertugliflozin + sitagliptin.”*

**Clinical study of monotherapy use of ertugliflozin (VERTIS MONO trial)***

A 26-week, double-blind, placebo-controlled study was performed in 461 patients with T2DM who were not controlled by diet and exercise (HbA1C, 7% to 10.5%) in order to determine the safety and efficacy of ertugliflozin. All patients, either treatment naïve or ≥ 8 weeks without antihyperglycemic treatment, entered a 2-week, single-blind, placebo run-in period. After the placebo run-in period, patients were then randomized to receive ertugliflozin 5 mg, ertugliflozin 15 mg, or placebo once daily. The primary endpoint, change from baseline HbA1C at week 26, was significantly higher the ertugliflozin groups compared to the placebo group. The mean reduction of HbA1C relative to the placebo group was -0.99% (95% confidence interval [CI], -1.22 to -0.76; *p*<0.001) in the ertugliflozin 5 mg group and -1.16% (95% CI, -1.39 to -0.93; *p*<0.001) in the ertugliflozin 15 mg group. Patients in the ertugliflozin 5 mg group were 3.59 times as likely to achieve a HbA1C < 7% than patients in the placebo group (95% CI, 1.85 to 6.95; *p*<0.001) and patients in the ertugliflozin 15 mg group were 6.77 times as likely to achieve a HbA1C < 7% than patients in the placebo group (95% CI, 3.46 to 13.24; *p*<0.001). Patients treated with ertugliflozin 5 mg and 15 mg once daily also had greater reductions in body weight compared to placebo with a difference of -1.76 kg (95% CI, -2.57 to -0.95; *p*<0.001) in patients taking ertugliflozin 5 mg and -2.16 kg (95% CI, -2.98 to -1.64; *p*<0.001) in patients taking ertugliflozin 15 mg.

**Ertugliflozin as add-on combination therapy with metformin (VERTIS MET trial)**

A 26-week, double-blind, placebo-controlled study was performed in 621 patients with T2DM who were not adequately controlled (HbA1C, 7% to 10.5%) on metformin monotherapy (≥ 1,500 mg/day for ≥ 8 weeks) in order to determine the safety and efficacy of ertugliflozin. Following a 2-week, single-blind, placebo run-in period, participants were randomized to receive ertugliflozin 5 mg, ertugliflozin 15 mg, or placebo once daily. Change from baseline HbA1C at week 26 was significantly higher in the ertugliflozin 5 mg and 15 mg groups compared to the placebo group (mean difference from placebo, -0.5% [95% CI, -0.7 to -0.4; *p*<0.001] and -0.7% [95% CI, -0.9 to -0.5; *p*<0.001], respectively). The percent of patients achieving a HbA1C < 7% was 74% in patients taking ertugliflozin 5 mg, 87% in patients taking ertugliflozin 15 mg, and 38% in patients taking placebo. Ertugliflozin 5 mg and 15 mg once daily also improved fasting plasma glucose (FPG) compared to placebo (-30.3 mg/dL and -40.9 mg/dL versus -8.7 mg/dL, respectively). Patients treated with ertugliflozin 5 mg and 15 mg once daily also had greater reductions in body weight compared to placebo (-3.2 kg and -3 kg versus -1.4 kg, respectively).

**Active controlled non-inferiority study of ertugliflozin versus glimepiride as add-on combo therapy with metformin (VERTIS SU trial)**

A 52-week, double-blind, placebo-controlled study was performed in 1,326 patients with T2DM who were not adequately controlled (HbA1C, 7% to 9%) on metformin (≥ 1,500 mg/day for ≥ 8 weeks) in order to determine the safety and efficacy of ertugliflozin in combination with metformin. Following a 2-week, single-blind, placebo run-in period participants were randomized to receive ertugliflozin 5 mg,
ertugliflozin 15 mg, or glimepiride 1 mg/day titrated up to the maximum approved dose in each country (6 or 8 mg/day) once daily with concurrent metformin background therapy. Glimepiride 3 mg was the mean daily dose. The primary efficacy endpoint was change in baseline in HbA1C at week 52, with a noninferiority margin of 0.3%. Ertugliflozin 15 mg was found to be noninferior to glimepiride with a least mean difference of 0.1% (95% CI, 0 to 0.2). However, ertugliflozin 5 mg did not demonstrate noninferiority to glimepiride with a mean difference of 0.2% (95% CI, 0.1 to 0.3). The pre-determined testing sequence stopped here for ertugliflozin 5 mg and other endpoints are provided for descriptive purposes only. Patients treated with ertugliflozin 5 mg and 15 mg once daily had greater reductions in body weight compared to glimepiride (-2.6 kg and -3 kg versus 0.6 kg, respectively).

**In combination with sitagliptin versus ertugliflozin alone and sitagliptin alone, as add-on to metformin (VERTIS FACTORIAL trial)**

A 26-week, double-blind, active-controlled study was performed in 1,233 patients with T2DM who were not adequately controlled (HbA1C, 7.5% to 11%) on metformin monotherapy (≥ 1,500 mg/day) in order to determine the safety and efficacy of ertugliflozin in combination with sitagliptin compared to the individual components. Participants were randomized to receive ertugliflozin 5 mg, ertugliflozin 15 mg, sitagliptin 100 mg, or coadministration of ertugliflozin/sitagliptin 5/100 mg or ertugliflozin/sitagliptin 15/100 mg once daily. The primary endpoint, change from baseline HbA1C at week 26, was significantly higher in the combination products. A -1.5% mean reduction of HbA1C was observed in patients taking ertugliflozin/sitagliptin 5/100 mg and 15/100 mg daily as compared to the individual agents ertugliflozin 5 mg (-1%), ertugliflozin 15 mg (-1.1%), and sitagliptin 100 mg (-1.1%) (p<0.001 for all comparisons). The percent of patients achieving a HbA1C < 7% was 26.4% in patients taking ertugliflozin 5 mg, 31.9% in patients taking ertugliflozin 15 mg, 32.8% in patients taking sitagliptin 100 mg, 52.3% in patients taking ertugliflozin/sitagliptin 5/100 mg, and 49.2% in patients taking ertugliflozin/sitagliptin 15/100 mg.

**Initial combination therapy of ertugliflozin with sitagliptin (VERTIS SITA trial)**

A 26-week, double-blind, placebo-controlled study was performed in 291 patients with T2DM who were not adequately controlled by diet and exercise (HbA1C, 8% to 10.5%) in order to determine the safety and efficacy of ertugliflozin in combination with sitagliptin. Patients not receiving hyperglycemic treatment for ≥ 8 weeks entered a 2-week, single-blind, placebo run-in period. After the placebo run-in period, patients were then randomized to receive ertugliflozin 5 mg, ertugliflozin 15 mg, or placebo in combination with sitagliptin 100 mg once daily. The primary endpoint, change from baseline HbA1C at week 26, was significantly higher in the active combination treatment groups compared to the placebo group. The mean reduction of HbA1C relative to the placebo group was -1.2% (95% CI, -1.5 to -0.8; p<0.001) in the ertugliflozin 5 mg + sitagliptin 100 mg group and -1.2% (95% CI, -1.6 to -0.9; p<0.001) in the ertugliflozin 15 mg + sitagliptin 100 mg group. Patients in the ertugliflozin 5 mg + sitagliptin 100 mg group were 6.9 times as likely to achieve a HbA1C < 7% than patients in the placebo group (95% CI, 2.8 to 16.8; p<0.001) and patients in the ertugliflozin 15 mg + sitagliptin 100 mg group were 7.4 times as likely to achieve a HbA1C < 7% than patients in the placebo group (95% CI, 3 to 18.3; P<0.001). Patients treated with ertugliflozin 5 mg and 15 mg + sitagliptin 100 mg once daily also had greater reductions in body weight compared to placebo with a difference in means of -2 kg (95% CI, -2.99 to -1.01; P<0.001) in patients taking ertugliflozin 5 mg + sitagliptin 100 mg and -2.1 kg (95% CI, -3.1 to -1.11; P<0.001) in patients taking ertugliflozin 15 mg + sitagliptin 100 mg.
Ertugliflozin as add-on combination therapy with metformin and sitagliptin (VERTIS SITA2 trial)\textsuperscript{10}

A 26-week, double-blind, placebo-controlled study was performed in 464 patients with T2DM who were not adequately controlled (HbA1C, 7% to 10.5%) on metformin (≥ 1,500 mg/day for ≥ 8 weeks) and sitagliptin 100 mg once daily in order to determine the safety and efficacy of ertugliflozin. Following a 2-week, single-blind, placebo run-in period participants were randomized to receive ertugliflozin 5 mg, ertugliflozin 15 mg, or placebo once daily. The primary endpoint, change from baseline HbA1C at week 26, was significantly higher in the ertugliflozin groups compared to the placebo group. The mean reduction of HbA1C relative to the placebo group was -0.7% (95% CI, -0.9 to -0.5; p<0.001) in the ertugliflozin 5 mg group and -0.8% (95% CI, -0.9 to -0.6; p<0.001) in the ertugliflozin 15 mg group. The percent of patients achieving a HbA1C < 7% was 32.1% in patients taking ertugliflozin 5 mg, 39.9% in patients taking ertugliflozin 15 mg, and 17% in patients taking placebo. Patients treated with ertugliflozin 5 mg and 15 mg once daily also had greater reductions in body weight compared to placebo (-3.4 kg, -3 kg, and -1.3 kg, respectively).

Ertugliflozin in patients with moderate renal impairment (VERTIS RENAL trial)\textsuperscript{11}

A 26-week, double-blind, placebo-controlled study was performed in 468 patients with T2DM and moderate renal impairment (eGFR, 30 to 59 mL/min/1.73 m\textsuperscript{2}). The patients who were undergoing standard treatment with insulin and/or sulfonylureas, excluding metformin, were randomized to once-daily ertugliflozin 5 mg, ertugliflozin 15 mg, or placebo. Patients taking metformin underwent a washout period prior to randomization. The primary efficacy endpoint, change from baseline HbA1C at week 26, was not statistically significant.

OTHER DRUGS USED FOR CONDITION

Patients and prescribers have many options available when selecting an oral antihyperglycemic medication such as DPP-4 inhibitors (e.g., sitagliptin [Januvia\textsuperscript{®}], saxagliptin [Onglyza\textsuperscript{®}], linagliptin [Tradjenta\textsuperscript{®}], alogliptin [Nesina\textsuperscript{®}]), alpha-glucosidase inhibitors, biguanides (e.g., metformin), meglitinides, sulfonylureas, and thiazolidinediones. Several convenient multi-strength combination products are also available.

There are currently 3 SGLT2 inhibitors available including empagliflozin (Jardiance\textsuperscript{®}), canagliflozin (Invokana\textsuperscript{®}), and dapagliflozin (Farxiga\textsuperscript{®}). No generic equivalents are available, empagliflozin was the first SGLT2 inhibitor to the market, approved in August, 2014. These are available in multi-strength combination products such as SGLT2 inhibitors/DPP-4 inhibitors (Glyxambi\textsuperscript{®} and Qtern\textsuperscript{®}) and SGLT2 inhibitors/biguanides (Synjardy/XR\textsuperscript{®}, Invokamet\textsuperscript{®}, and Xigduo XR\textsuperscript{®}).

PLACE IN THERAPY\textsuperscript{12,13,14}

Diabetes was the seventh leading cause of death in the United States (U.S.) in 2015. A large percentage of the U.S. population lives with diabetes (9.4%).

According to the 2018 American Diabetes Association (ADA) Standards of Medical Care in Diabetes the selection of medications should be patient-centric and prescribers should consider potential issues such as efficacy, cost, side effects, comorbidities, hypoglycemic risk, and patient preferences. At diagnosis of T2DM, lifestyle management should always be started and pharmacologic therapy initiated based on HbA1C. If HbA1C is < 9%, initiate metformin if well tolerated and not contraindicated. The HbA1C should
be monitored every 3 to 6 months and medication therapy should be escalated to dual therapy, triple therapy or combination injectable therapy, as warranted, considering drug-specific effects and patient factors. If HbA1C is ≥ 9% at diagnosis, initiate metformin and a second agent for dual therapy. If a patient has ASCVD risk, the second agent should be one that has proven to reduce major adverse cardiovascular events (MACE) and/or cardiovascular mortality. Both canagliflozin and empagliflozin have completed FDA post-marketing cardiovascular outcome (CVOT) trials. Empagliflozin was shown to reduce cardiovascular mortality and canagliflozin was shown to reduce MACE events. At this time, only empagliflozin has received an FDA approved indication to reduce the risk of cardiovascular death in adult patients with T2DM and established cardiovascular disease. CVOT trials for dapagliflozin and ertugliflozin are not available.

The American Association of Clinical Endocrinologists (AACE) established a new treatment algorithm in 2018 for glycemic control. Like the ADA’s position, the AACE guidelines also state the choice of therapy must be based on the individual patient and medications. Choosing an antihyperglycemic medication should be based on hypoglycemia risk, weight gain, cost, ease of use, and effects on the kidney, heart, or liver. The 2018 AACE treatment algorithm stratifies choice of therapy based on the patient’s initial HbA1C level: < 7.5%, ≥ 7.5%, and > 9%. The guidelines suggest patients with a HbA1C level < 7.5% start with monotherapy; whereas patients with a HbA1C level ≥ 7.5 percent begin with dual therapy. Patients with an HbA1C > 9% and no symptoms may start on either dual or triple antihyperglycemic therapy; patients with an HbA1C > 9% with symptoms should begin insulin therapy with or without other agents. The patient’s HbA1C should be reassessed every 3 months, and failure to improve may warrant additional complementary therapy for optimal glycemic control. Within each therapy group (monotherapy, dual therapy, and triple therapy) the guidelines provide prescribers a hierarchical order of the usage of drugs where, like the ADA guidelines, metformin is the preferred treatment of choice for monotherapy and first-line agent for dual and triple therapy. The AACE guidelines suggest SGLT2 inhibitors as a third choice secondary to metformin and glucagon-like peptide-1 receptor agonists (GLP-1 RA). The guideline indicates the use of SGLT2 inhibitors have few adverse events and/or possible benefits.

Ertugliflozin has efficacy in reducing HbA1C, FPG, blood pressure, and weight in comparison to other SGLT2 inhibitors. Additionally, ertugliflozin has a similar side effect profile. However, ertugliflozin has not demonstrated cardiovascular outcomes unlike other agents within this class.
# SUGGESTED UTILIZATION MANAGEMENT

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<td><strong>Clinical Edit</strong></td>
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**Steglatro**

**Initial**

Patient must:
- Be age 18 years or older; **AND**
- Have a diagnosis of T2DM; **AND**
- Have had a trial and failure of (or contraindication to) metformin; **AND**
- Have had a trial and failure of at least 1 preferred products; **AND**
- Not have an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m², end-stage renal disease (ESRD), or be on dialysis.

**Renewal**

Patient must:
- Continue to meet above criteria; **AND**
- Have documentation of clinical benefit (e.g., improvement in HbA1c); **AND**
- Have absence of unacceptable toxicity from the drug (e.g., significant hypotension, ketoacidosis, renal impairment, lower limb amputation, repeated urinary tract or genital mycotic infections, significant increases in low-density-lipoprotein cholesterol (LDL-C)).

**Segluromet (ertugliflozin/metformin HCl)**

**Initial**

Patient must:
- Be age 18 years or older; **AND**
- Have a diagnosis of T2DM; **AND**
- Have had a trial and failure of metformin monotherapy; **AND**
- Have had a trial and failure of at least 2 preferred products from 2 separate classes; **AND**
- Not have an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m², end-stage renal disease (ESRD), or be on dialysis. **AND**
- Not have metabolic acidosis

**Renewal**

Patient must:
- Continue to meet above criteria; **AND**
- Have documentation of clinical benefit (e.g., improvement in HbA1c); **AND**
- Have absence of unacceptable toxicity from the drug.
Suggested Utilization Management (continued)

<table>
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<tr>
<th>Clinical Edit (continued)</th>
<th>Steglujan (ertugliflozin/sitagliptin)</th>
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<tr>
<td>▪ Have had a trial and failure of at least 2 preferred products from 2 separate classes; AND</td>
<td></td>
</tr>
<tr>
<td>▪ Not have an estimated glomerular filtration rate (eGFR) &lt; 30 mL/min/1.73 m², end-stage renal disease (ESRD), or be on dialysis.</td>
<td></td>
</tr>
<tr>
<td>Renewal</td>
<td></td>
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<tr>
<td>Patient must:</td>
<td></td>
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<tr>
<td>▪ Continue to meet above criteria; AND</td>
<td></td>
</tr>
<tr>
<td>▪ Have documentation of clinical benefit (e.g., improvement in HbA1c); AND</td>
<td></td>
</tr>
<tr>
<td>Have absence of unacceptable toxicity from the drug.</td>
<td></td>
</tr>
</tbody>
</table>

| Quantity Limit             |                                      |
| Ertugliflozin: 30 tablets/30days |                                      |
| Ertugliflozin/metformin: 60 tablets/30 days |                                      |
| Ertugliflozin/sitagliptin: 30 tablets/30 days |                                      |

| Duration of Approval        | 1 year                               |

| Drug to Disease Hard Edit   | Ertugliflozin and ertugliflozin/sitagliptin: severe renal impairment; end stage renal disease; dialysis  |
| Ertugliflozin/metformin: severe renal impairment; end stage renal disease; dialysis; metabolic acidosis |

REFERENCES

1 Steglatro [package insert]. Whitehouse Station, NJ; Merck; December 2017.
2 Segluromet [package insert]. Whitehouse Station, NJ; Merck; December 2017.
3 Steglujan [package insert]. Whitehouse Station, NJ; Merck; December 2017.
5 Steglatro [package insert]. Whitehouse Station, NJ; Merck; December 2017.
6 Segluromet [package insert]. Whitehouse Station, NJ; Merck; December 2017.