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

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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 managment.[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.[2] 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). Steglatro® (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%).[5] 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.

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Table 1 | Selectivity of SGLT-2 Inhibitors Available in the USA[4]

Molecule	SGLT-2 (IC50 nM)	SGLT-1 (IC50 nM)	SGLT-2/SGLT-1 selectivity ratio
Empagliflozin	3.1	8,300	2,500-fold
Ertugliflozin	0.87	1,960	2,000-fold
Dapagliflozin	1.2	1,400	1,200-fold
Canagliflozin	2.7	710	250-fold

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

Phase II

Amin et al. conducted a 12-week, randomized, double-blind, placebo- and active-controlled, parallel group, double-dummy, phase II dose-ranging study.[8] 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[9], 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 sitagliptin 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.[10] 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 ADA guidelines, with inadequate glycemic control with a HbA1c concentration between 7.0% and 10.5%.[9] 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/1.73m^2 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.[10] 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. Secondary efficacy endpoints were changes from baseline at week 26 in fasting plasma glucose (FPG), body weight, 2-hour postprandial glucose (PPG), systolic blood pressure (SBP), diastolic blood pressure (DBP), and the proportion of participants with HbA1c <7% at week 26. Both ertugliflozin 5 mg and 15 mg achieved significantly greater reductions in FPG (ertugliflozin 5 mg (mean change = -34.59 mg/dL; 95% CI, 42.70 to 26.31); ertugliflozin 15 mg (mean change = -43.96 mg/dL; 95% CI, -52.25 to -35.67)), body weight (ertugliflozin 5 mg (mean change = -1.76 kg; 95% CI, -2.57 to -0.95); ertugliflozin 15 mg (mean change = -2.16 kg; 95% CI, -2.98 to -1.34)) and 2-hour PPG (ertugliflozin 5 mg (mean change = -69.01 mg/dL; 95% CI, -83.24 to -54.78); ertugliflozin 15 mg (mean change = -67.39 mg/dL; 95% CI, -81.80 to -52.97)) compared with placebo at week 26. Ertugliflozin 15 mg vs placebo comparison for SBP was not significant so the prespecified hypothesis testing sequence stopped and testing of ertugliflozin 5 mg versus placebo for SBP and for both ertugliflozin groups versus placebo for DBP was not performed.

Table 2 | Steglatro Pharmacokinetics[7]

Parameters	Value
Absorption	
T_{max}	~1.0 hours
Distribution	
V_d	~85.5 liters
Protein Binding	~94%
Metabolism	
Enzymes	UGT1A9, UGT2B7
Metabolites	Inactive
Elimination	
Half-life	~17 hours
Renal	~50%
Clearance	~11.2 liters/hour

t_{max} = time to **C_{max}** ; **V_d** = volume of distribution

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, multicenter, 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 perimenopausal 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 duel energy x-ray absorptiometry of lumbar spine, femoral neck, total hip and distal forearms 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 FACTORIAL

In the VERTIS FACTORIAL 52-week, randomized, double-blind, 2-phase study, the efficacy and safety of combination ertugliflozin and sitagliptin was evaluated compared to the individual agents in patients with inadequately controlled T2DM on metformin.[13] Phase A evaluated the primary endpoint of the study which was change from baseline in HbA1c at Week 26. Phase B considered longer term efficacy and safety has not been published at the time of this manuscript writing. Participants had an HbA1c of 7.5% to 11.0% with at least 8 weeks of metformin monotherapy ≥ 1500 mg per day. Participants were randomly assigned to ertugliflozin 5 mg (E5; n=250), ertugliflozin 15 mg (E15; n=248), sitagliptin 100 mg (S100; n=247), ertugliflozin 5 mg + sitagliptin 100 mg (E5+S100; n=243), and ertugliflozin 15 mg + sitagliptin 100 mg (E15+S100; n=244). Primary outcome results were the following: E5 difference = -1.0 (95% CI, -1.1% to -0.9%), E15 difference = -1.1% (95% CI, -1.2% to -1.0%), S100 difference = -1.1% (95% CI, -1.2% to -0.9%), E5+S100 difference = -1.5% (95% CI, -1.6% to -1.4%), E15+S100 difference = -1.5% (95% CI, -1.6% to -1.4%). Reductions in HbA1c were greater with the E15+S100 group co-administered treatment group compared with the individual therapies (E15+S100 vs. ertugliflozin difference = -0.4%; 95% CI, -0.6% to -0.3%: E15+S100 vs. sitagliptin difference = -0.5%; 95% CI, -0.6% to -0.3%). Ertugliflozin 15 mg dose combinations achieved greater reductions in HbA1c compared to the other groups; however, the study was not powered to detect outcome differences between doses. Secondary endpoints included changes in FPG, body weight, and SBP. Compared to individual ertugliflozin and individual sitagliptin, mean reductions from baseline in FPG at week 26 were significantly greater in the ertugliflozin 5 mg plus sitagliptin 100 mg group (difference versus ertugliflozin = -8.2 mg/dL; -13.8 to -2.7; difference versus sitagliptan = -18.4 mg/dL; -24.0 to -12.8) and the ertugliflozin 15 mg plus sitagliptin 100 mg group (difference versus ertugliflozin = -11.8 mg/dL; -17.3 to -6.2; difference versus sitagliptan -23.1 mg/dL; -28.8 to -17.5)). After 52 weeks of treatment, about 40% of participants achieved an HbA1c < 7% with ertugliflozin + sitagliptin compared with 25% of participants using individual therapies.

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 ≥8 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 3 | Summary of Ertugliflozin Clinical Trials

Trial	Interventions	*ΔHbA1c (%) (mean change from baseline)	ΔWt (kg) (from baseline)
VERTIS MONO[10]	• 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[11]	• ERTU 5 mg • ERTU 15 mg	**ERTU 5 mg**: -0.9 **ERTU 15 mg**: -1.0 (No statistical comparisons made at Week 52)	**ERTU 5 mg**: -3.6 **ERTU 15 mg**: -3.7 (No statistical comparisons made at Week 52)
VERTIS MET[12] **(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[13] **(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)	• -1.0 (95% CI, -1.1, -0.9) • -1.1 (95% CI, -1.2, -1.0) • -1.1 (95% CI, -1.2, -0.9) • -1.5 (95% CI, -1.6, -1.4) • -1.5 (95% CI, -1.6, -1.4)	• -2.7 (95% CI, -3.1, -2.2) • -3.7 (95% CI, -4.2, -3,3) • -0.7 (95% CI, -1.1, -0.2) • -2.5 (95% CI, -3.0, -2.1) • -2.9 (95% CI, -3.4, -2.5)
VERTIS SITA[14] **(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)	• -0.44 (95% CI, -0.7, -0.2) • -1.6 (95% CI, -1.8, -1.4) • -1.7 (95% CI, -1.9, -1.5)	• -0.9 (95% CI, -1.7, -0.2) • -2.9 (95% CI, -3.6, -2.3) • -3.0 (95% CI, -3.7, -2.4)
VERTIS SITA2[15] **(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)	• -1.0 (95% CI, -1.6, -0.3) • -3.5 (95% CI, -4.1, -2.9) • -2.8 (95% CI, -3.4, -2.2)

VERTIS SU[16] (Add-on to metformin)	ERTU 5 mg (n=448)	• -0.6 (95%CI, -0.6, -0.5)	• -3.0 (95% CI, -3.3, -2.6)
	ERTU 15 mg (n=440)	• -0.6 (95%CI, -0.7, -0.5)	• -3.4 (95% CI, -3.7, -3.0)
	Titrated glimepiride (n=437)	• -0.7 (95%CI, -0.8, -0.7)	• 0.9 (95% CI, 0.6, 1.3)

95% CI = 95% confidence interval; **ΔHbA1c (%)** = change in hemoglobin A1c; **Δwt (kg)** = change in weight, kilograms; **BLV** = baseline value; **ERTU**= ertugliflozin; **mg** = milligram; **SITA** = sitagliptin; **PBO** = placebo

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-hr PPG (E5+S100 2-hr PPG (difference = -64.4 mg/dL; 95% CI, -80.5 to -44.4); (E15+S100 2-hr 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 ≥2% 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 VERTIS 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-

Table 4 | Adverse Reactions Reported in ≥2% of Patients[7]

Adverse Event	Placebo (n=515)	Ertugliflozin 5 mg (n=519)	Ertugliflozin 15 mg (n=510)
Female genital mycotic infections	3.0%	9.1%	12.2%
Male genital mycotic infections	0.4%	3.7%	4.2%
Urinary tract infections	3.9%	4.0%	4.1%
Headache	2.3%	3.5%	2.9%

pairment, and acute prerenal failure are possible with use of ertugliflozin. Ertugliflozin causes intravascular volume contraction which can result in renal impairment. Use of ertugliflozin is contraindicated in patients with severe renal impairment (eGFR <30mL/minute/1.73m^2) or dialysis.[7] Initiation nor continued use is recommended in those with eGFR 30-60 mL/minute/1.73m^2. Renal function should be evaluated prior to initiation and periodically thereafter.[7] 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. Information 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]

Dosing and Administration

Steglatro® is available as a 5 mg and 15 mg tablet. Recommended starting dose is 5 mg by mouth once daily, taken in the morning with or without food. Dose may be increased to maximum 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 qualifying patients along with savings up to $460 per prescription according to Merck's product website for Steglatro®, making the medication $0 charge for some privately insured patients. No discounts 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 pressure. Common adverse reactions are similar to other SGLT2 inhibitors 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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