Brand Name: Steglatro

Generic Name: ertugliflozin

Manufacturer[1,5]: Merck Sharp & Dohme Corp.

Drug Class[1,2,3,4,5]: Antidiabetic Agent, SGLT-2 inhibitor

Uses[1,2,3,4,5]:

Labeled Uses: Indicated as a treatment of type 2 diabetes in adjunct with diet and exercise.
Unlabeled Uses: No unlabeled uses have been indicated.

Mechanism of Action[1,2,3,4,5]: Sodium-glucose co-transporter 2 (SGLT2) reabsorbs glucose, that has been filtered by the tubular lumen, in the proximal renal tubules. Ertugliflozin inhibits SGLT2, reducing the reabsorption of filtered glucose and lowering the renal threshold for glucose (RTG); a reduction in plasma glucose concentrations is obtained.

Pharmacokinetics[1,2,3,4,5]:

Absorption:

T_{max}	1 hour (fasting), 2 hours (administered with high-fat, high calorie meal)
V_d	85.5 L
$t_{1/2}$	16.6 hours
Clearance	11.2 L/hr
Protein Binding	93.6%
Bioavailability	~100%

Metabolism: Ertugliflozin is metabolized into two inactive glucuronides by UGT1A9 and UGT2B7; cytochrome P450 mediated metabolism is minimal (12%).

Excretion: Ertugliflozin is excreted into urine (50.2%) and in feces (40.9%). Approximately 1.5% and 33.8% of unchanged drug is excreted in the urine and feces, respectively.

Efficacy:

Rosenstock J, Frias J, Páll D, Charbonnel B, Pascu R, Saur D, Darekar A, Huyck S, Shi H, Lauring B, Terra SG. Effect of ertugliflozin on glucose control, body weight, blood pressure and bone density in type 2 diabetes mellitus inadequately controlled on metformin monotherapy (VERTIS MET). Diabetes Obes Metab. 2018 Mar;20(3):520-529.

Study Design: Phase III, randomized, double-blind, placebo-controlled, parallel group, 26-week multicenter study.

Description of Study: *Methods:* The 621 patients randomized in the trial were type 2 diabetics that were stabilized on metformin monotherapy. Patients were excluded if they had renal impairment, poor compliance, bariatric surgery, a history of ketoacidosis, osteoporosis or low bone mineral density. The patients were counseled on appropriate dietary and lifestyle guidelines for type 2 diabetes before the start of the study. Participants were randomly assigned to placebo, 5 mg or 15 mg of ertugliflozin. Patients received a glycemic rescue therapy of open-label glimepiride if they met the prespecified criteria and continued the ertugliflozin or matching placebo. *Outcome Measures:* The primary efficacy endpoint was HbA1c change from baseline at week 26. Secondary efficacy endpoints included changes from baseline at week 26 in: fasting plasma glucose, body weight, systolic and diastolic blood pressure, and number of participants with HbA1c less than 7.0%. The primary safety assessments included: adverse events, bone mineral density, biomarkers of bone turnover, and physical examination. *Results:* At week 26, the placebo-adjusted least-squares mean change from baseline HbA1c (8.1%) was -0.7% and -0.9% for ertugliflozin 5 mg and 15 mg (both $P<0.001$), respectively. Ertugliflozin significantly lowered fasting plasma glucose, body weight, systolic blood pressure and diastolic blood pressure when compared to placebo. The likelihood of HbA1c less than 7.0% was significantly higher in both ertugliflozin groups. Incidence of genital mycotic infections was higher in both ertugliflozin groups, especially in female participants. There was also an increase in urinary tract infections and symptomatic hypoglycemia. There was no impact on bone mineral density by week 26.

Limitations: Multiple authors were employed and owned stock in Pfizer and Merck Sharp & Dohme; both companies funded the study. Merck Sharp & Dohme is also the manufacturer of the medication. The study may not be long enough to determine bone mineral density changes. The study neither explained if lifestyle and dietary modifications were executed by the participants nor did it report individual adverse effects.

Conclusion: When administered in addition to metformin, ertugliflozin was found to be effective at lowering HbA1c over a 26 week period when compared to placebo. The medication

was also effective at lowering fasting plasma glucose and blood pressure. Ertugliflozin had very few side effects; genital mycotic infections were of the most concern. Incidence of hypoglycemic events were also increased in both ertugliflozin groups. The study supports ertugliflozin as a safe and effective add-on therapy to metformin for lowering blood glucose in patients with uncontrolled hyperglycemia, but more studies should be conducted to ensure that the medication is safe for use in the geriatric population due to hypoglycemic and hypovolemic concerns. Longer studies should also be conducted to better determine alterations to the bone mineral density.

Terra SG, Focht K, Davies M, 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, Obesity and Metabolism*. 2017;19(5):721-728.

Study Design: Phase III, randomized, double-blind, placebo-controlled, parallel group, 26-week multicenter study.

Description of Study: *Methods:* The study was conducted over 67 sites across seven countries and included patients with type 2 diabetes, an HbA1c of 7.0% to 10.5%, and who had not received treatment with an antihyperglycemic agent for greater than or equal to eight weeks prior to screening. Patients were excluded if they had uncontrolled hyperglycemia, renal impairment, a history of ketoacidosis, or a cardiovascular event within three months of screening. A total of 461 participants were randomized to either placebo, ertugliflozin 5 mg, or ertugliflozin 15 mg. Glycemic rescue therapy with open-label metformin was used when patients met prespecified criteria. *Outcome Measures:* The primary efficacy endpoint was the change from baseline in HbA1c at week 26. Secondary efficacy endpoints include changes from baseline at week 26 of the following: fasting plasma glucose, body weight, two-hour postprandial glucose level, systolic blood pressure, diastolic blood pressure, and the proportion of participants with HbA1c less than 7.0%. Safety endpoints included adverse events, physical examination, and an echocardiogram. *Results:* At week 26, the placebo-adjusted least-squares mean change from baseline HbA1c was -0.99% and -1.16% for ertugliflozin 5 mg and 15 mg (both $P<0.001$), respectively. Participants with an HbA1c greater than or equal to 8% received reductions in HbA1c of -1.11% and -1.52% for ertugliflozin 5 mg and 15 mg, respectively. At week 26, ertugliflozin 5 mg and 15 mg achieved significantly greater reductions in fasting plasma glucose, body weight, and two-hour postprandial glucose level compared with placebo. Adverse effects were similar between the ertugliflozin groups and the placebo group, with the exception of genital mycotic infections associated more with the ertugliflozin group. All other safety endpoints were similar among all groups.

Limitations: The majority of the investigators were employees and owned stock in either Pfizer or Merck & Co., Inc.; both companies funded the study. The study excluded patients that had

previously had a cardiac event, reducing the ability to extrapolate the findings to this particular population. The efficacy of ertugliflozin seemed to rise as the HbA1c increased, but patients with an extremely high HbA1c were excluded. It is unclear if the medication is more efficacious when the patient has a higher HbA1c. Differences in diet and exercise were not assessed and adverse effects were not individually reported.

Conclusion: When administered as monotherapy, ertugliflozin was found to be effective at lowering HbA1c over a 26 week period when compared to placebo. The medication also lowered HbA1c more in patients with a higher baseline HbA1c. Ertugliflozin lowered fasting blood glucose and two-hour postprandial glucose significantly when compared to placebo. The only notable adverse event was the increase of occurrence in genital mycotic infections in women. The study supports ertugliflozin as an effective and safe monotherapy for type 2 diabetes. The trend of ertugliflozin lowering HbA1c more at higher baseline HbA1c levels should be further studied. More studies need to be conducted to ensure safety and efficacy in patients with a history of cardiac events. Lastly, ertugliflozin should be compared to current first-line therapy in studies to determine its utility as a first-line agent

Dagogo-Jack S, Liu J, Eldor R, 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, Obesity and Metabolism*. 2017;20(3):530-540.

Study Design: Phase III, randomized, double-blind, placebo-controlled, parallel group, 26-week multicenter study with a 26-week study extension.

Description of Study: *Methods:* The study was conducted over 104 centers across 12 countries and included patients with type 2 diabetes, an HbA1c between 7.0% and 10.5% and who were stable on metformin and sitagliptin for more than eight weeks at the screening visit. Patients were excluded if they had renal impairment, uncontrolled hyperglycemia, a history of prespecified cardiovascular events, or ketoacidosis. 464 participants were randomly assigned to a placebo, 5 mg or 15 mg of ertugliflozin for 52 weeks. Glycemic rescue therapy with open-label glimepiride was used when patients met prespecified criteria. *Outcome Measures:* The primary efficacy endpoint was HbA1c change from baseline at week 26. Secondary efficacy endpoints included changes from baseline at week 26 in: fasting plasma glucose, body weight, systolic blood pressure, and number of participants with HbA1c less than 7.0%. Assessments were performed at weeks 0, 6, 12, 18, 26, 39, and 52. The safety assessments included number of patients with adverse effects, hypoglycemia, laboratory values, electrocardiogram, and postural blood pressure reading. *Results:* After 26 weeks, placebo-adjusted least squares mean changes in HbA1c from baseline were -0.7% and -0.8% for ertugliflozin 5 and 15 mg, respectively (P<0.001). Patients with an HbA1c less than 7.0% were 17.0%, 32.1%, 39.9% in the placebo, 5

mg, and 15 mg ertugliflozin groups, respectively. Reductions in fasting blood glucose, body weight, and systolic blood pressure were observed with ertugliflozin relative to placebo. These reductions were maintained through week 52. A higher incidence of genital mycotic infections were observed in both groups compared to placebo through week 52. Incidence of urinary tract infection, symptomatic hypoglycemia and hypovolemia adverse events were not meaningfully different across the study groups.

Limitations: The majority of the investigators were employees and owned stock in either Pfizer or Merck & Co., Inc.; both companies funded the study. Sponsors also became unblinded after the first 26-week phase. The study excluded patients with a variety of different cardiac conditions, which prevents extrapolation of the safety and efficacy data to the population with these conditions. Differences in diet and exercise were not assessed and adverse effects were not individually reported. The study also accepted people that were not initially on the appropriate dosage of metformin or sitagliptin. These participant's medications were adjusted to the study requirement and stabilized for at least eight weeks before patients began the study. An HbA1c after eight weeks of stabilization of a new medication regimen may still have residual effects from the previous medication regimen, which may skew the HbA1c.

Conclusion: When administered in addition to metformin and sitagliptin, ertugliflozin was found to be effective at lowering HbA1c over a 26 week period when compared to placebo. Ertugliflozin also lowered fasting blood glucose and systolic blood pressure in comparison to placebo. All results were maintained through 52 weeks of therapy. Ertugliflozin was reported to be well tolerated in the majority of patients. The study supports ertugliflozin as a safe and effective third line therapy for lowering blood glucose in patients with uncontrolled hyperglycemia already taking metformin and sitagliptin. The study did not include patients with a variety of cardiac conditions; more studies should be conducted to ensure safety in patients with cardiac disease states. Future studies should ensure the HbA1c is stabilized at baseline before entering the patient into the study.

Contraindications[1,2,3,4,5]: History of serious hypersensitivity reactions; severe renal impairment, end stage renal disease, or dialysis.

Precautions[1,2,3,4,5]:

Hypotension: Ertugliflozin may cause symptomatic hypotension through intravascular volume contraction. Hypotension is of increased concern in elderly, in patients with low systolic blood pressure, in patients concurrently on a diuretic, and in patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2). Volume status should be assessed and corrected if indicated before initiating ertugliflozin. Monitor for signs and symptoms of hypotension after initiating therapy.

Ketoacidosis: Ketoacidosis has been reported in clinical trials in patients with type 1 and type 2 diabetes while receiving SGLT2 inhibitors. People being treated with ertugliflozin that report with signs and symptoms of severe metabolic acidosis should be assessed for ketoacidosis. These patients may present with blood glucose levels less than 250 mg/dL. If ketoacidosis is suspected, stop ertugliflozin and begin treatment immediately. Before beginning ertugliflozin, consider factors that may predispose the patient to ketoacidosis. In patients on ertugliflozin, monitor for ketoacidosis and temporarily discontinue the medication when a situation predisposes the patient to ketoacidosis.

Renal Effects: Acute kidney injury (AKI) and renal impairment have been reported with this medication. Before initiating ertugliflozin, consider factors that may predispose the patient to increased risks of AKI. Discontinue the use of ertugliflozin if oral intake reduces or fluid losses occur. If AKI occurs, discontinue ertugliflozin immediately and begin treatment.

Ertugliflozin increases serum creatinine and decreases eGFR; patients with moderate renal impairment may be more susceptible. Renal function should be evaluated before initiation and ertugliflozin is not recommended in patients with an eGFR between 30 mL/min/1.73 m^2 and 60 mL/min/1.73 m^2. The use of ertugliflozin is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m^2.

Urinary Tract Infection: Treatment with SGLT2 inhibitors increase the risk of urinary tract infections. Severe infections, including urosepsis and pyelonephritis requiring hospitalization have been reported. If a patient presents with signs and symptoms of a urinary tract infection, begin treatment promptly when indicated.

Lower Limb Amputation: An increase in lower limb amputation risk have been observed with another SGLT2 inhibitor. Across Phase 3 trials for ertugliflozin, one (0.1%) patient from the comparator group, three (0.2%) from the ertugliflozin 5 mg group, and eight (0.5%) from the ertugliflozin 15 mg group required lower limb amputations. Before initiating ertugliflozin, consider factors that may predispose the patient to lower limb amputations. Counsel patients on importance of routine preventative foot care and monitor for signs of infection and ulcers involving the lower limb. Discontinue ertugliflozin if these complications occur.

Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues: When used in combination with insulin or an insulin secretagogue, ertugliflozin may increase the risk of hypoglycemia. A lower dose of insulin or insulin secretagogue may be necessary after initiating ertugliflozin.

Genital Mycotic Infections: Ertugliflozin increases the risk of genital mycotic infections. Females, uncircumcised patients and patients with a history of genital mycotic infections are at

an increased risk of developing these infections. Monitor for infections and treat appropriately when indicated.

Increases in Low-Density Lipoprotein Cholesterol: Ertugliflozin may cause dose-related increases in low-density lipoprotein cholesterol. Monitor the low-density lipoprotein cholesterol and treat appropriately when indicated.

Adverse effects[1,2,3,4,5]:

Occuring in >10% of patients
- *Genitourinary*
  - Genital candidiasis (females: 9.1% to 12.2%; males: 3.7% to 4.2%)

Occuring in 1% to 10% of patients
- *Central Nervous System*
  - Headache (2.9% to 3.5%)
- *Cardiovascular*
  - Hypovolemia (1.9% to 4.4%)
- *Endocrine & Metabolic*
  - Hypoglycemia (1.3% to 3.4%)
  - Increased thirst (1.4% to 2.7%)
  - Weight loss (1.2% to 2.4%)
  - Severe hypoglycemia (2% to 7.8%; 27.3% to 35.8% with insulin and/or insulin secretagogue therapy)
- *Genitourinary*
  - Urinary frequency (2.4% to 2.7%)
  - Vulvovaginal pruritus (2.4% to 2.8%)
- *Neuromuscular & Skeletal*
  - Back Pain (1.7% to 2.5%
- *Respiratory*
  - Nasopharyngitis (3%)

Uncommon (<1%), but serious
- *Endocrine & Metabolic*
  - Ketoacidosis (0.1%)
- *Renal*
  - AKI
  - Pyelonephritis
- *Miscellaneous*
  - Lower limb amputation (0.2% to 0.5%)

Frequency undefined
- *Endocrine & Metabolic*

Increased LDL cholesterol
Increased serum phosphate

Genitourinary

Decreased eGFR

Drug Interactions[1,2,3,4,5]:

Co-administration enhances hypoglycemic effect:

- Alpha-lipoic acid
- Androgens
- Angiotensin converting enzyme inhibitor
- Guanethidine
- Hypoglycemia-Associated Agents
- Insulin- consider insulin dose decrease when administering ertugliflozin
- Monoamine Oxidase Inhibitors
- Pegvisomant
- Prothionamide
- Salicylates
- Selective Serotonin Reuptake Inhibitors
- Sulfonylureas
- Thioctic acid

Co-administration diminishes therapeutic effect of ertugliflozin:

- Hyperglycemia-associated agents
- Ritodrine
- Thiazide and Thiazide-Like Diuretics

Co-administration may increase risk of hyperglycemia or hypoglycemia:

- Fluoroquinolones
- Beta-adrenergic blockers

Co-administration may result in impaired glucose regulation:

- Somatostatin analogues

Ertugliflozin may interact with the following tests:

- Positive test for glucosuria
- Interference with 1,5-anhydroglucitol assay

Dosing/Administration[1,2,3,4,5]:

Adult Dose:
Starting dose: 5 mg orally once daily. This dose may be increased to a MAXIMUM of 15 mg a day if optimal blood glucose control is not reached.

Geriatric Dose:
Refer to adult dosing.

Pediatric Dose:
Safety and efficacy is not established in pediatric patients.

Renal Impairment Dose:
eGFR ≥ 60 mL/min/1.73 m^2: No dosage adjustment
eGFR 30 to <60 mL/min/1.73 m^2: Not recommended for initiation on ertugliflozin
eGFR <30 mL/min/1.73 m^2: Use is contraindicated
End stage renal disease or dialysis: Use is contraindicated

Hepatic Impairment dose:
Mild or moderate impairment (Child-Pugh A or B): No dosage adjustment
Severe impairment (Child-Pugh C): Use is not recommended due to a lack of studies

Use in Special Circumstances[1,2,3,4,5]:

Pregnancy: There are no adequate human studies of ertugliflozin use during pregnancy. Based on animal studies, there is a potential risk for adverse renal events in the second and third trimester. These events included renal pelvic and tubule dilations and mineralization during periods of renal development. Advise patients of potential risk to fetus, especially during the second and third trimester.

Breastfeeding: The presence of ertugliflozin in breast milk is unknown; it is not recommended to use this medication while breastfeeding.

Pediatrics: There are no adequate studies to determine the safety and efficacy of ertugliflozin in pediatric patients.

Geriatrics: There is a higher incidence of adverse reactions related to a decrease in intravascular volume and renal function.

Renal Impairment: There is a higher incidence of adverse reactions related to a decrease

in intravascular volume and renal function.

Conclusion:

Ertugliflozin is an effective monotherapy and second or third line medication for patients with type 2 diabetes. More studies should be conducted comparing the efficacy of monotherapy ertugliflozin to the current first-line monotherapy before considering the class a first-line option. Ertugliflozin is safe and tolerated well in most patients at both 5 mg and 15 mg. More studies need to be conducted to ensure the safety in the geriatric population and in patients with cardiac related diseases. A study determining the effect on lowering HbA1c as baseline HbA1c rises should also be conducted; if the trend continues as shown in some studies, ertugliflozin has the potential to become a better second line option for patients with extremely uncontrolled hyperglycemia. The efficacy and safety of ertugliflozin should be compared to other medications in both the SGLT-2 inhibitor class and other classes of glucose-lowering drugs in order to better understand the drug's place in therapy. The cost of ertugliflozin is considerably lower than the other SGLT-2 inhibitors and many of the new diabetic medications, but is still more expensive than older available agents. Considering the cost, tolerability and effectiveness of ertugliflozin to lower HbA1c, ertugliflozin is another clinically relevant second or third line medication for type 2 diabetes.

Recommended References:

1. Ertugliflozin. Clinical Pharmacology [Internet database]. Gold Standard, Inc., 2007. Available at: http://www.clinicalpharmacology.com. Accessed: May 30, 2018.
2. Ertugliflozin. In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Micromedex. Updated periodically. Accessed May 30, 2018.
3. Ertugliflozin. Lexi-Drugs [database online]. Lexi-Comp, Inc; May 30, 2018.
4. Ertugliflozin. Facts & Comparisons 4.0 Online [Internet database]. Wolters Kluwer. Available at: http://online.factsandcomparisons.com. Accessed May 30, 2018.
5. Steglatro [package insert]. Whitehouse Station, NJ: Merck Sharp & Dohme Corp; 2017
6. Rosenstock J, Frias J, Páll D, Charbonnel B, Pascu R, Saur D, Darekar A, Huyck S, Shi H, Lauring B, Terra SG. Effect of ertugliflozin on glucose control, body weight, blood pressure and bone density in type 2 diabetes mellitus inadequately controlled on metformin monotherapy (VERTIS MET). Diabetes Obes Metab. 2018 Mar;20(3):520-529. doi: 10.1111/dom.13103. Epub 2017 Oct 2.
7. Terra SG, Focht K, Davies M, 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, Obesity and Metabolism*. 2017;19(5):721-728. doi:10.1111/dom.12888.
8. Dagogo-Jack S, Liu J, Eldor R, 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, Obesity and Metabolism*. 2017;20(3):530-540. doi:10.1111/dom.13116.

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