Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY POLICY AND CRITERIA ORPTCGEN008.0625	**GENITOURINARY AGENTS** **HYPEROXALURIA AGENTS** See Table 3 for Medications
Effective Date: 8/1/2025	**Review/Revised Date**: 02/21, 07/21, 01/22, 01/23, 12/23, 03/24, 06/24, 01/25, 06/25 (ZJN)
Original Effective Date: 04/21	**P&T Committee Meeting Date**: 02/21, 08/21, 02/22, 02/23, 02/24, 04/24, 06/24, 02/25, 06/25
Approved by: Oregon Region Pharmacy and Therapeutics Committee	

SCOPE:
Providence Health Plan and Providence Health Assurance as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Medicare Part B

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit.

REQUIRED MEDICAL INFORMATION:
1. For **initiation of therapy** (new starts), all the following criteria must be met:
    a. Patient has a diagnosis of primary hyperoxaluria type 1 (PH1), confirmed by one of the following:
        i. Genetic testing demonstrating mutation in the alanine:glyoxylate aminotransferase (AGXT) gene
        ii. Liver biopsy demonstrating significantly decreased or absent alanine:glyoxylate aminotransferase (AGT) enzyme activity
    b. Documentation of one of the following (*See Appendix for Reference Ranges*):
        i. Elevated urine oxalate (UOx) excretion as measured by body surface area-normalized daily UOx output greater than upper limit of normal (ULN)
        ii. Elevated UOx excretion as measured by UOx:creatinine ratio above age-specific upper limit of normal (ULN) OR
        iii. Elevated plasma oxalate (POx) concentration (POx concentration greater than ULN)
    c. Concurrent use of pyridoxine or failure to achieve normalization of UOx excretion levels after at least three months of pyridoxine (vitamin B6) at the maximally indicated dose, unless contraindicated or clinically significant adverse effects are experienced

   d. Documentation of current patient weight and dosing not exceeding FDA-recommended dosing
2. For patients **established on therapy** (within the previous year):
   a. Documentation of a clinically significant reduction in urine or plasma oxalate levels relative to pre-treatment baseline
   b. Patient continues with concurrent pyridoxine (unless individual is a pyridoxine non-responder)
   c. Documentation of patient's current weight and updated dosing not exceeding FDA-recommended dosing

EXCLUSION CRITERIA:
1. Patients with a history of liver transplant
2. Patients with secondary hyperoxaluria or genetic test positive for another form of primary hyperoxaluria such as type 2 and type 3 primary hyperoxaluria

AGE RESTRICTIONS:
Age must be appropriate based on FDA-approved indication

PRESCRIBER RESTRICTIONS:
Must be prescribed by, or in consultation with, a nephrologist or urologist

COVERAGE DURATION:
Initial authorization will be approved for six months. Reauthorization will be approved for 12 months

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Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:
Lumasiran reduces the amount of available glyoxylate, a substrate for oxalate production, by targeting hydroxyacid oxidase 1 (HAO1) messenger RNA in hepatocytes through RNA interference, subsequently decreasing glycolate oxidase enzyme levels. Nedosiran reduces hepatic lactate dehydrogenase (LDH) levels and hepatic oxalate production by degrading LDHA messenger ribonucleic acid (mRNA).

PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY POLICY AND CRITERIA ORPTCGEN008	GENITOURINARY AGENTS HYPEROXALURIA AGENTS See Table 3 for Medications

FDA APPROVED INDICATIONS:
Oxlumo® (lumasiran): Treatment of primary hyperoxaluria type 1 (PH1) to lower urinary and plasma oxalate levels in pediatric and adult patients

Rivfloza® (nedosiran): To lower urinary oxalate levels in children 2 years of age and older and adults with primary hyperoxaluria type 1 (PH1) and relatively preserved kidney function (eGFR ≥ 30 mL/min/1.73 m^2)

POSITION STATEMENT:
- Primary hyperoxaluria type 1 (PH1) is a rare genetic metabolic disorder characterized by the hepatic overproduction of oxalate. Oxalate is poorly soluble and combines with calcium to form kidney and urinary stones. It is a progressive disease that can lead to kidney dysfunction and ultimately to end-stage renal disease (ESRD). As a patient's glomerular filtration rate (GFR) decreases throughout their lifetime, plasma oxalate levels will increase, and calcium oxalate deposits form in other areas of the body, such as the heart, bones, and retina. In the absence of effective treatment, ESRD and/or complications from systemic oxalosis can be fatal. There are other types of primary hyperoxaluria, but PH1 is considered the most severe.
- Lumasiran and nedosiran are both FDA-approved therapies for the treatment of PH1. Other therapies include conservative treatment such as increasing fluid intake to at least 3 L/m^2 body surface area (BSA) per day, alkalizing the urine, and trialing pyridoxine.
    - Approximately 30% of patients with PH1 may respond to pyridoxine after three months of treatment.
    - Therapeutic doses of pyridoxine are 5 to 8 mg/kg/day, up to a maximum dose of 20 mg/kg/day.
- Alkalinizing the urine with potassium citrate can reduce urinary calcium oxalate saturation by forming complexes with calcium, which decreases stone formation. Other calcium oxalate crystallization inhibitors include neutral phosphate and magnesium oxide.
- Dialysis is typically started when a patient's estimated glomerular filtration rate (eGFR) is between 20 and 30 mL/min/1.73m^2.
- Liver transplantation is the only potentially curative option to normalize oxalate production. It has significant risks and limitations, but transplantation of liver, kidney, or combined liver and kidney transplantation can be considered for some patients.

Lumasiran for PH1:
- The efficacy was established based on two small Phase 3 studies, ILLUMINATE-A and ILLUMINATE-B.

- ILLUMINATE-A was a randomized, double-blind, placebo-controlled study in 39 patients six years of age and older with PH1. Patients received three loading doses of 3 mg/kg lumasiran or placebo administered once monthly, followed by maintenance doses of 3 mg/kg lumasiran or placebo every three months.
- The primary endpoint was the percent reduction from baseline in 24-hour urinary oxalate excretion corrected for BSA averaged over months three through six.
    - The least squares (LS) mean percent change from baseline in 24-hour urinary oxalate in the lumasiran group was -65% vs. -12% in the placebo group (between-group LS mean difference of 53%, 95% CI: 45, 62; $p < 0.0001$).
    - By month six, 52% of patients treated with lumasiran achieved a normal 24-hour urinary oxalate corrected for BSA vs. 0% of placebo-treated patients ($p = 0.001$).
- ILLUMINATE-B was a single-arm study in pediatric patients less than six years of age with PH1. The primary endpoint was the percent reduction from baseline in spot urinary oxalate:creatinine ratio averaged over months three through six.
    - Patients treated with lumasiran achieved a reduction in spot urinary oxalate:creatinine ratio from baseline of 71% (95% CI: 65, 77).
- Both studies excluded participants with liver transplant and other clinical manifestations of systemic oxalosis.
- These two studies provide low-quality of evidence that lumasiran significantly lowers urinary oxalate (a surrogate marker) compared to placebo in adult and pediatric patients with PH1 and relatively preserved renal function. Long-term studies are needed to confirm that this therapy will lead to improved outcomes, such as preservation of renal function or reduction in kidney stones. Additionally, data are needed for patient with more advanced renal impairment (these patients will be included in the planned ILLUMINATE-C trial).
- The recommended dosing regimen consists of loading doses followed by maintenance doses administered subcutaneously by a healthcare provider, as shown in the table below. Dosing is based on actual body weight.

Table 1. Recommended dosing regimens for lumasiran for PH1

Body Weight	Loading Dose	Maintenance Dose (Begin 1 Month After the Last Loading Dose)
Less than 10 kg	6 mg/kg once monthly for three doses	3 mg/kg once monthly
10 kg to less than 20 kg	6 mg/kg once monthly for three doses	6 mg/kg once every three months (quarterly)
20 kg and above	3 mg/kg once monthly for three doses	3 mg/kg once every three months (quarterly)

Nedosiran for PH1:

- The efficacy was established based on one small Phase 2 study, PHYOX2.
- PHYOX2 was a randomized, double-blind, placebo-controlled study with 35 patients six years of age and older. Patients received doses of nedosiran based on age and weight: 170 mg (age 12 years and older, weighing 50 kg or more), 136 mg (age 12 years and older, weighing less than 50 kg), and 3.5 mg/kg (age 6–11 years).
- The primary endpoint was the percent change from baseline in 24-hour urinary oxalate excretion, as assessed by the area under the curve (AUC) from day 90 to day 180. This was designed to capture the reduction in oxalate burden over time rather than at a single time point at the end of the study.
    - The LS mean percentage change from baseline in 24-hour urinary oxalate, averaged over Days 90, 120, 150, and 180, in the nedosiran group showed a significant decrease of 37% vs. an increase of 12% in the placebo group ($p < 0.001$).
- This study excluded participants with liver transplants and other clinical manifestations of systemic oxalosis.
- The recommended dosing is subcutaneous administered by a healthcare provider, as shown in the table below. Dosing is based on actual body weight.

Table 2. Recommended dosing regimens for nedosiran for PH1

Body Weight	Body Weight	Dosing Regimen
Children 9 – 11 years	Less than 50 kg	3.3 mg/kg once monthly, not to exceed 128 mg (Vial, dose volume rounded to nearest 0.1 mL)
	Equal or higher than 50 kg	160 mg once monthly (pre-filled syringe, 1 mL)
Adults and adolescents 12 years and older	Less than 50 kg	128 mg once monthly (pre-filled syringe, 0.8 mL)
	Equal or higher than 50 kg	160 mg once monthly (pre-filled syringe, 1 mL)

REFERENCE/RESOURCES:

1. Oxlumo (lumasiran) [Package Insert]. Alnylam Pharmaceuticals, Inc. Cambridge, MA: October 2023.
2. Oxlumo In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically. (Accessed January 6, 2025).
3. Oxlumo In: Lexi-Drugs Online [Internet database]. Hudson, OH: Lexi-Comp, Inc. Updated periodically. Accessed January 6, 2025.

4. Frishberg Y, Hayes W, Shasha-Lavsky H, et al. Efficacy and safety of lumasiran for infants and young children with primary hyperoxaluria type 1: 30-month analysis of the phase 3 ILLUMINATE-B trial. Front Pediatr. 2024;12:1392644. Published 2024 Sep 16. doi:10.3389/fped.2024.1392644
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14. 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. doi:10.1038/s41581-022-00661-1.
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Table 3: BILLING GUIDELINES AND CODING

DRUG CODES*		
Oxlumo	J0224	Injection, lumasiran, 0.5 mg
Rivfloza	J3490	Unclassified drugs or biologicals
ADMINISTRATION CODES*		
	96372	Ther/proph/diag inj sc/im

*Coding Notes:
• The above code list is provided as a courtesy and may not be all-inclusive. Inclusion or omission of a code from this policy neither implies nor guarantees reimbursement or coverage. Some codes may not require routine review for medical necessity, but they are subject to provider contracts, as well as member benefits, eligibility and potential utilization audit.
• HCPCS/CPT code(s) may be subject to National Correct Coding Initiative (NCCI) procedure-to-procedure (PTP) bundling edits and daily maximum edits known as "medically unlikely edits" (MUEs) published by the Centers for Medicare and Medicaid Services (CMS). This policy does not take precedence over NCCI edits or MUEs. Please refer to the CMS website for coding guidelines and applicable code combinations.

Appendix: Reference Ranges[14,15]

Measurement	Normal Values
BSA-normalized daily urine oxalate output	< 0.5 mmol/1.73 m^2 per day *(Values > 1.0 mmol/1.73 m^2 per day is strongly suggestive of PH)*
Plasma oxalate concentration	1-3 µmol/L or eGFR > 40 mL/min/1.73 m^2

Urine Oxalate Excretion:Creatinine Ratio Age-Specific Reference Ranges

Age	Normal Values
0-6 months	< 325-360 mmol/mol (< 253-282 mg/g)
7-24 months	< 132-174 mmol/mol (< 103-136 mg/g)
2-5 years	< 98-101 mmol/mol (< 76-79 mg/g)
5-14 years	< 70-82 mmol/mol (< 55-64 mg/g)
> 16 years	< 40 mmol/mol (< 32 mg/g)