Drug Coverage Policy

Effective Date.....05/01/2026
Coverage Policy Number.....IP0629
Policy Title.....Rivfloza

Metabolic Disorders – Primary Hyperoxaluria Medications – Rivfloza

- Rivfloza™ (nedosiran subcutaneous injection – Novo Nordisk)

INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment where appropriate and have discretion in making individual coverage determinations. Where coverage for care or services does not depend on specific circumstances, reimbursement will only be provided if a requested service(s) is submitted in accordance with the relevant criteria outlined in the applicable Coverage Policy, including covered diagnosis and/or procedure code(s). Reimbursement is not allowed for services when billed for conditions or diagnoses that are not covered under this Coverage Policy (see "Coding Information" below). When billing, providers must use the most appropriate codes as of the effective date of the submission. Claims submitted for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

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
Children 2 to < 12 years of age	≥ 50 kg	160 mg once monthly
	39 kg to < 50 kg	128 mg
	< 39 kg	3.3 mg/kg

Coverage Policy

POLICY STATEMENT
Prior Authorization is required for 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, prescription receipts, and/or other information. Subsequent coverage reviews for a patient who has previously met the documentation requirements and

related criteria in the Rivfloza Coverage 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. All documentation must include patient-specific identifying information.

Rivfloza is considered medically necessary when the following is met:

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 the following (i, ii, iii, iv, v, vi, and vii):
     - **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 $meters^2$ with the absence of secondary sources of oxalate **[documentation required]**; OR
         - **(2)** Patient has a urinary oxalate:creatinine ratio above 2 times the 95^{th} 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 $meters^2$ 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.
     - **vii.** Preferred product criteria is met for the product as listed in the below table; OR
   - **B)** Patient is Currently Receiving Rivfloza. Approve for 1 year if the patient 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 160mg once monthly.
B) If weight is 39 kg to < 50 kg, approve for 128mg once monthly.
C) If weight is < 39 kg, approve 3.3 mg/kg once monthly, not to exceed 128 mg.

Employer Plans:

Product	Criteria
Rivfloza (nedosiran subcutaneous injection)	ONE of the following (1 or 2) **[documentation required]**: 1. The patient has tried and, according to the prescriber, has experienced inadequate efficacy OR significant intolerance with Oxlumo; OR 2. The patient has already been started on therapy with Rivfloza.

Individual and Family Plans:

Product	Criteria
Rivfloza (nedosiran subcutaneous injection)	ONE of the following (1 or 2) **[documentation required]**: 1. The patient has tried and, according to the prescriber, has experienced inadequate efficacy OR significant intolerance with Oxlumo; OR 2. The patient has already been started on therapy with Rivfloza.

Conditions Not Covered

Rivfloza for any other use is considered not medically necessary, including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

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.

Coding Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPCS Codes	Description
C9399	Unclassified drugs or biologics
J3490	Unclassified drugs

References

1. Rivfloza™ subcutaneous injection [prescribing information]. Plainsboro, NJ: Novo Nordisk; March2025.
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.

Revision Details

Summary of Changes	Review Date	Effective Date
New policy	04/11/2024	06/01/2024
No criteria changes.	12/19/2024	02/15/2025
Added and defined documentation requirements to the policy. **Primary Hyperoxaluria Type 1:** For Initial Therapy - the statement "a genetic test confirming the diagnosis of Primary Hyperoxaluria Type 1 via identification of an alanine:glyoxylate aminotransferase gene (AGXT) mutation" was updated to "a genetic test confirming the diagnosis of Primary Hyperoxaluria Type 1 via identification of biallelic pathogenic variants in the alanine: glyoxylate aminotransferase gene (AGXT)"; the option of approval that "the patient has a urinary oxalate excretion ≥ 0.7 mmol/24 hours/1.73 m^2 was updated to the patient has a	01/30/2025	03/01/2025

urinary oxalate excretion ≥ 0.5 mmol/24 hours/1.73 m^2 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 updated 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).		
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 provided), or patients has a urinary oxalate:creatinine ratio above 2 times the 95th percentile for age. **Added** Individual and Family Plan Preferred Product Criteria **Coding Information.** **Added:** C9399	04/24/2025	6/1/2025
No criteria changes.	04/16/2026	05/01/2026

The policy effective date is in force until updated or retired.