Netarsudil Ophthalmic Solution (Rhopressa)

Manufacturer: Aerie Pharmaceuticals, Inc., Irvine, California  
Date of Approval: December 18, 2017  
Indication: Netarsudil ophthalmic solution 0.02% is a Rho kinase inhibitor indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.  
Drug Class: Ophthalmics  
Uniqueness of Drug: Netarsudil is a novel, once-daily eye drop believed to work at the cellular level within the trabecular meshwork to improve outflow of aqueous humor (the fluid inside the eye). Most treatments lower IOP by decreasing aqueous humor production or by increasing outflow through the uveoscleral pathway, ignoring the normal outflow pathway through the trabecular meshwork.  
Warnings and Precautions:

Bacterial keratitis. There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.  

Use with contact lenses. Contact lenses should be removed prior to instillation of netarsudil and may be reinserted 15 minutes following its administration.  

Dosage and Administration: The recommended dosage of netarsudil is one drop in the affected eye(s) once daily in the evening. If one dose is missed, treatment should continue with the next dose in the evening. Twice-a-day dosing is not well tolerated and is not recommended. If netarsudil is to be used concomitantly with other topical ophthalmic drug products to lower IOP, administer each drug product at least five minutes apart.  

Commentary: The Food and Drug Administration’s approval of netarsudil was based on three randomized, controlled clinical trials that involved 1,875 patients with open-angle glaucoma or ocular hypertension. The phase 3 clinical trials compared netarsudil once-daily solution with timolol twice-daily solution; netarsudil demonstrated a consistent lowering of IOP from day 90 through 12 months. The average diurnal IOP in the netarsudil arm was 21.4 mm Hg, which decreased to 17.4 mm Hg at day 90—with changes beginning as early as week 2. The most common ocular adverse reaction observed in controlled clinical studies with netarsudil dosed once daily was conjunctival hyperemia, reported in 53% of patients. Other common (approximately 20%) ocular adverse reactions were corneal verticillata, instillation-site pain, and conjunctival hemorrhage. Instillation-site erythema, corneal staining, blurred vision, increased lacrimation, erythema of the eyelid, and reduced visual acuity were reported in 5% to 10% of patients.  

Sources: Aerie Pharmaceuticals, Inc., Rhopressa prescribing information

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Ertugliflozin (Steglatro)

Manufacturer: Merck and Co., Inc., Whitehouse Station, New Jersey  
Date of Approval: December 19, 2017  
Indication: Ertugliflozin is an oral sodium-glucose cotransporter 2 (SGLT2) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type-2 diabetes mellitus.  
Drug Class: SGLT2 inhibitors  
Uniqueness of Drug: More than 30 million Americans are estimated to have diabetes, about 90% of whom have type-2 diabetes, according to the Centers for Disease Control and Prevention. The Food and Drug Administration (FDA) approved ertugliflozin as a standalone therapy and in combination with sitagliptin (Januvia, Merck), a dipeptidyl peptidase-4 inhibitor, or metformin.  

Warnings and Precautions:

Hypotension. Ertugliflozin causes intravascular volume contraction; therefore, symptomatic hypotension may occur after initiating ertugliflozin, particularly in patients with impaired renal function (estimated glomerular filtration rate [eGFR] less than 60 mL/min/1.73 m²); in elderly patients (65 years of age and older); in patients with low systolic blood pressure; and in patients on diuretics. Before initiating ertugliflozin, volume status should be assessed and corrected if indicated. Monitor patients for signs and symptoms of hypotension during therapy.  

Ketoacidosis. Reports of ketoacidosis have been identified in clinical trials and post-marketing surveillance in patients with type-1 and type-2 diabetes mellitus receiving SGLT2 inhibitors. Patients treated with ertugliflozin who present with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of presenting blood glucose levels; ketoacidosis associated with ertugliflozin may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, ertugliflozin should be discontinued, the patient should be evaluated, and prompt treatment should be instituted. Treatment of ketoacidosis may require insulin and fluid and carbohydrate replacement.  

In many of the reported cases, and particularly in patients with type-1 diabetes, the presence of ketoacidosis was not immediately recognized and treatment was delayed because presenting blood glucose levels were below those typically expected for diabetic ketoacidosis (often less than 250 mg/dL). Signs and symptoms at presentation were consistent with dehydration and severe metabolic acidosis and included nausea, vomiting, abdominal pain, generalized malaise, and shortness of breath. In some but not all cases, factors predisposing the patient to ketoacidosis were identified, such as insulin dose reduction, acute febrile illness, reduced caloric intake due to illness or surgery, pancreatic disorders suggesting insulin deficiency (e.g., type-1 diabetes, history of pancreatitis or pancreatic surgery), and alcohol abuse. Before initiating ertugliflozin, consider factors in the patient history that may predispose to ketoacidosis, including pancreatic insulin deficiency from...
any cause, caloric restriction, and alcohol abuse. Patients may require monitoring and temporary discontinuation of therapy in clinical situations known to predispose them to ketoacidosis (e.g., prolonged fasting due to acute illness or surgery).

**Acute kidney injury and impairment in renal function.** Ertugliflozin causes intravascular volume contraction and can cause renal impairment. Before initiating ertugliflozin, consider factors that may predispose patients to acute kidney injury, including hypovolemia, chronic renal insufficiency, congestive heart failure, and concomitant medications (i.e., diuretics, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, nonsteroidal anti-inflammatory drugs). Consider temporarily discontinuing ertugliflozin in any setting of reduced oral intake (such as acute illness or fasting) or fluid losses (such as gastrointestinal illness or excessive heat exposure); monitor patients for signs and symptoms of acute kidney injury. If acute kidney injury occurs, promptly discontinue ertugliflozin and institute treatment. Ertugliflozin increases serum creatinine and decreases eGFR. Renal function should be evaluated prior to initiating ertugliflozin and periodically thereafter. Use of ertugliflozin is not recommended when eGFR is persistently between 30 mL/min/1.73 m² and less than 60 mL/min/1.73 m² and is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m².

**Urosepsis and pyelonephritis.** Treatment with SGLT2 inhibitors increases the risk for urinary tract infections. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated.

**Lower limb amputation.** An increased risk for lower limb amputation (primarily of the toe) has been observed in clinical studies with another SGLT2 inhibitor. Before initiating ertugliflozin, consider factors in the patient history that may predispose them to the need for amputations, such as a history of prior amputation, peripheral vascular disease, neuropathy, and diabetic foot ulcers. Counsel patients about the importance of routine preventive foot care. Monitor patients receiving ertugliflozin for signs and symptoms of infection (including osteomyelitis), new pain or tenderness, and sores or ulcers involving the lower limbs; discontinue ertugliflozin if these complications occur.

**Hypoglycemia with concomitant use of insulin and insulin secretagogues.** Consider a lower dose of insulin or insulin secretagogue (e.g., sulfonylurea) to reduce risk of hypoglycemia when used in combination with ertugliflozin.

**Genital mycotic infections.** Ertugliflozin increases the risk of genital mycotic infections, especially in patients who have a history of genital mycotic infections and in men who are uncircumcised.

**Increased low-density lipoprotein-cholesterol (LDL-C).** Dose-related increases in LDL-C can occur with ertugliflozin. Monitor and treat as appropriate.

**Dosage and Administration:** Ertugliflozin is available as 5-mg and 15-mg tablets. The recommended starting dose is 5 mg once daily, taken in the morning, with or without food. In patients tolerating ertugliflozin 5 mg once daily, the dose may be increased to a maximum recommended dose of 15 mg once daily if additional glycemic control is needed. In patients with volume depletion, correct this condition prior to initiation of ertugliflozin.

No dose adjustment is needed in patients with mild renal impairment.

**Commentary:** Ertugliflozin approval was based on data from seven phase 3 studies, which evaluated the drug as monotherapy or in combination with sitagliptin and/or metformin. Data from the studies showed that ertugliflozin alone or in combination with sitagliptin significantly reduced hemoglobin A1c levels compared with placebo. Ertugliflozin also significantly reduced body weight in patients who were already receiving a combination of sitagliptin and metformin versus placebo, and achieved significant reductions in systolic blood pressure.

**Sources:** Merck and Co., Inc., Steglatro prescribing information

## Lutetium Lu 177 Dotatate (Lutathera)

**Manufacturer:** Advanced Accelerator Applications USA, Inc., Millburn, New Jersey

**Date of Approval:** January 26, 2018

**Indication:** Lutathera is a radiolabeled somatostatin analogue indicated for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut, and hindgut NETs, in adults.

**Drug Class:** Radiopharmaceuticals

**Uniqueness of Drug:** Lutathera, which received orphan drug designation from the Food and Drug Administration, is a first-in-class drug and the first available peptide receptor radionuclide therapy, a form of treatment comprising a target molecule that carries a radioactive component.

**Warnings and Precautions:**

**Risk from radiation exposure.** Minimize radiation exposure during and after treatment with Lutathera consistent with institutional good radiation safety practices and patient management procedures.

**Myelosuppression.** Monitor patient blood cell counts. Withhold, reduce dose, or permanently discontinue therapy based on the severity of symptoms.

**Secondary myelodysplastic syndrome (MDS) and leukemia.** The median time to the development of MDS and acute leukemia was 28 months and 55 months, respectively.

**Renal toxicity.** Advise patients to urinate frequently during and after administration of Lutathera. Monitor serum creatinine and calculated creatinine clearance. Withhold, reduce dose, or permanently discontinue based on severity.

**Hepatotoxicity.** Monitor patient transaminases, bilirubin, and albumin. Withhold, reduce dose, or permanently discontinue based on severity.

**Neuroendocrine hormonal crisis.** Monitor patients for flushing, diarrhea, hypotension, bronchoconstriction, or other signs and symptoms of neuroendocrine hormonal crisis.

**Embryofetal toxicity.** Lutathera can cause fetal harm. Advise men and women of reproductive potential of the potential risk to a fetus and to use effective contraception.

**Risk of infertility.** Lutathera may cause infertility.

**Dosage and Administration:** The recommended dose of Lutathera is 7.4 GBq (200 mCi) every eight weeks for a total of four doses. Premedicate with antiemetics 30 minutes before the recommended amino acid solution. Initiate recommended intravenous amino acid solution 30 minutes before Lutathera infusion as outlined in the full prescribing information; continue continued on page 227
during and for three hours after Lutathera infusion. Do not reduce the dose of amino acid solution if the Lutathera dose is reduced. In addition, administer long-acting octreotide 30 mg intramuscularly four to 24 hours after each Lutathera dose and short-acting octreotide for symptomatic management. Continue long-acting octreotide 30 mg intramuscularly every four weeks after completing Lutathera until disease progression or for up to 18 months following treatment initiation.

**Commentary:** The FDA approval of Lutathera was based on a phase 3 study that demonstrated a 79% reduction in the risk of disease progression or death in the Lutathera plus best-standard-of-care arm (octreotide LAR 30 mg every four weeks) compared with 60 mg of octreotide LAR alone (hazard ratio, 0.21; 95% confidence interval, 0.13–0.32; \( P < 0.0001 \)). The most common grade 3–4 adverse reactions with a 4% or greater incidence in the Lutathera arm were lymphopenia, increased gamma-glutamyltransferase, vomiting, nausea, increased alanine transaminase, increased aspartate transaminase, hyperglycemia, and hypokalemia.

**Sources:** Advanced Accelerator Applications USA, Inc., Lutathera prescribing information