Brand name: Steglatro

Generic name: Ertugliflozin (er too gli FLOE zin)

Manufacturer: Merck

Drug Class: Sodium-glucose co-transporter 2 (SGLT2) inhibitor

Uses:

Labeled: Indicated as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

Unlabeled: n/a

Mechanism of Action: SGLT2 is the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. Ertugliflozin is an inhibitor of SGLT2, which reduces renal reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion

Pharmacokinetics:

Tmax: 1 hour (fasting), 2 hours (administered with high-fat, high-calorie meal)

Vd: 85.5 L

T1/2: 16.6 hours

Bioavailability: ~100%

Protein Binding: 93.6%

Metabolism: Primarily by UGT1A9 and UGT2B7-mediated O-glucuronidation to inactive metabolites; minimal CYP involvement

Excretion: Urine (40.9%); feces (50.2%)

Efficacy:

Terra SG, Focht K, Davies M, Frias J, Derosa G, Darekar A, et al. Phase III, efficacy and safety study of Ertugliflozin monotherapy in people with type 2 diabetes mellitus inadequately controlled with diet and exercise alone. Diabetes Obes Metab. 2017: 19(5); 721-728.

Study design:

- Objective: conduct a phase III study to evaluate efficacy and safety of ertugliflozin monotherapy in people with type 2 diabetes
- This was a 52-week, double-blind, multicenter, randomized, parallel-group study with a 26-week, placebo-controlled treatment period (phase A), followed by a 26-week active-controlled treatment period

Description of study:

- 461 men and women, aged ≥18 years with inadequate glycemic control (glycated hemoglobin [HbA1c] concentration 7.0% to 10.5% [53-91 mmol/mol], inclusive) despite diet and exercise.
- The primary endpoint was the change in HbA1c from baseline to week 26

Results:

- At week 26, the placebo-adjusted least squares mean HbA1c changes from baseline were -0.99% and -1.16% for the Ertugliflozin 5 and 15 mg doses, respectively ($P < .001$ for both doses).
- The odds of having HbA1c <7.0% (53 mmol/mol) were significantly greater in the ertugliflozin 5 and 15 mg groups compared with the placebo group
- Both doses of ertugliflozin significantly lowered fasting plasma glucose and 2-hour postprandial glucose levels and body weight
- The placebo-adjusted differences in changes from baseline in systolic blood pressure were not statistically significant
- There were significantly more genital mycotic infections in the ertugliflozin groups

Limitations:

- Only results from the first 26 weeks reported
- Changes in diet, exercise, or other factors that could influence results were not detailed or accounted for
- Study was funded and several authors were employed by the manufacturer

Conclusion:

- Ertugliflozin 5 and 15 mg treatment for 26 weeks provided effective glycemic control, reduced body weight and was generally well tolerated, when used as monotherapy. Genital mycotic infections were more common with ertugliflozin.

Dagogo-Jack S, Liu J, Eldor R, Lic GA, Johnson J, Hille D, et al. Efficacy and safety of the addition of Ertugliflozin in patients with type 2 diabetes mellitus inadequately controlled with metformin and sitagliptin: the VERTIS SITA2 placebo-controlled randomized study. Diabetes Obes Metab. 2018: 20; 530-540.

Study design:

- Double-blind, randomized, clinical trial
- Objective: To assess ertugliflozin in patients with type 2 diabetes mellitus who are inadequately controlled by metformin and sitagliptin

Description of study:

- Patients had glycated hemoglobin (HbA1c) 7.0%-10.5% receiving metformin $\geq$1500 mg/day and sitagliptin 100 mg/day and an estimated glomerular filtration rate $\geq$60 mL/min/1.73 m^2
- Ertugliflozin 5-mg once daily, 15-mg once daily, or placebo

- Primary efficacy endpoint: change from baseline in HbA1c at Week 26; treatment continued until week 52

Results:

- After 26 weeks, placebo-adjusted least squares (LS) mean changes in HbA1c from baseline were −0.7% (−7.5 mmol/mol) and −0.8% (−8.3 mmol/mol) for ertugliflozin 5 and 15 mg, respectively (both P < .001); 17.0%, 32.1% and 39.9% of patients receiving placebo, ertugliflozin 5 mg or ertugliflozin 15 mg, respectively, had HbA1c <7.0% (53 mmol/mol)
- Significant reductions in fasting plasma glucose, body weight (BW) and systolic blood pressure (SBP) were observed with ertugliflozin relative to placebo
- The positive effects of ertugliflozin on glycemic control, BW and SBP were maintained through Week 52
- There were significantly more genital mycotic infections in the ertugliflozin groups

Limitations:

- Study was funded and several authors were employed by the manufacturer
- Compared ertugliflozin to placebo instead of another SGLT2 inhibitor
- Mostly conducted outside of the US (Europe)
- Predominantly white patient population

Conclusion:

- Ertugliflozin can be considered a safe, effective adjunctive therapy for patients with type 2 diabetes mellitus taking metformin and sitagliptin who need more glycemic control. There were more genital mycotic infections in the ertugliflozin groups.

Amin NB, Wang X, Jain SM, Lee DS, Nucci G, Rusnak JM. Dose-ranging efficacy and safety study of Ertugliflozin, a sodium-glucose co-transporter 2 inhibitor, in patients with type 2 diabetes on a background of metformin. Diabetes Obes Metab. 2015: 17; 591-598.

Study design:

- 12-week, randomized, double-blind placebo- and active-controlled, parallel group, double-dummy, dose-ranging study
- Objective: investigate the efficacy and safety of Ertugliflozin, in a phase II dose-ranging study, in patients with type 2 diabetes mellitus (T2DM) inadequately controlled on metformin

Description of study:

- 328 patients randomized to once-daily ertugliflozin (1, 5, 10, 25 mg), sitagliptin (100 mg), or placebo for 12 weeks
- Primary outcome: change from baseline to week 12 in HbA1c concentration
- Secondary outcomes: changes from baseline to week 12 in body weight, fasting plasma glucose (FPG), and systolic/diastolic blood pressure (SBP/DBP)

Results:

- Ertugliflozin (1–25mg/day) produced significant reductions in HbA1c concentration [placebo-corrected least-squares mean (LSM) −0.45% (1 mg) to −0.72% (25mg); p≤0.002, similar to sitagliptin (−0.76%; p=0.0001)], FPG (LSM −1.17 to −1.90 mmol/l; p<0.0001) and body weight (−1.15 to −2.15%; p<0.0001).
- The LSM SBP decreased by −3.4 to −4.0 mmHg from baseline with Ertugliflozin 5–25 mg/day.
- No reductions in body weight or blood pressure were observed with sitagliptin.
- No dose-related increase in AE frequency occurred with ertugliflozin. .

Limitations:

- Authors all associated with manufacturer of ertugliflozin
- Short trial duration
- Uses dosing outside normal scope of practice
- Limited HbA1c to 11% (if on metformin monotherapy) and 9.5% (if on metformin plus one oral antidiabetic medication)

Conclusion:

- Ertugliflozin at higher doses may have similar efficacy as sitagliptin in reduction of HbA1c in patients not well controlled on metformin alone
- Ertugliflozin may be considered a safe, efficacious option for patients needing additional glycemic control who have suboptimal control with metformin

Amin NB, Wang X, Mitchell JR, Lee DS, Nucci G, Rusnak JM. Blood pressure-lowering effect of the sodium glucose co-transporter-2 inhibitor Ertugliflozin, assessed via ambulatory blood pressure monitoring in patients with type 2 diabetes and hypertension. Diabetes Obes Metab. 2015: 17(8); 805-808

Study design:

- Objective: assess the dose-response effect of ertugliflozin administered once daily for 4 weeks on systolic blood pressure (SBP) in adults with type 2 diabetes (T2DM) and hypertension using ambulatory blood pressure monitoring (ABPM) with hydrochlorothiazide (HCTZ) as a positive control

Description of study:

- Endpoints: (change from baseline to week 4) were: 24-h mean systolic blood pressure (SBP; primary); daytime, night-time, seated pre-dose SBP, 24-h, daytime, night-time, seated pre-dose diastolic blood pressure, 24-h urinary glucose excretion and fasting plasma glucose (FPG; secondary).
- After screening, patients entered a run-in period of at least 3 (maximum 6) weeks, where agents that block the renin–angiotensin–aldosterone system (RAAS) were withdrawn and baseline re-established. Patients with inadequately controlled T2DM [HbA1c 7.0–10%; FPG <15mmol/l(270mg/dl; conversion: 18mmol/l), despite receiving up to two oral antidiabetic agents] and hypertension [seated in-office blood pressure ≤159/≤99mmHg

(untreated or stable doses of 1–2 non-RAAS agents)] were randomized to once-daily Ertugliflozin (1, 5, 25mg), HCTZ (12.5mg [10]) or placebo; instructed to take study medication with their morning meal and asked to follow the Dietary Approaches to Stop Hypertension diet

Results:

- Significant decreases in placebo-corrected 24-h mean SBP (−3.0 to −4.0 mmHg) were recorded for all doses of ertugliflozin (for HCTZ, this was −3.2 mmHg).
- Daytime, but not night-time SBP was consistently reduced.
- Ertugliflozin produced dose-dependent significant decreases in FPG and increases in urinary glucose excretion

Limitations:

- Patients with persistent, severe uncontrolled hypertension [SBP/diastolic blood pressure (DBP) ≥180/110mmHg], chronic/recurrent atrial/ventricular dysrhythmias, secondary hypertension, and history of myocardial infarction, stroke/transient ischemic attack, frequent hypoglycemia/diabetic complications with significant end-organ damage, or other significant morbidity 6 months before screening were excluded.
- All authors associated with manufacturer of ertugliflozin
- Doses of ertugliflozin not what are normally seen in practice
- HCTZ used at approved dose, but 25 mg/day may be more commonly used

Conclusion:

- Ertugliflozin may have similar efficacy in blood-pressure control as HCTZ when used as a T2DM medication
- Ertugliflozin may cause blood pressure lowering through osmotic diuresis
- Patients may experience positive blood-pressure lowering effects through use of ertugliflozin

Contraindications:

1. Ertugliflozin is contraindicated in patients with a history of serious hypersensitivity reaction to ertugliflozin
2. Ertugliflozin should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis (DKA)
3. Ertugliflozin is contraindicated in patients with severe renal impairment, end stage-renal failure, or patients on dialysis

Precautions:

1. Ertugliflozin causes intravascular volume contraction; symptomatic hypotension can occur after initiation
2. Cases of serious urinary tract infections (UTI), including urosepsis and pyelonephritis, requiring hospitalization, have been reported in patients receiving SGLT2 inhibitors

3. Use with caution in those with increased risk for hypoglycemia
4. An increased risk of lower limb amputation (primarily of the toe) has been reported with clinical studies with another SGLT2 inhibitor (canagloflozin)
5. Dose-related increases in LDL cholesterol may occur
6. Use has not been studied in patients with severe hepatic impairment
7. Geriatric patients receiving Ertugliflozin experienced higher incidence of adverse reactions related to volume depletion

Adverse effects:

	Number (%) of Patients		
	Placebo N= 515	Steglatro 5 mg N= 519	Steglatro 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%
Vaginal pruritus	0.4%	2.8%	2.4%
Increased urination	1.0%	2.7%	2.4%
Nasopharyngitis	2.3%	1.7%	2.5%
Weight decreased	1.0%	1.2%	2.4%
Thirst	0.6%	2.7%	1.4%

Drug Interactions:

1. Beta blockers- may hide/mask the signs and symptoms of hypoglycemia; use with caution
2. ACE inhibitors- may hide/mask the signs and symptoms of hypoglycemia; use with caution
3. Fluoroquinolone antibiotics- concurrent therapy may lead to increased risk of hypoglycemia or hyperglycemia; dose adjustment may be required after discontinuation of fluoroquinolone; closely monitor blood glucose
4. Insulin- concurrent use with insulin may increase risk of hypoglycemia; dose adjustment and more frequent glucose monitoring may be warranted

Dosing/Administration:

Usual dose: Starting dose is 5 mg once daily in the morning with or without food. May be increased to a maximum of 15 mg once daily if additional glycemic control is needed.

Geriatric dose: refer to adult

Pediatric dose: n/a

Renal impairment:

eGFR $\geq$60 mL/min/1.73m^2: No dosage adjustment necessary

eGFR 30- <60 mL/min/1.73m^2: Not recommended for initiation of therapy in pre-existing renal impairment or continued use when eGFR is persistently within this range during therapy

eGFR <30 mL/min/1.73m^2: Use is contraindicated

ESRD or dialysis: Use is contraindicated

Hepatic impairment:

Mild or moderate impairment (Child-Pugh Class A or B): No adjustment necessary

Severe impairment (Child-Pugh Class C): Use not recommended (not studied)

Use in special populations:

Pregnancy: Based on animal data showing adverse renal effects, ertugliflozin is not recommended for use during 2nd or 3rd trimesters of pregnancy

Breast-feeding: Due to potential serious adverse reactions in breast-fed infants, advise women that the use of ertugliflozin is not recommended while breastfeeding

Conclusion: Ertugliflozin has been shown to be an effective oral antidiabetic medication in T2DM patients who are currently using metformin with inadequate glycemic control OR in patients as monotherapy who are not well controlled on diet and exercise alone and cannot tolerate metformin. Ertugliflozin is generally well tolerated but does have an increased risk of genital mycotic infections. In addition, ertugliflozin is contraindicated in severe renal impairment (eGFR < 30 mL/min/1.73m^2) and is not recommended in patients with moderate renal impairment (eGFR < 60 mL/min/1.73m^2). Patients should be made aware of signs and symptoms of DKA and hypoglycemia. Patients' HbA1c should be monitored frequently and adjustments made to the medication regimen made as needed. Additional studies are needed to compare ertugliflozin with other currently available anti-diabetic medications in regards to efficacy, safety, and cost parameters to help establish ertugliflozin's place in therapy.

References:

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