PDL DRUG REVIEW

Proprietary Name: Steglatro®
Common Name: ertugliflozin
PDL Category: Diabetic - Other

Comparable Products	Preferred Drug List Status
Farxiga	Preferred with Conditions
Invokana	Non-Preferred with Conditions
Jardiance	Preferred with Conditions

Summary

Pharmacology/Usage: Ertugliflozin L-pyroglutamic acid, the active ingredient of Steglatro®, is a sodium glucose co-transporter 2 (SGLT2) inhibitor, the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. By inhibiting SGLT2, ertugliflozin reduces renal reabsorption of filtered glucose and lowers the renal threshold for glucose, thus increases urinary glucose excretion.

Indications: Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (DM). It is not recommended in patients with type 1 DM or for the treatment of diabetic ketoacidosis.

There is no pregnancy category for this product; however, the risk summary indicates that based on animal data showing adverse renal effects, Steglatro® is not recommended during the second and third trimesters of pregnancy. The limited available data with use in pregnant women are not sufficient to determine a drug-associated risk of adverse developmental outcomes. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy. Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, and spontaneous abortions, among others, while poorly controlled diabetes increases the fetal risk for major birth defects, still births, and macrosomia related morbidity. The safety and efficacy of use in the pediatric population have not been established.

Dosage Forms: Tablets: 5mg, 15mg

Recommended Dosage: Correct volume depletion prior to starting treatment. Take 5mg QAM, with or without food. The dose may be increased to a maximum recommended dose of 15mg daily if additional glycemic control is needed in patients tolerating the 5mg dose. Assess renal function prior to starting treatment and periodically thereafter. Starting treatment is not recommended in patients with an eGFR of 30ml/min/1.73m^2 to <60ml/min/1.73m^2. Continued use is not recommended when eGFR is persistently between 30 and <60ml/min/1.73m^2.

Dose adjustments are not required with mild renal impairment. Use is not recommended with moderate renal impairment and is contraindicated with severe renal impairment, end-stage renal disease, or receiving dialysis. Dose adjustments are not required for mild or moderate hepatic impairment, and use has not been studied and is not recommended with severe hepatic impairment.

Drug Interactions: A lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with Steglatro®. Monitoring glycemic control with urine glucose tests or with 1,5-AG assay is not recommended in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Steglatro® 5mg) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or that the active drug was less than its comparator.* The most frequently reported adverse events included female genital mycotic infections (6.1%), male genital mycotic infections (3.3%), urinary tract infections (0.1%), headache (1.2%), vaginal pruritus (2.4%), increased urination (1.7%), nasopharyngitis (0.2%), back pain (0%), weight decreased (0.2%), and thirst (2.1%). Overall hypoglycemia (1.9%) was reported in clinical trials. The incidence of severe hypoglycemia was not reported with Steglatro® 5mg (0%) but was reported more with Steglatro® 15mg than placebo (1.3% vs 0%).

Steglatro® causes intravascular volume contraction. Thus, symptomatic hypotension may occur after starting treatment, especially in patients with impaired renal function, elderly patients, in patients with low systolic blood pressure, and in patients on diuretics. Monitor for signs of hypotension after starting treatment.

There have been post-marketing reports of serious urinary tract infections, including urosepsis and pyelonephritis in patients receiving SGLT2 inhibitors. Cases of pyelonephritis have also been reported in Steglatro®-treated patients. Assess for signs and symptoms and treat promptly.

An increased risk for lower limb amputation has seen been in clinical studies with another SGLT2 inhibitor. Across seven phase 3 clinical trials in the Steglatro® development program, non-traumatic lower limb amputations were reported in 1 patient in the comparator group (0.1%), 3 patients in the Steglatro® 5mg group (0.2%), and 8 patients in the Steglatro® 15mg group (0.5%). A causal association between Steglatro® and lower limb amputation has not been definitively established. Before starting Steglatro®, consider factors in the patient's history that may predispose them to the need for amputations. In addition, monitor for signs and symptoms of infection, new pain or tenderness, sores or ulcers involving the lower limbs. Discontinue treatment if these complications occur.

Contraindications: Severe renal impairment, end-stage renal disease (ESRD), or dialysis; History of a serious hypersensitivity reaction to Steglatro®

Manufacturer: Merck Sharp & Dohme

Analysis: The safety and efficacy of Steglatro® have been assessed in 7 multicenter, randomized, double-blind, placebo- or active-controlled studies that included adults with type 2 DM.

One randomized, placebo-controlled study included adults (N=461) with type 2 DM inadequately controlled on diet and exercise who were either treatment naïve or not receiving any background antihyperglycemic treatment. At 26 weeks, Steglatro® 5mg and 15mg daily resulted in statistically significant reductions in HbA1c as compared with placebo. Results can be seen in the table below, which was adapted from the prescribing information.

	Placebo	Steglatro® 5mg	Steglatro® 15mg
HbA1c	N=153	N=155	N=151
Baseline (mean)	8.1	8.2	8.4
Change from baseline (least squares mean)	-0.2	-0.7	-0.8

	Placebo	Steglatro® 5mg	Steglatro® 15mg
Difference from placebo (least squares mean)		-0.6; p<0.001	-0.7; p<0.001
Patients with HbA1c <7%	16.9% (N=26)	30.1% (N=47)	38.8% (N=59)
Fasting Plasma Glucose (FPG), mg/dl	N=150	N=151	N=149
Baseline (mean)	180.2	180.9	179.1
Change from baseline (LS mean)	-11.6	-31.0	-36.4
Difference from placebo (LS mean)		-19.4; p<0.001	-24.8; p<0.001
Baseline Body Weight, kg	94.2	94.0	90.6
Change from baseline body weight (LS mean)	-1.0	-3.0	-3.1
Difference from placebo (LS mean)		-2.0	-2.1

A second randomized, double-blind study included adults (N=621) inadequately controlled on metformin monotherapy who were randomized to Steglatro® or placebo in combination with metformin. At week 26, treatment with Steglatro® 5mg and 15mg resulted in statistically significant reductions in HbA1c as compared with placebo. The results can be seen in the table below, which was adapted from the prescribing information.

	Placebo + metformin	Steglatro® 5mg + metformin	Steglatro® 15mg + metformin
HbA1c	N=207	N=205	N=201
Baseline (mean)	8.2	8.1	8.1
Change from baseline (least squares mean)	-0.2	-0.7	-0.9
Difference from placebo (least squares mean)		-0.5; p<0.001	-0.7; p<0.001
Patients with HbA1c <7%	18.4% (N=38)	36.3% (N=74)	43.3% (N=87)
Fasting Plasma Glucose (FPG), mg/dl	N=202	N=199	N=201
Baseline (mean)	169.1	168.1	167.9
Change from baseline (LS mean)	-8.7	-30.3	-40.9
Difference from placebo (LS mean)		-21.6; p<0.001	-32.3; p<0.001
Baseline Body Weight, kg	84.5	84.9	85.3
Change from baseline body weight (LS mean)	-1.4	-3.2	-3.0
Difference from placebo (LS mean)		-1.8	-1.7

A multicenter, randomized, double-blind, active-controlled trial included adults with type 2 DM (N=1326) in adequately controlled on metformin who were randomized to glimepiride, Steglatro® 5mg, or Steglatro® 15mg in combination with metformin. After 52 weeks of treatment, Steglatro® 15mg was non-inferior to glimepiride. Results can be seen in the table below, which was adapted from the prescribing information.

	Glimepiride + metformin	Steglatro® 5mg + metformin	Steglatro® 15mg + metformin
HbA1c	N=437	N=447	N=440
Baseline (mean)	7.8	7.8	7.8
Change from baseline (least squares mean)	-0.6	-0.5	-0.5
Difference from glimepiride (least squares mean)		0.2	0.1
Patients with HbA1c <7%	47.7% (N=208)	39.5% (N=177)	42.2% (N=186)
Baseline Body Weight, kg	86.8	87.9	85.6
Change from baseline body weight (LS mean)	0.6	-2.6	-3.0
Difference from glimepiride (LS mean)		-3.2	-3.6

A separate study included adults with type 2 DM inadequately controlled on metformin monotherapy (N=1233) who were randomized in a double-blind study to assess the efficacy of Steglatro® 5mg or 15mg in combination with sitagliptin 100mg as compared to the individual components. The 5 treatment arms included Steglatro® 5mg, Steglatro® 15mg, sitagliptin 100mg, Steglatro® 5mg plus sitagliptin 100mg or Steglatro® 15mg plus sitagliptin 100mg. Results suggested that at 26 weeks, Steglatro® 5mg or 15mg plus sitagliptin 100mg provided statistically significantly greater reductions in HbA1c as compared to Steglatro® (5mg or 15mg) alone or sitagliptin 100mg monotherapy. The mean change from baseline in HbA1c was -1.4% for Steglatro® 5mg or 15mg plus sitagliptin 100mg versus -1.0% for Steglatro® 5mg, Steglatro® 15mg, or sitagliptin, respectively. In addition, a larger number in the Steglatro® 5mg or 15mg plus sitagliptin 100mg group achieved an HbA1c <7% (53.3% and 50.9%, respectively) as compared to the individual components (29.3% Steglatro® 5mg, 33.7% Steglatro® 15mg, or 38.5% sitagliptin 100mg).

A multicenter, randomized, double-blind, placebo-controlled study included adults with type 2 DM inadequately controlled on metformin and sitagliptin 100mg to assess the safety and efficacy of Steglatro® as compared with placebo as add-on therapy. At week 26, results suggested that Steglatro® 5mg or 15mg in combination with metformin and sitagliptin 100mg provided statistically significant reductions in HbA1c as compared with placebo plus metformin and sitagliptin 100mg, and resulted in a higher proportion of patients achieving an HbA1c <7% as compared with placebo. Results can be seen in the table below, which was adapted from the prescribing information.

	Placebo	Steglatro® 5mg	Steglatro® 15mg
HbA1c	N=152	N=155	N=152
Baseline (mean)	8.0	8.1	8.0
Change from baseline (least squares mean)	-0.2	-0.7	-0.8
Difference from placebo (least squares mean)		-0.5; p<0.001	-0.6; p<0.001
Patients with HbA1c <7%	20.2% (N=31)	34.6% (N=54)	42.3% (N=64)
Fasting Plasma Glucose (FPG), mg/dl	N=152	N=156	152
Baseline (mean)	169.6	167.7	171.7

	Placebo	Steglatro® 5mg	Steglatro® 15mg
Change from baseline FPG (LS mean)	-6.5	-25.7	-32.1
Difference from placebo FPG (LS mean)		-19.2; p<0.001	-25.6; p<0.001
Baseline Body Weight, kg	86.5	87.6	86.6
Change from baseline body weight (LS mean)	-1.0	-3.0	-2.8
Difference from placebo (LS mean)		-1.9	-1.8

Another randomized, double-blind, placebo-controlled study assessed the safety and efficacy of Steglatro® in combination with sitagliptin as compared with placebo plus sitagliptin 100mg in adults with type 2 DM inadequately controlled on diet and exercise (N=291). At week 26, treatment with Steglatro® 5mg and 15mg in combination with sitagliptin 100mg provided statistically significant reductions in HbA1c as compared with placebo. In addition, Steglatro® 5mg and 15mg in combination with sitagliptin 100mg resulted in a higher proportion achieving an HbA1c <7% and greater reductions in fasting plasma glucose as compared with placebo. Specific data was not included in the prescribing information for this study.

The efficacy of Steglatro® was assessed in a multicenter, randomized, double-blind, placebo-controlled study that included adults with type 2 DM and moderate renal impairment (N=468). In this study, 202 in the Steglatro® group had an eGFR between 45 and 60ml/min/1.73m^2 and 111 in the Steglatro® group had an eGFR between 30 and 45ml/min/1.73m^2. Most patients were receiving background insulin (55.9%) and/or sulfonylurea (40.3%). In addition, about 50% had a history of cardiovascular disease or heart failure. Results suggested that Steglatro® did not show efficacy in the study, and that the HbA1c reductions from baseline to week 26 were not significantly different between placebo and Steglatro® 5mg or 15mg.

Place in Therapy: Steglatro® is an oral SGLT2 inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2DM. It is not recommended in patients with type 1 DM or for the treatment of diabetic ketoacidosis. It is contraindicated for use in severe renal impairment and use is not recommended in those with moderate renal impairment. Steglatro® was found to be statistically significantly superior to placebo for reducing HbA1c in patients with type 2 DM in clinical trials, and was found to be non-inferior to glimepiride after 52 weeks of treatment but with greater changes in body weight.

There is no evidence at this time to support that Steglatro® is safer or more effective than the currently available, more cost effective, medications. It is therefore recommended that Steglatro® remain non-preferred and require prior authorization and be available to those who are unable to tolerate or who have failed on preferred medications.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred with Conditions**

References

[1] Steglatro [package insert]. Whitehouse Station, NJ: Merck Sharp & Dohme; 2017.