nedosiran (Rivfloza™)

EOCCO POLICY

Policy Type:PA/SP Pharmacy Coverage Policy: EOCCO295

Description

Nedosiran (Rivfloza) is a subcutaneously injected *LDHA*-directed small interfering RNA indicated to lower urinary oxalate levels in those with primary hyperoxaluria type 1 (PH1).

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
nedosiran (Rivfloza)	Primary hyperoxaluria type 1 (PH1) with relatively preserved kidney function (e.g., eGFR ≥ 30 mL/min/1.73 m^2)	80mg vial*	2 vials/28 days
		128mg pre-filled syringe*	1 pre-filled syringe/28 days
		160mg pre-filled syringe*	

**Dosing is based on member's weight. Please see appendix.*

Initial Evaluation

I. **Nedosiran (Rivfloza)** may be considered medically necessary when the following criteria are met:
   A. Member is 9 years of age or older; **AND**
   B. Documentation of member's weight; **AND**
   C. Medication is prescribed by, or in consultation with, a nephrologist, urologist, or medical geneticist; **AND**
   D. Medication will not be used in combination with lumasiran (Oxlumo); **AND**
   E. A diagnosis of **primary hyperoxaluria type 1 (PH1)** when the following are met:
      1. Diagnosis of PH1 confirmed with alanine glyoxylate aminotransferase (*AGXT*) mutation via genetic testing or liver enzyme analysis; **AND**
      2. Member has not undergone a liver transplant; **AND**
      3. Provider attestation that the member has an eGFR ≥30mL/min/1.73m^2; **AND**
      4. Documentation of baseline for one or more of the following:
         i. Urinary oxalate excretion level (corrected for BSA)
         ii. Spot urinary oxalate: creatinine ratio
         iii. Estimated glomerular filtration rate (eGFR)
         iv. Plasma oxalate level; **AND**
      5. Medication will be used in combination with pyridoxine; **OR**
         i. Member has been classified as a non-responder to pyridoxine after a three-month trial

II. Nedosiran (Rivfloza) is considered investigational when used for all other conditions, including but not limited to:
   A. Primary hyperoxaluria type 2 (PH2)
   B. Primary hyperoxaluria type 3 (PH3)
   C. When used in combination with lumasiran (Oxlumo)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Documentation of member's weight; **AND**
IV. Medication will not be used in combination with lumasiran (Oxlumo); **AND**
V. Member has not undergone a liver transplant; **AND**
VI. Attestation member has an eGFR ≥30mL/min/1.73m2; **AND**
VII. Member has exhibited improvement or stability of disease symptoms as evidenced by at least one of the following:
   A. Decrease in urinary oxalate excretion from baseline
   B. Reduction in spot urinary oxalate: creatinine ratio from baseline
   C. Stabilization of glomerular filtration rate
   D. Decrease in plasma oxalate level from baseline; **AND**
VIII. Medication will be used in combination with pyridoxine; **OR**
   A. Member has been classified as a non-responder to pyridoxine after a three-month trial

Supporting Evidence

I. Nedosiran (Rivfloza) is a *LDHA*-directed small interfering RNA, FDA-approved to lower urinary oxalate levels in those nine years of age and older with primary hyperoxaluria type 1 (PH1) and relatively preserved kidney function (e.g., eGFR ≥ 30 mL/min/1.73 m^2). The efficacy and safety of nedosiran (Rivfloza) has not been established in patients under the age of nine. Dosing of nedosiran (Rivfloza) is based on actual body weight.
II. Primary hyperoxaluria (PH) is a group of autosomal recessive disorders of hepatic glyoxylate metabolism that cause the overproduction of endogenous oxalate — a redundant metabolic end product that is excreted primarily via the kidneys. Primary hyperoxaluria type 1 (PH1) is the most common and severe type of PH, due to mutations of the *AGXT* gene. Variants of this gene

result in enhanced oxalate production. In high levels, oxalate forms crystals which can deposit in various parts of the body. As oxalate is typically excreted in the urine, the kidney is the prime target for oxalate deposition resulting in nephrocalcinosis, kidney stones, and end-stage kidney disease (ESKD). Some patients progress to systemic oxalosis when the GFR falls <30 to 40 mL/min per 1.73 m^2 which results in calcium oxalate deposits in the heart, blood vessels, joints, bones, and retinas.

III. PH1, which accounts for approximately 80% of PH cases, has an estimated prevalence of one to three per million in Europe and North America. Age at diagnosis varies, with some not being diagnosed until adulthood, and the median age at diagnosis is 5 years old. Those with more severe disease present earlier in life with a diagnosis in infancy, accounting for approximately 26% of patients.

IV. Given the complexities related to diagnosis, treatment, and management of PH1, treatment in this disease space must be initiated by, or in consultation with, a specialist (e.g., nephrologist, urologist, or medical geneticist).

V. Nedosiran (Rivfloza) was studied in a Phase 2, multinational, double-blind, placebo-controlled trial (PHYOX2) of 35 patients with genetically confirmed PH1 (n=29) or PH2 (n=6). Participants also had to have a 24-hour urinary oxalate (Uox) excretion of ≥0.7 mmol and an estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73 m^2. Patients were randomized 2:1 to receive nedosiran (Rivfloza) or placebo. All participants were instructed to continue their standard of care (conservative) therapies. Median age: 20 years (range: 9–46 years), 51% female, 71% White, 17% Asian. Baseline demographic and disease characteristics were generally balanced between the two treatment arms, with the exception of 24-hour Uox excretion at baseline, which was higher in the placebo arm (1.33 vs 1.96 mmol/24 hr). The primary efficacy outcome was the percent change from baseline in 24-hour Uox excretion, as assessed by area under the curve (AUC) from day 90 to day 180. Key secondary endpoints included the proportion of participants reaching normal or near-normal 24-hour Uox excretion on at least two consecutive visits, starting at day 90.

VI. The least-squares (LS) mean AUC 24-hour Uox was -3486 (95% CI: -5025, -1947) in the nedosiran (Rivfloza) group compared to 1490 (95% CI: 781, 3761) in the placebo group; a between group difference of 4976 (95% CI: 2803, 7149; p< 0.0001) was detected. 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% (95% CI: -53%, -21%) in the nedosiran (Rivfloza) group and 12% (95% CI: -12%, 36%) in the placebo group, for a between group difference of 49% (95% CI: 26%, 72%). Among patients with PH1, the between group difference was 56% (95% CI: 33%, 80%).

VII. While nedosiran (Rivfloza) demonstrated statistically significant results for the primary endpoint and this surrogate endpoint is accepted as a clinically meaningful endpoint by the FDA, the magnitude of AUC reduction correlating to a clinically significant impact is unclear at this time. The key secondary endpoint was only achieved in 48% of patients and was driven by patients

who achieved a near-normalized 24-hour Uox, rather than those with normalized 24-hour Uox. Additionally, the secondary endpoint results may be difficult to reconcile as baseline characteristics between the treatment groups were unbalanced, and results may favor the study drug. Therefore, the quality of evidence is considered low.

VIII. Per the clinical practice recommendations for primary hyperoxaluria genetic testing is the gold standard for the diagnosis of all three types of PH. The consensus statement recommends that all patients who are suspected to have PH should undergo genetic assessment, as genetic confirmation of PH and typing are pivotal to the management of these patients. PH1 is due to mutations of the AGXT gene. Whereas PH2 is due to a deficiency in glyoxylate and hydroxypyruvate reductase (GRHPR) and PH3 is due to the loss of function of the mitochondrial enzyme 4-hydroxy-2-oxoglutarate adolase (HOGA). Biochemical assessment has an important role in the diagnostic workup of patients with symptoms suggestive of PH and can focus genetic testing. It can also be used as an indication of therapeutic response. However, measurement of oxalate and relevant metabolites is not without difficulty, and one must interpret the results carefully, taking all potential flaws into account.

IX. Liver transplantation is the only curative intervention for PH1 as it corrects the underlying enzymatic defect due to mutations of the *AGXT* gene. Use and efficacy of nedosiran (Rivfloza) after transplant has not been evaluated in clinical trials.

IX. While the primary endpoint in clinical trials was 24-hour urinary oxalate excretion, it may be difficult for some patients to obtain a 24-hour urine collection in clinical practice. This can especially be noted in infants and small children who are not toilet trained, working adults, and school aged children. As a result, oxalate excretion can be evaluated by measuring the molar oxalate:creatinine ratio in spot urine samples. A 24-hour oxalate excretion does not correlate perfectly with oxalate-to-creatinine ratio, possibly as a consequence of imperfect urine collections and the effect of body size, which influences creatinine excretion and may therefore affect the oxalate-to-creatinine ratio. However, available evidence suggests that either measurement can be used to monitor response to treatment. Plasma oxalate can be a useful biomarker in PH1 as urinary oxalate measurements may be falsely low in patients with kidney insufficiency and progressive disease, which is common in patients with type 1 disease. In this setting, plasma oxalate levels may be useful, as there is an inverse relation between plasma oxalate and kidney function in children with early stages of chronic kidney disease where oxalate excretion has declined to such an extent that urine results are misleading. Lastly, estimated glomerular filtration rate can help to assess progression in ESKD in PH1 patients.

X. The efficacy and stability of symptoms can be assessed by multiple surrogate endpoints as compared to baseline (i.e., a decrease in urinary oxalate excretion from baseline, reduction in spot urinary oxalate: creatinine ratio from baseline, stabilization of glomerular filtration rate, decrease in plasma oxalate level from baseline). Therefore, improvement or stability in one metric provides enough evidence to support continuation of therapy.

X. Aside from drug therapies general measures used in all patients with PH1 include: hyperhydration, citrate and magnesium supplements to increase urinary oxalate solubility, and pyridoxine (vitamin B6). Pyridoxine is variably effective in some genotypes and is trialed for three to 6 months to see if the patient is a responder. Liver transplant is curative as it corrects the mutation in the AGXT gene but is associated with significant morbidity. Some patients may undergo sequential or isolated liver-kidney transplants.

Investigational or Not Medically Necessary Uses

I. Nedosiran (Rivfloza) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Primary hyperoxaluria type 2 (PH2)
      i. Only six patients diagnosed with PH2 were included in the nedosiran (Rivfloza) pivotal trial (PHYOX2). There was no consistent pattern observed for 24-hour Uox excretion in treated or untreated PH2 participants, thus the safety and efficacy of nedosiran (Rivfloza) in PH2 remains investigational.
   B. Primary hyperoxaluria type 3 (PH3)
      i. Nedosiran (Rivfloza) has not been FDA-approved, or sufficiently studied for safety and efficacy for PH3.
   C. When used in combination with lumasiran (Oxlumo)
      i. On November 23, 2020, FDA approved lumasiran (Oxlumo) to lower urinary oxalate levels, a surrogate for kidney stones and loss of kidney function, in pediatric and adult patients with PH1 who have relatively preserved kidney function. Lumasiran (Oxlumo) is a small interfering ribonucleic acid (siRNA) that reduces levels of the glycolate oxidase enzyme by targeting the hydroxyacid oxidase 1 (HAO1) messenger ribonucleic acid (mRNA) in hepatocytes. On October 6, 2022, lumasiran (Oxlumo) was also approved to lower plasma oxalate, a surrogate for systemic manifestations of PH1, in patients with more advanced kidney disease. While both lumasiran (Oxlumo) and nedosiran (Rivfloza) are siRNA therapies approved for the treatment of PH1, their concurrent use has not been evaluated for safety or efficacy.

Appendix

Table 1: FDA approved dosing

Age	Body Weight	Dosing Regimen
Adults and adolescents 12 years and older	≥ 50 kg	160 mg once monthly (Pre-filled Syringe, 1mL)
	< 50 kg	128 mg once monthly (Pre-filled Syringe, 0.8mL)
Children 9 to 11 years	≥ 50 kg	160 mg once monthly (Pre-filled Syringe, 1mL)

	< 50 kg	3.3 mg/kg once monthly, not to exceed 128 mg (Vial, dose volume rounded to nearest 0.1 mL)

References

1. Rivfloza. Package Insert. Novo Nordisk Inc; September 2023.
2. Baum MA, Langman C, Cochat P, et al. PHYOX2: a pivotal randomized study of nedosiran in primary hyperoxaluria type 1 or 2. Kidney Int. 2023;103(1):207-217.
3. Groothoff JW, Metry E, Deesker L, et al. Clinical practice recommendations for primary hyperoxaluria: an expert consensus statement from ERKNet and OxalEurope. Nat Rev Nephrol. 2023;19(3):194-211.

Related Policies

Currently there are no related policies.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created.	02/2024