Steglatro® (ertugliflozin): A New SGLT-2 Inhibitor for the Treatment of Type 2 Diabetes Mellitus

Crysta Stepniak, PharmD Candidate

Diabetes remains one of the most prevalent health concerns in the United States with an estimate of 30.3 million people of all ages having diabetes, type 1 (T1DM) or type 2 (T2DM) diabetes mellitus, and approximately 84.1 million people having prediabetes.1 Initial monotherapy with metformin is still recommended first-line for T2DM but most patients will require combination oral drug therapy for management.2 Other oral antihyperglycemics include: sulfonylureas, thiazolidinediones (TZD), dipeptidyl peptidase-4 inhibitors (DPP-4i), and sodium glucose co-transporter 2 (SGLT2) inhibitors. Each option has their own possible adverse effects including increased hypoglycemia and weight gain. Therefore, a patient-centered approach should be used to guide the choice of pharmacologic agents. Important factors to consider include efficacy of therapy, history of cardiovascular disease, weight, renal impacts, potential side effects, cost, and patient preferences.3 SGLT2 inhibitors are a successful class of medications targeting kidney physiology in maintaining glucose homeostasis.4 Because SGLT2 inhibitors have a unique insulin-independent mode of action, they potentially can have a significant impact on the early management of T2DM.5 SGLT2 inhibitors may also contribute to reducing cardiovascular risk factors such as lowering blood pressure, decreasing body weight, and improving glycemic control. Current FDA approved SGLT2 inhibitors include Farxiga® (dapagliflozin), Invokana® (canagliflozin), and Jardiance® (empagliflozin). Steгlatro® (ertugliflozin), the newest in this class of medications, has an FDA approved indication as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. The purpose of this article is to review the pharmacological aspects of ertugliflozin, its clinical trials, and any unique properties this drug has within the SGLT2 class of medication.

Pharmacology

Pharmacodynamics

Reabsorption of glucose is mainly localized in the proximal convoluted tubule of the nephron and is mediated by sodium glucose co-transporter 1 (SGLT1) (~10%) and SGLT2 (~90%).3 Ertugliflozin is an inhibitor of SGLT2 with 2,000-fold selectivity for SGLT2 over SGLT1 (see Table 1 comparing selectivity among SGLT inhibitors), however the clinical implications of this is not yet fully understood. Inhibition of SGLT2 leads to increased glycosuria, improved beta cell insulin secretion, increased insulin sensitivity in the periphery,6 and overall lower plasma glucose concentrations.4

Pharmacokinetics

The various pharmacokinetic characteristics of ertugliflozin are summarized in Table 2. Ertugliflozin plasma concentration peaks 1 hour after oral administration in fasting patients. Administration with a high-fat and high-calorie meal decreases ertugliflozin C_{max} by 29% and prolongs T_{max} by 1 hour, however it does not alter AUC as compared to fasting state and is not clinically relevant. Absolute oral bioavailability after administration of ertugliflozin 15 mg is approximately 100%. Ertugliflozin 5 mg has a mean steady state plasma AUC of 398 ng·hr/mL and a C_{max} of 81.3 ng/mL, ertugliflozin 15 mg once daily has a mean AUC of 1,193 ng·hr/mL and a C_{max} of 268 ng/mL.7 Steady state is reached after 4 to 6 days of once-daily dosing and plasma C_{max} and AUC increase in a dose-proportional manner. Ertugliflozin is primarily metabolized in the liver via UGT1A9 and UGT2B7-mediated O-glucuronidation into pharmacologically inactive metabolites. Ertugliflozin is excreted renally (50.2%) and in feces (40.9%). CYP-mediated metabolism is minimal with ertugliflozin (12%) leading to limited drug-drug interactions. In vitro studies of ertugliflozin and ertugliflozin glucuronides showed no clinically relevant CYP interactions and no meaningful P-glycoprotein inhibition and therefore should have limited other drug interactions.7

Clinical Trials

The following section will review a Phase II dose-ranging study as well as several Phase III studies from the VERTIS clinical trial series (Selected Phase III clinical trials are listed in Table 3). The VERTIS Studies (eValuation of ERTugliflozin efficacy and Safety) evaluated the efficacy and safety in the treatment of T2DM. In the VERTIS series of studies, ertugliflozin was evaluated as monotherapy as well as with other common diabetic medications. Safety data from the clinical trials will be mostly be discussed later on in the safety section of this article.
Amin et al. conducted a 12-week, randomized, double-blind, placebo- and active-controlled, parallel group, double-dummy, phase II dose-ranging study. The study aimed to evaluate the dose-response of ertugliflozin in patients with T2DM inadequately controlled on metformin. Participants were randomly assigned to once daily oral placebo (n=54), ertugliflozin 1 mg (n=54), 5 mg (n=55), 10 mg (n=55), 25 mg (n=55), or sitagliptin 100 mg (n=55). Participants were aged 18-70 years with T2DM according to American Diabetes Association (ADA) criteria, body mass indexes of 23-45 kg/m², and Hemoglobin A1c (HbA1c) concentrations at screening of 7.0-11.0% (if on metformin monotherapy) or 6.5-9.5% (if on metformin plus another oral antidiabetic medication excluding TZD). During the study, patients were instructed to take study medication at the same time each day with their morning meal. The primary endpoint analysis was change in HbA1c from baseline to week 12. Ertugliflozin at all doses tested yielded significant reductions in HbA1c concentration (mean change: ertugliflozin 1 mg = -0.56%; ertugliflozin 5 mg = -0.80%; ertugliflozin 10 mg = -0.73%; ertugliflozin 25 mg = -0.83%) compared with placebo (mean change: -0.11%; and sitaglipitin 100 mg (mean change: = -0.87%). Ertugliflozin generally was well tolerated and no dose-related increase in adverse event frequency was observed. The most common adverse events were upper respiratory tract infection, diarrhea, and UTIs.

**VERTIS MONO & VERTIS MONO Extension**

In the VERTIS MONO trial, the efficacy and safety of ertugliflozin monotherapy was evaluated in patients with T2DM and inadequate glycemic control despite diet and exercise. The VERTIS MONO trial was a Phase III, 52-week, randomized, double-blind, multicenter, parallel-group study with a 26-week, placebo-controlled treatment period (phase A), followed by a 26-week active-controlled treatment period (phase B). Participants included 461 men and women, aged 18 years of age and older, diagnosed in accordance with ADA guidelines, with inadequate glycemic control with a HbA1c concentration between 7.0% and 10.5%. Participants could not have been treated with any other antihyperglycemic agent for at least 8 weeks prior to screening. Exclusion criteria were T1DM, history of ketoacidosis, uncontrolled hyperglycemia (glucose >270 mg/dL), estimated glomerular filtration (eGFR) <55 mL/min/1.73 m² or serum creatinine (SCR) ≥1.3 mg/dL in men or ≥1.2 mg/dL in women, or a history of a cardiovascular event within 3 months of screening. Participants were randomly assigned (1:1:1) to placebo (n=153), ertugliflozin 5 mg (n=155), or ertugliflozin 15 mg (n=151) orally once daily taken in the morning. The primary efficacy endpoint was the change from baseline in HbA1c at week 26. Compared to placebo, the mean reductions from baseline in HbA1c at week 26 were significantly greater in the ertugliflozin 5 mg (difference = -0.99%; 95% CI, -1.22% to -0.76%) and 15 mg (difference = -1.16%; 95% CI, -1.39% to -0.93%) groups compared with the placebo group.

**Table 1 | Selectivity of SGLT-2 Inhibitors Available in the USA**

<table>
<thead>
<tr>
<th>Molecule</th>
<th>SGLT-2 (IC50 nM)</th>
<th>SGLT-1 (IC50 nM)</th>
<th>SGLT-2/SGLT-1 selectivity ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empagliflozin</td>
<td>3.1</td>
<td>8,300</td>
<td>2,500-fold</td>
</tr>
<tr>
<td>Ertugliflozin</td>
<td>0.87</td>
<td>1,960</td>
<td>2,000-fold</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>1.2</td>
<td>1,400</td>
<td>1,200-fold</td>
</tr>
<tr>
<td>Canagliflozin</td>
<td>2.7</td>
<td>710</td>
<td>250-fold</td>
</tr>
</tbody>
</table>

IC50 = half-maximum inhibitor concentration; nM = nanomolar; SGLT = sodium-glucose transporter.

**Table 2 | Steglatro Pharmacokinetics**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Absorption</strong></td>
<td></td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt;</td>
<td>~1.0 hours</td>
</tr>
<tr>
<td><strong>Distribution</strong></td>
<td></td>
</tr>
<tr>
<td>V&lt;sub&gt;d&lt;/sub&gt;</td>
<td>~85.5 liters</td>
</tr>
<tr>
<td><strong>Protein Binding</strong></td>
<td></td>
</tr>
<tr>
<td>~94%</td>
<td></td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td></td>
</tr>
<tr>
<td>Enzymes</td>
<td>UGT1A9, UGT2B7</td>
</tr>
<tr>
<td>Metabolites</td>
<td>Inactive</td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
<td></td>
</tr>
<tr>
<td>Half-life</td>
<td>~17 hours</td>
</tr>
<tr>
<td>Renal clearance</td>
<td>~50%</td>
</tr>
<tr>
<td>Clearance</td>
<td>~11.2 liters/hour</td>
</tr>
</tbody>
</table>

<sub>t<sub>max</sub> = time to C<sub>max</sub>; V<sub>d</sub> = volume of distribution</sub>

[http://pharmacy.ufl.edu/pharmanote/](http://pharmacy.ufl.edu/pharmanote/)
Phase B results were reported in the VERTIS MONO extension study which was aimed at assessing ertugliflozin safety and tolerability through week 52.11 During Phase B, to maintain blinding, participants in the ertugliflozin groups received placebo in addition to ertugliflozin resulting in 52 weeks of treatment with ertugliflozin. The control group received 26 weeks of placebo followed by 26 weeks of metformin therapy and those in the ertugliflozin were given a metformin placebo. Due to metformin use in Phase B, formal comparisons between ertugliflozin and placebo/metformin group were not made. At week 52, the mean change from baseline in HbA1c was -1.0% for placebo (metformin), -0.9% for ertugliflozin 5 mg, and -1.0% for ertugliflozin 15 mg, demonstrating sustained efficacy of ertugliflozin.

Results at week 52 also showed reductions from baseline in FPG, body weight, and SBP. The incidence of drug-related adverse events in Phase B was lower in the ertugliflozin groups compared with the placebo/metformin group. Safety assessments included adverse event monitoring, physical examination, vital signs, laboratory evaluations and ECG and are discussed in the safety section of this article.

VERTIS MET

The VERTIS MET trial was a double-blind, 104-week, multi-center, randomized, parallel-group study including a 26-week, double-blind treatment period (Phase A) followed by an ongoing 78-week double-blind treatment extension not published at the time of this manuscript writing (Phase B).12 The study purpose was to evaluate the efficacy and safety of ertugliflozin in T2DM inadequately controlled with metformin monotherapy. Bone mineral density (BMD) and biomarkers of bone turnover were also evaluated as a safety aspect and are unique to this study. The study included 621 participants aged 24 to 79 years, 40% of which were women postmenopausal ≥3 years. Participants had a minimum 8-week duration of metformin monotherapy with a stable dose of ≥1,500 mg per day followed by two weeks, single-blind, run-in period with placebo prior to being randomly assigned (1:1:1) to placebo (n=209), ertugliflozin 5 mg (n=207) or ertugliflozin 15 mg (n=205). Randomization was stratified into 4 groups: (1) men, (2) premenopausal women, (3) women postmenopausal or postmenopausal <3 years after last menstrual period or who underwent bilateral oophorectomy <3 years prior to screening, and (4) women who were postmenopausal ≥3 years after their last menstrual period or who underwent bilateral oophorectomy ≥3 years prior to screening. The primary efficacy endpoint was change in baseline at week 26 in HbA1c. Compared to placebo in patients inadequately treated with just metformin, the mean reduction from baseline in HbA1c were significant for ertugliflozin 5 mg (difference = -0.7%; 95% CI, -0.9% to -0.5%) and ertugliflozin 15 mg (difference = -0.9%; 95% CI, -1.0% to -0.7%). Secondary endpoints showed significant reductions from baseline in FPG, body weight, SBP, and DBP compared with placebo. Bone mineral density was evaluated using dual energy x-ray absorptiometry of lumbar spine, femoral neck, total hip and distal forearm regions. DXA scanning was completed at baseline and at week 26. Ertugliflozin demonstrated no clinical or statistical difference in BMD change at week 26 when compared to placebo.

VERTIS SITA

The VERTIS SITA trial was a randomized, double-blind, multi-center, placebo-controlled, parallel-group 26-week study. The trial evaluated the safety and efficacy of the combination of ertugliflozin and sitagliptin in patients with inadequately controlled T2DM (HbA1c between 8% and 10.5%) on diet and exercise regimens.14 The 26 weeks included a 28 weeks wash-off period and a 2-week, single-blind, placebo run-in period. Participants were at least 18 years of age or older with T2DM according to ADA guidelines with a HbA1c of 8.0% to 10.5% on diet and exercise alone for ≥8 weeks prior to screening. Participants who were previously taking an antihyperglycemic agent prior to wash-off period were either on metformin, alpha glucosidase inhibitors, sulfonylureas, or glinides. Participants were then randomized to placebo (n=97), E5+S100 combination (n=98) or E15+S100 combination (n=96) once daily. The primary outcome was mean change from baseline in HbA1c at week 26 and after this time the mean HbA1c change for each group was reported at: placebo -0.4%; 95% CI, -0.7% to -0.2%; E5+S100 -1.6%; 95% CI, -1.8% to -1.4%; E15+S100 -1.7%; 95% CI, -1.9% to -1.5%. At week 26, treatment with ertugliflozin 5 mg and 15 mg in combination with sitagliptin at 100 mg daily provided statistically significant reductions in HbA1c compared to placebo (E5+S100 difference = -
<table>
<thead>
<tr>
<th>Trial</th>
<th>Interventions</th>
<th>*ΔHbA1c (%) (mean change from baseline)</th>
<th>ΔWt (kg) (from baseline)</th>
</tr>
</thead>
</table>
| **VERTIS MONO**<sup>10</sup> | • PBO (n=153)  
• ERTU 5 mg (n=155)  
• ERTU 15 mg (n=155) | ERTU 5 mg vs PBO  
-0.99 (95% CI, -1.22, -0.76)  
ERTU 15 mg vs PBO  
-1.16 (95% CI, -1.39, -0.93) | ERTU 5 mg vs PBO  
-1.76 kg (95% CI, -2.57, -0.95)  
ERTU 15 mg vs PBO  
-2.16 kg (95% CI, -2.98, -1.34) |
| **VERTIS MONO Extension**<sup>11</sup> | • ERTU 5 mg  
• ERTU 15 mg | ERTU 5 mg:  
-0.9  
ERTU 15 mg:  
-1.0 | ERTU 5 mg:  
-3.6  
ERTU 15 mg:  
-3.7 |
| **VERTIS MET**<sup>12</sup> (Add-on to metformin) | • PBO (n=290)  
• ERTU 5 mg (n=207)  
• ERTU 15 mg (n=205) | ERTU 5 mg vs PBO:  
-0.70 (95% CI, -0.9, -0.5)  
ERTU 15 mg vs PBO:  
-0.90 (95% CI, -1.0, -0.7) | ERTU 5 mg vs PBO:  
-3.0  
ERTU 15 mg vs PBO:  
-2.9 |
| **VERTIS FACTORIAL**<sup>13</sup> (Add-on to metformin) | • ERTU 5 mg (n=250)  
• ERTU 15 mg (n=248)  
• SITA 100 mg (n=247)  
• ERTU 5 mg + SITA 100 mg (n=243)  
• ERTU 15 mg + SITA 100 mg (n=244) | ERTU 5 mg vs PBO:  
-1.0 (95% CI, -1.1, -0.9)  
ERTU 15 mg vs PBO:  
-1.1 (95% CI, -1.2, -1.0)  
ERTU 5 mg vs PBO:  
-1.1 (95% CI, -1.2, -0.9)  
ERTU 15 mg vs PBO:  
-1.5 (95% CI, -1.6, -1.4)  
ERTU 5 mg vs PBO:  
-1.5 (95% CI, -1.6, -1.4)  | ERTU 5 mg vs PBO:  
-2.7 (95% CI, -3.1, -2.2)  
ERTU 15 mg vs PBO:  
-3.7 (95% CI, -4.2, -3.3)  
ERTU 5 mg vs PBO:  
-0.7 (95% CI, -1.1, -0.2)  
ERTU 15 mg vs PBO:  
-2.5 (95% CI, -3.0, -2.1)  
ERTU 5 mg vs PBO:  
-2.9 (95% CI, -3.4, -2.5)  |
| **VERTIS SITA**<sup>14</sup> (Add-on to diet and exercise) | • PBO (n=153)  
• ERTU 5 mg + SITA 100 mg (n=156)  
• ERTU 15 mg + SITA 100 mg (n=155) | ERTU 5 mg vs PBO:  
-0.44 (95% CI, -0.7, -0.2)  
ERTU 15 mg vs PBO:  
-1.6 (95% CI, -1.8, -1.4)  
ERTU 15 mg vs PBO:  
-1.7 (95% CI, -1.9, -1.5) | ERTU 5 mg vs PBO:  
-0.9 (95% CI, -1.7, -0.2)  
ERTU 15 mg vs PBO:  
-2.9 (95% CI, -3.6, -2.3)  
ERTU 15 mg vs PBO:  
-3.0 (95% CI, -3.7, -2.4)  |
| **VERTIS SITA2**<sup>15</sup> (Add-on to metformin) | • PBO (n=153)  
• ERTU 5 mg (n=156)  
• ERTU 15 mg (n=155) | ERTU 5 mg vs PBO:  
-0.7 (95% CI, -0.9, -0.5)  
ERTU 15 mg vs PBO:  
-0.8 (95% CI, -0.9, -0.6) | ERTU 5 mg vs PBO:  
-1.0 (95% CI, -1.6, -0.3)  
ERTU 15 mg vs PBO:  
-3.5 (95% CI, -4.1, -2.9)  
ERTU 15 mg vs PBO:  
-2.8 (95% CI, -3.4, -2.2)  |
1.2%; 95% CI, -1.5% to -0.8%); E15+S100 difference = -1.2%; 95%, -1.6% to -0.9%). Secondary endpoints included change in FPG, 2-h PPG, proportions of patients with HbA1c <7%, body weight, SBP, and DBP. When compared to placebo, significantly greater reductions from baseline were observed for the E5+S100 and E15+S100 groups in FPG (E5+S100 FPG (difference = -38.9 mg/dL; 95% CI, -49.9 to -28.0); (E15+S100 FPG (difference = -46.1 mg/dL; 95% CI, -57.1 to -35.0), 2-h PPG (E5+S100 2-h PPG (difference = -64.4 mg/dL; 95% CI, -80.5 to -44.4); (E15+S100 2-h PPG (difference = -69.6 mg/dL; 95% CI, -87.8 to -51.5), body weight (E5+S100 body weight (difference = -2.0 kg; 95% CI, -3.0 to -1.0); (E15+S100 (difference = -2.1 kg; 95% CI, -3.1 to -1.1)), and SBP. Clinically meaningful reductions in SBP were observed in the treatment groups as approximately 50% of patients were receiving blood pressure medication at baseline. Compared to placebo, the mean difference among treatment groups was significant in SBP change (E5+S100 SBP difference = -4.4 mmHg; 95% CI, -7.9 to -1.0 mmHg; E15+S100 SBP difference = -6.4 mmHg; 95% CI, -9.8 to -3.0 mmHg).

VERTIS SITA2

The VERTIS SITA2 trial compared the addition ertugliflozin (5 mg and 15 mg orally daily) to placebo in patients with uncontrolled T2DM already receiving metformin ≥1500 mg daily and sitagliptin 100 mg daily.15 Participants had a HbA1c level of 7.0% to 10.5% at screening. A total of 462 patients with T2DM were analyzed over 52 weeks. The primary efficacy endpoint was change from baseline HbA1c at week 26; however, treatment was continued until week 52 for safety data but statistical testing was not performed. Results of the primary outcome demonstrated superiority with ertugliflozin 5 mg (difference in HbA1c compared to placebo = -0.7%; 95% CI, -0.9% to -0.5%) and ertugliflozin 15 mg (difference in HbA1c compared to placebo = -0.8%; 95% CI, -0.9% to -0.6%). Secondary endpoints included FPG, body weight, proportion of patients with HbA1c <7% and SBP. Significant reductions in FPG, body weight, and SBP blood pressure were found when compared to placebo.

VERTIS SU

In the VERTIS SU trial, the safety and efficacy of ertugliflozin was compared to glimepiride in patients with T2DM inadequately controlled on metformin.16 This 52-week study was a double-blind, 2-phase, non-inferiority study in which 1,326 patients with HbA1c ≥7.0% to ≤9.0% on stable metformin ≥1,500 mg/day were randomly assigned 1:1:1 to ertugliflozin 5 mg (n=448), ertugliflozin 15 mg (n=440) once daily or glimepiride titrated from 1 mg once daily to an average of 3 mg per day (n=437). The primary outcome was change from baseline in HbA1c at week 52. At week 52, the mean change from baseline in HbA1c for ertugliflozin 5 mg was -0.6%; 95% CI, -0.6% to -0.5%; ertugliflozin 15 mg -0.6%; 95% CI, -0.7% to -0.5%; and glimepiride -0.7%; 95% CI, -0.8% to -0.7%. The difference in primary outcome of HbA1c change for ertugliflozin 15 mg compared to glimepiride was 0.1%; 95% CI, 0.0% to 0.2% and met non-inferiority criteria. Secondary endpoints included patients with HbA1c <7%, and changes in FPG and DBP. Composite endpoints included HbA1c decrease ≥0.5% with no symptomatic hypoglycemia and no body weight gain and HbA1c <7% and no symptomatic hypoglycemia. Ertugliflozin groups had a greater reduction in body weight while glimepiride patients gained weight on average. Ertugliflozin groups also had lower SBP compared with glimepiride and rates of adverse events were similar among groups. The incidence of symptomatic hypoglycemia was lower in the ertugliflozin 5 mg (5.6%) and ertugliflozin 15 mg (8.2%) groups compared with the glimepiride group (27.2%). The incidence of genital mycotic infections was increased in the ertugliflozin groups (2.1-10.0%) compared with the glimepiride group (0.1-4%).

**Safety**

In general, ertugliflozin was well tolerated among users in Phase III clinical trials. Table 4 summarizes the top four adverse reactions reported in ≥22% of the trial population from three ertugliflozin clinical trials including ertugliflozin monotherapy and combination therapy with metformin or sitagliptin. Among Phase III clinical trials, female and male genital mycotic infections were the most common adverse reactions reported.7,10,15 In the VER-TIS Mono study, genital mycotic infections occurred in 19.8% of patients in the ertugliflozin 5 mg group and in 28.2% of patients in the ertugliflozin 15 mg group compared to 6.8% in the placebo group.10 In the VERTIS Mono study, hypovolemia occurred in 1.3% of patients in the ertugliflozin 5 mg group and 2.0% of patients in the ertugliflozin 15 mg group compared to 3.9% in the placebo group.10 In the phase II dose-ranging study mentioned previously, the overall frequency of adverse events potentially related to volume depletion such as dehydration, hypotension, hypovolemia, and dizziness occurred in fewer than 3 patients out of all 219 patients in all ertugliflozin groups.8 A concern with canagliflozin, a fellow SGLT2 inhibitor, is increased incidence of below the knee amputations; however, out of seven Phase III clinical trials for ertugliflozin only 1 patient in comparator group, 3 patients in ertugliflozin 5 mg group, and 8 patients in the ertugliflozin 15 mg group reported non-traumatic lower limb amputations. A causal association between ertugliflozin and lower limb amputation has not been definitively made but should be considered prior to starting this medication in patients who may have a history that predisposes them to the need for amputations.7

**Warnings and Precautions**

Renal-related reactions such as acute kidney injury, renal im-
pairment, and acute prerenal failure are possible with use of er-
tugliflozin. Ertugliflozin causes intravascular volume contraction
which can result in renal impairment. Use of ertugliflozin is con-
traindicated in patients with severe renal impairment (eGFR
<30mL/minute/1.73m²) or dialysis. Initiation nor continued use
is recommended in those with eGFR 30-60 mL/minute/1.73m².
Renal function should be evaluated prior to initiation and periodi-
cally thereafter. Renal function was evaluated at week 6 and end
of study period at week 26 or week 52 in the VERTIS studies.

Special populations
Data on use of ertugliflozin in pregnancy is limited. Informa-
tion gathered from animal studies with ertugliflozin shows
adverse renal effects during times of renal development in rats.
Use is not recommended during the second and third trimesters
of pregnancy. Data is lacking on the presence of ertugliflozin in
human milk, the effects on breastfed infant, or effects on milk
production. Because kidney maturation in humans occurs in utero
and during the first couple years of life, there may be a risk to the
developing kidneys. Use is not recommended while breastfeeding.
Safety and effectiveness of ertugliflozin has not been established
in patients younger than 18 years of age. Notably, based on data
from clinical trials no dose adjustment is necessary for elderly
patients.7

Steglatro® is available as a 5 mg and 15 mg tablet. Recom-
manded starting dose is 5 mg by mouth once daily, taken in the
morning with or without food. Dose may be increased to maxi-
mum recommended dose of 15 mg once daily as tolerated. Of
note, the studies reviewed in this manuscript did not appear to
show any significant reductions in HbgA1c with the higher dose
compared to the lower dose.

Cost and Availability
Merck©, the manufacturer of Steglatro®, has collaborated
with Pfizer© to promote Steglatro®. Merck has established a list
price (Wholesale Acquisition Cost) of ~$9 per day for
Steglatro®.17 Merck© is also offering a free 30-day trial to qualify-
ing patients along with savings up to $460 per prescription ac-
cording to Merck’s product website for Steglatro®, making the
medication $0 charge for some privately insured patients. No dis-
counts are available for patients with public insurance programs
such as Medicare and Medicaid.

Summary
Ertugliflozin is the fourth SGLT2 inhibitor available in the
United States for improved glycemic control in adults with
T2DM. Ertugliflozin significantly improves HbA1c and may also
have some slight benefit on reducing body weight and blood pres-
sure. Common adverse reactions are similar to other SGLT2 in-
hibitors with female genital mycotic infections being the most
prevalent. Ertugliflozin has shown to be a safe and efficacious
oral antidiabetic agent when use as monotherapy and as an add-on
to oral antidiabetic agents such as sitagliptin and metformin in
patients with T2DM.

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and its potential in the treatment of type 2 diabetes: evidence

Table 4 | Adverse Reactions Reported in ≥2% of Patients7

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo (n=515)</th>
<th>Ertugliflozin 5 mg (n=519)</th>
<th>Ertugliflozin 15 mg (n=510)</th>
</tr>
</thead>
</table>
| Female genital mycotic infec-
tions                        | 3.0%           | 9.1%                      | 12.2%                       |
| Male genital mycotic infec-
tions                          | 0.4%           | 3.7%                      | 4.2%                        |
| Urinary tract infections       | 3.9%           | 4.0%                      | 4.1%                        |
| Headache                      | 2.3%           | 3.5%                      | 2.9%                        |
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