Utilization Review Policy 331

POLICY: Metabolic Disorders – Primary Hyperoxaluria Medications – Rivfloza Utilization Management Medical Policy

- Rivfloza™ (nedosiran subcutaneous injection – Novo Nordisk)

EFFECTIVE DATE: 3/15/2024
LAST REVISION DATE: 04/02/2025

COVERAGE CRITERIA FOR: ALL UCARE PLANS

OVERVIEW

Rivfloza, a lactate dehydrogenase A-directing (LDHA) small interfering RNA, is indicated for the treatment of **primary hyperoxaluria type 1** (PH1) to lower urinary and plasma oxalate levels in adults and children ≥ 2 years of age with relatively preserved kidney function.[1]

Disease Overview

PH1 is a rare autosomal recessive inborn error of glyoxylate metabolism that results in the overproduction of oxalate, which forms insoluble calcium oxalate crystals that accumulate in the kidney and other organs, leading to issues such as nephrocalcinosis, formation of renal stones, and renal impairment.[2] Mutations in the alanine:glyoxylate aminotransferase gene (*AGXT*) cause PH1.[3] Liver transplantation is the only curative intervention for PH1 as it corrects the underlying enzymatic defect due to mutations of the *AGXT* gene.[2-4]

Clinical Efficacy

The efficacy of Rivfloza for the treatment of PH1 has been evaluated in one pivotal study.[1,5] The study included patients ≥ 9 years of age with genetically confirmed PH1 and urinary oxalate excretion ≥ 0.7 mmol/24 hr/1.73 m^2. An ongoing open-label extension trial is following patients for up to 4 years.[6] The primary efficacy endpoint of the area under the curve (AUC) percent change from baseline in 24-hour urinary oxalate excretion was assessed following 6 months of Rivfloza therapy. The least-squares mean $AUC_{24\text{-hour urinary oxalate}}$ was -3486 in the Rivfloza group compared to 1490 (in the placebo group, for a between group difference of 4976 ($P < 0.0001$).

An open-label multicenter study evaluated the efficacy of Rivfloza in pediatric patients 2 to < 12 years of age with PH1.[1,8] The primary endpoint was the percent change from baseline in spot urinary oxalate:creatinine ratio at Month 6. Patients taking Rivfloza had a 64% reduction in spot urinary oxalate:creatinine ratio and an absolute reduction in spot urinary oxalate:creatinine ratio of 0.25 mmol/mmol at Month 6.

Dosing

Dosing of Rivfloza is a weight-based monthly subcutaneous injection.[1]

Table 1. Rivfloza Dosing Regimen.[1]

Age	Body Weight	Dosing Regimen
Adults and adolescents ≥ 12 years of age	≥ 50 kg	160 mg once monthly
	< 50 kg	128 mg once monthly
	≥ 50 kg	160 mg once monthly

Children 2 to < 12 years of age	39 kg to < 50 kg	128 mg
	< 39 kg	3.3 mg/kg

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Rivfloza. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Rivfloza as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Rivfloza to be prescribed by or in consultation with a physician who specializes in the condition being treated. All reviews will be forwarded to the Medical Director for evaluation.

Documentation: Documentation is required for use of Rivfloza as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to chart notes, laboratory tests, claims records, and/or other information. Subsequent coverage reviews for a patient who has previously met the documentation requirements and related criteria in the *Rivfloza Utilization Management Medical Policy* through the Coverage Review Department, and who is requesting reauthorization, are NOT required to re-submit documentation for reauthorization, except for the criterion requiring documentation of a continued benefit from Rivfloza therapy.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Rivfloza is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Primary Hyperoxaluria Type 1.** Approve Rivfloza for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, iii, iv, v, and vi):
     - **i.** Patient is ≥ 2 years of age; AND
     - **ii.** Patient has had a genetic test confirming the diagnosis of Primary Hyperoxaluria Type 1 via identification of biallelic pathogenic variants in the alanine:glyoxylate aminotransferase gene (*AGXT*) **[documentation required]**; AND
     - **iii.** Patient has an estimated glomerular filtration rate (eGFR) ≥ 30 ml/min per 1.73 m^2 **[documentation required]**; AND
     - **iv.** Patient meets ONE of the following (a or b):
       - **a)** Patient is 2 to < 12 years of age and meets ONE of the following [(1) or (2)]:
         - **(1)** Patient has a urinary oxalate excretion ≥ 0.5 mmol/24 hours/1.73 m^2 with the absence of secondary sources of oxalate [documentation required]; OR
         - **(2)** Patient has a urinary oxalate:creatinine ratio above 2 times the 95th percentile for age; AND

b) Patient is ≥ 12 years of age and meets ONE of the following [(1), (2), or (3)]:
- **(1)** Patient has a urinary oxalate excretion ≥ 0.5 mmol/24 hours/1.73 m^2 with the absence of secondary sources of oxalate **[documentation required]**; OR
- **(2)** Patient has a urinary oxalate:creatinine ratio above the age-specific upper limit of normal **[documentation required]**; OR
- **(3)** Patient has a plasma oxalate level ≥ 20 µmol/L **[documentation required]**; AND

v. Patient has not previously received a liver transplant for Primary Hyperoxaluria Type 1; AND
vi. The medication is prescribed by or in consultation with a nephrologist or urologist; OR

B) Patient is Currently Receiving Rivfloza. Approve for 1 year if the patients meets BOTH of the following (i and ii):
i. The patient is continuing to derive benefit from Rivfloza, according to the prescriber, **[documentation required]**; AND
Note: Examples of responses to Rivfloza therapy are reduced urinary oxalate excretion, decreased urinary oxalate:creatinine ratio, or reduced plasma oxalate levels from baseline (i.e., prior to Rivfloza therapy) or improved or stabilized clinical signs/symptoms of Primary Hyperoxaluria Type 1 (e.g., nephrocalcinosis, formation of renal stones, renal impairment).
ii. Patient has not previously received a liver transplant for Primary Hyperoxaluria Type 1.

Dosing. Approve ONE of the following dosing regimens (A, B, or C):
A) If weight is ≥ 50 kg, approve for 160 mg once monthly.
B) If weight is 39 kg to < 50 kg, approve for 128 mg once monthly.
C) If weight is < 39 kg, approve 3.3 mg/kg once monthly, not to exceed 128 mg.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Rivfloza is not recommended in the following situations:

1. **Primary Hyperoxaluria Type 2 (PH2).** Rivfloza may have benefit in PH2; however, the efficacy and safety of Rivfloza in patients with PH2 have not been established. Clinical trials are ongoing.

2. **Primary Hyperoxaluria Type 3 (PH3).** Rivfloza may have benefit in PH3; however, the efficacy and safety of Rivfloza in patients with PH3 have not been established. Clinical trials are ongoing.

3. **Primary Hyperoxaluria with end stage renal disease (ESRD).** Rivfloza may have benefit in patients with PH1 or PH2 and ESRD; however, the efficacy and safety of Rivfloza in this patient population have not been established. Clinical trials are ongoing.

4. **Concurrent use of Rivfloza with Oxlumo (lumasiran subcutaneous injection).** Oxlumo is another small interfering RNA agent and should not be used with Rivfloza.

5. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Rivfloza™ subcutaneous injection [prescribing information]. Plainsboro, NJ: Novo Nordisk; March 2025.
2. Milliner DS, Harris PC, Sas DJ, et al. Primary Hyperoxaluria Type 1. Gene Reviews® Available at: https://www.ncbi.nlm.nih.gov/books/NBK1283/#:~:text=In%20primary%20hyperoxaluria%20type%201,deposit%20in%20the%20renal%20parenchyma. Updated August 15, 2024. Accessed on March 31, 2025.

3. Primary Hyperoxaluria: MedlinePlus Genetics. U.S. National Library of Medicine; National Institutes of Health; Department of Health and Human Services. Available at: https://medlineplus.gov/genetics/condition/primary-hyperoxaluria/#resources. Accessed on March 31, 2025.
4. Cochat P, Rumsby G. Primary hyperoxaluria. *N Engl J Med*. 2013;369(7):649-658.
5. 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.
6. Hoppe B, Coenen M, Schalk G, et al. Nedosiran in primary hyperoxaluria subtype 1: interim results from an open label extension trial (PHYOX3) [poster]. Presented at: 19th International Pediatric Nephrology Association (IPNA) Congress. Calgary, Canada. September 7-11, 2022.
7. Michael M, Harvey E, Milliner DS, et al. Diagnosis and management of primary hyperoxalurias: best practices. *Pediatr Nephrol*. 2024;39(11):3143-3155.
8. Sas DJ, Bakkaloglu SA, Belostotsky V, et al. Nedosiran in pediatric patients with PH1 and relatively preserved kidney function, a phase 2 study (PHYOX8). *Pediatr Nephrol*. Published online ahead of print January 28, 2025.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy		11/22/2023
UCare P&T Review	Policy reviewed and approved by UCare P&T committee. Annual review process	09/16/2024
Annual Revision	No criteria changes.	11/20/2024
Selected Revision	**Primary Hyperoxaluria Type 1:** For Initial Therapy, the option of approval that the patient has a urinary oxalate excretion ≥ 0.7 mmol/24 hours/1.73 m2 was revised to the patient has a urinary oxalate excretion ≥ 0.5 mmol/24 hours/1.73 m2 with the absence of secondary sources of oxalate. For Patient is Currently Receiving Rivfloza, the requirement that the patient is continuing to derive benefit from Rivfloza was revised to remove the qualifier that this was "as determined by the most recent (i.e., within the past 6 months) objective measurement". Also, the requirement that the patient has not previously received a liver transplant was added to the Patient is Currently Receiving Rivfloza criteria set (previously, was only in the Initial Therapy criteria set).	12/18/2024
Selected Revision	**Primary Hyperoxaluria Type 1:** For diagnosis confirmed by genetic testing, rephrased the term "mutation" to "biallelic pathogenic variants".	02/05/2025
Early Annual Revision	**Primary Hyperoxaluria Type 1:** For Initial Therapy, the option of approval was changed to the patients is ≥ 2 years of age (previously ≥ 9 years of age). The requirement for urinary oxalate excretion ≥ 0.5 mmol/24 hours/1.73 m^2 with the absence of secondary sources of oxalate, or urinary oxalate:creatinine ratio above the age-specific upper limit of normal, or plasma oxalate level ≥ 20 µmol/L were changed to apply only to a patient who is ≥ 12 years of age (previously applied to all patients ≥ 9 years of age). For a patient between 2 and < 12 years of age, a requirement was added for urinary oxalate excretion ≥ 0.5 mmol/24 hours/1.73 m^2 with the absence of secondary sources of oxalate (with documentation required), or patients has a urinary oxalate:creatinine ratio above 2 times the 95th percentile for age.	04/02/2025
UCare P&T Review	Policy reviewed and approved by UCare P&T committee. Annual review process	09/15/2025