PDL DRUG REVIEW

Proprietary Name: Rivfloza®
Common Name: nedosiran injection
PDL Category: Endocrine and Metabolic Agents

Comparable Products	Preferred Drug List Status
Oxlumo (lumasiran)	Medical Benefit

Pharmacology/Usage: Nedosiran, the active ingredient of Rivfloza®, is a double-stranded small interfering RNA (siRNA) with four covalently attached N-acetyl-D-galactosamine (GalNAc) residues. After subcutaneous administration, the GalNAc-conjugated sugars bind to asialoglycoprotein receptors (ASGPR) to deliver nedosiran to hepatocytes.

Nedosiran reduces levels of hepatic lactate dehydrogenase (LDH) via the degradation of LDHA messenger ribonucleic acid (mRNA) in hepatocytes through RNA interference. The reduction of hepatic LDH by nedosiran reduces the production of oxalate by the liver, thus reducing subsequent oxalate burden.

Indication: To lower urinary oxalate levels in children 9 years of age and older and adults with primary hyperoxaluria type 1 (PH1) and relatively preserved kidney function (e.g., eGFR ≥30ml/min/1.73m^2).

There is no pregnancy category for this medication; however, the risk summary indicates that available data from reports of pregnancy in clinical trials with Rivfloza® are not sufficient to assess for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. The safety and efficacy of use in the pediatric population younger than 9 years of age have not been established.

Dosage Form: Solution for Injection, preservative-free:

- 80mg (0.5ml) single-dose Vial
- 128mg (0.8ml) single-dose Pre-filled Syringe
- 160mg (1ml) single-dose Pre-filled Syringe

Recommended Dosage: Rivfloza® is administered subcutaneously once monthly at the recommended doses presented in the table below. Dosing is based on actual body weight. The table below, adapted from the prescribing information, presents the Rivfloza® dose regimens in adults and pediatric patients.

Age	Body Weight	Dosing Regimen
Adults & adolescents 12 years and older	≥50kg	160mg QM (prefilled syringe, 1ml)
	<50kg	128mg QM (pre-filled syringe, 0.8ml)
Children 9 to 11 years	≥50kg	160mg QM (pre-filled syringe, 1ml)
	<50kg	3.3mg/kg QM, not to exceed 128mg (vial, dose volume rounded to nearest 0.1ml)

If a planned dose is missed, administer Rivfloza® as soon as possible. If the planned dose is missed by more than 7 days, administer Rivfloza® as soon as possible and resume monthly dosing from the most recently administered dose.

A healthcare professional, caregiver, or patient 12 years of age and older may inject Rivfloza® using the prefilled syringe. In pediatric patients 9 to 11 years of age who weigh ≥50kg, a healthcare professional or caregiver may inject Rivfloza® using the prefilled syringe. The vials are intended for use under the guidance and supervision of a healthcare professional. A caregiver may administer Rivfloza® to pediatric patients after proper training in preparing Rivfloza® vials, if a healthcare professional determines that it is appropriate, and with medical follow-up as necessary. Administer Rivfloza® by subcutaneous injection to the abdomen (at least 2 inches from the navel) or the upper thigh. Do not inject into a vein or into scarred or bruised skin.

Dose adjustments are not recommended for mild hepatic impairment; however, Rivfloza® has not been studied in patients with moderate or severe hepatic impairment. Dose adjustments are not recommended in patients with an estimated glomerular filtration rate (eGFR) of ≥30ml/min/1.73m^2; however, Rivfloza® has not been studied in PH1 patients with severe renal impairment.

Drug Interactions: There are no drug interactions listed with this product.

Box Warning: There is no box warning listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Rivfloza®) minus reported % incidence for placebo in a small trial (N=29). Please note that an incidence of 0% means the incidence was the same as or less than placebo.* The most frequently reported adverse event included injection site reactions (39%). Injection site reactions included erythema, pain, bruising, and rash and were generally mild and did not lead to discontinuation of treatment.

In a single-arm extension study that included 40 patients with PH1, additional injection site reactions included atrophy in one patient.

Contraindications: There are no contraindications listed with this product.

Manufacturer: Novo Nordisk

Analysis: The efficacy of Rivfloza® was assessed in a randomized, double-blind study (PHYOX2) that compared Rivfloza® and placebo in patients aged 6 years or older with PH1 or PH2 and an eGFR ≥30ml/min/1.73m^2. Too few PH2 patients were enrolled to assess efficacy in the PH2 population. Thus, Rivfloza® is only indicated for patients with PH1. Unless otherwise noted, data are presented for the complete study population (PH1 and PH2).

Patients received monthly doses of Rivfloza® (n=23) or placebo (N=12). The median age of included patients was 20 years (range 9 to 46 years), while 51% were female, 71% were white, 83% had PH1, and 17% had PH2. At baseline, mean 24-hour urinary oxalate excretion, normalized by 1.73m^2 body surface area (BSA) in patients less than 18 years of age, was 1547µmol/24 hour. Mean plasma oxalate was 8.2µmol/L, while 43% had an eGFR ≥90ml/min/1.73m^2, 34% had an eGFR 60 to <90ml/min/1.73m^2, 23% had an eGFR 30 to <60 ml/min/1.73m^2, and 60% were taking pyridoxine.

The primary efficacy endpoint was the area under the curve, from days 90 to 180, of the percent change from baseline in 24-hour urinary oxalate excretion (AUC24-hour Uox). The least squares (LS) mean AUC24-hour Uox was -3486 in the Rivfloza® group compared to 1490 in the placebo group, for a between group difference of 4976 ($p<0.0001$).

The LS mean percent change from baseline in 24-hour urinary oxalate excretion (corrected for BSA in patients <18 years of age) averaged over days 90, 120, 150, and 180 was -37% in the Rivfloza® group and 12% in the placebo group, for a between group difference of 49%. Among patients with PH1, the between group difference was 56%.

After 6 months of treatment in PHYOX2, patients could enroll in an ongoing single-arm extension study, PHYOX3, in which all patients were treated with Rivfloza®. The reduction in urinary oxalate was maintained in the 13 patients with PH1 who received an additional 6 months of treatment in PHYOX3.

Place in Therapy: Rivfloza® is an *LDHA*-directed small interfering RNA indicated to lower urinary oxalate levels in children 9 years of age and older and adults with primary hyperoxaluria type 1 (PH1) and relatively preserved kidney function (e.g., eGFR ≥30ml/min/1.73m^2). It is for once monthly subcutaneous injection, with dosing based on actual body weight. The safety and efficacy of Rivfloza® were assessed in a randomized, double-blind study that included patients with PH1 or PH2 and an eGFR ≥30ml/min/1.73m^2. The primary endpoint was the area under the curve, from days 90 to 180, of the percent change from baseline in 24-hour urinary oxalate excretion (AUC24-hour Uox), and Rivfloza® was significantly more effective than placebo for the primary endpoint. Rivfloza® offers providers and patients an at-home treatment option that may be self-administered or administered by a caregiver.

Summary

It is recommended that Rivfloza® should be non-preferred in order to confirm the appropriate diagnosis and clinical parameters for use.

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

References

[1] Rivfloza [package insert]. Plainsboro, NJ: Novo Nordisk Inc; 2023.