Oxlumo® (Lumasiran) and Rivfloza® (Nedosiran)

Policy Number: IEXD0102.09
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Ü Instructions for Use

Table of Contents **Page**

Related Policies
None

Applicable States

This Medical Benefit Drug Policy applies to Individual Exchange benefit plans in all states except for Massachusetts, Nevada, and New York.

Coverage Rationale

This policy provides information about the use of certain specialty pharmacy medications administered by either the subcutaneous (SC) or intravenous (IV) route by a healthcare professional (HCP).

Oxlumo is proven and medically necessary for the treatment of primary hyperoxaluria type 1 (PH1) in patients who meet all of the following criteria:

- For **initial therapy**, **all** of the following:
  - Diagnosis of PH1 by, or in consultation with, a specialist (e.g., geneticist, nephrologist, urologist) with expertise in the diagnosis of PH1; **and**
  - Confirmation of the PH1 diagnosis based on **both** of the following:
    - Metabolic testing demonstrating **one** of the following:
      - Increased urinary oxalate excretion [e.g., greater than 1 mmol/1.73 m^2 per day (90 mg/1.73 m^2 per day), increased urinary oxalate:creatinine ratio relative to normative values for age]; **or**
      - Increased plasma oxalate and glyoxylate concentrations

      and
    - Genetic testing has confirmed a mutation in the alanine:glyoxylate aminotransferase (AGT or AGXT) gene

    and
  - Patient has not received a liver transplant; **and**
  - Prescribed by, or in consultation with, a specialist (e.g., geneticist, nephrologist, urologist) with expertise in the treatment of PH1; **and**
  - Patient is not receiving Oxlumo in combination with Rivfloza (nedosiran); **and**
  - Dosing is in accordance with the United States Food and Drug Administration approved labeling; **and**
  - Initial authorization will be for no more than 12 months
- For **continuation of therapy**, **all** of the following:
  - Submission of medical records (e.g., chart notes, laboratory values) documenting a positive clinical response to therapy from pre-treatment baseline (e.g., decreased urinary oxalate concentrations, decreased urinary oxalate:creatinine ratio, decreased plasma oxalate concentrations); **and**
  - Patient has not received a liver transplant; **and**
  - Patient is not receiving Oxlumo in combination with Rivfloza (nedosiran); **and**

- Prescribed by, or in consultation with, a specialist (e.g., geneticist, nephrologist, urologist) with expertise in the treatment of PH1; **and**
- Dosing is in accordance with the United States Food and Drug Administration approved labeling; **and**
- Reauthorization will be for no more than 12 months

Rivfloza for provider administration is proven and medically necessary for the treatment of PH1 in patients who meet all of the following criteria:

- For **initial therapy**, **all** of the following:
  - Diagnosis of PH1 by, or in consultation with, a specialist (e.g., geneticist, nephrologist, urologist) with expertise in the diagnosis of PH1; **and**
  - Confirmation of the PH1 diagnosis based on **both** of the following:
    - Metabolic testing demonstrating **one** of the following:
      - Increased urinary oxalate excretion [e.g., greater than 1 mmol/1.73 m2 per day (90 mg/1.73 m2 per day), increased urinary oxalate: creatinine ratio relative to normative values for age]; **or**
      - Increased plasma oxalate and glyoxylate concentrations

      and
    - Genetic testing has confirmed a mutation in the alanine: glyoxylate aminotransferase (AGT or AGXT) gene

    and
  - Patient has not received a liver transplant; **and**
  - Patient is at least 2 years of age and older; **and**
  - Patient has relatively preserved kidney function (e.g., eGFR ≥ 30 mL/min/1.73 m^2); **and**
  - Patient is not receiving Rivfloza in combination with Oxlumo (lumasiran); **and**
  - Prescribed by, or in consultation with, a specialist (e.g., geneticist, nephrologist, urologist) with expertise in the treatment of PH1; **and**
  - Dosing is in accordance with the United States Food and Drug Administration approved labeling; **and**
  - Initial authorization will be for no more than 12 months
- For **continuation of therapy**, **all** of the following:
  - Submission of medical records (e.g., chart notes, laboratory values) documenting a positive clinical response to therapy from pre-treatment baseline (e.g., decreased urinary oxalate concentrations, decreased urinary oxalate: creatinine ratio, decreased plasma oxalate concentrations); **and**
  - Patient has not received a liver transplant; **and**
  - Patient has relatively preserved kidney function (e.g., eGFR ≥ 30 mL/min/1.73 m^2); **and**
  - Patient is not receiving Rivfloza in combination with Oxlumo (lumasiran); **and**
  - Prescribed by, or in consultation with, a specialist (e.g., geneticist, nephrologist, urologist) with expertise in the treatment of PH1; **and**
  - Dosing is in accordance with the United States Food and Drug Administration approved labeling; **and**
  - Reauthorization will be for no more than 12 months

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS Code	Description
J0224	Injection, lumasiran, 0.5 mg
C9399	Unclassified drugs or biologicals
J3490	Unclassified drugs

Diagnosis Code	Description
E72.53	Primary hyperoxaluria

Background

Primary hyperoxaluria (PH) is a rare inborn error of glyoxylate metabolism characterized by the overproduction of oxalate, which is deposited as calcium oxalate in various organs. In particular, the kidney is a prime target for oxalate deposition,

as excessive urinary excretion of oxalate may lead to end-stage renal disease (ESRD). PH is primarily caused by autosomal recessive enzymatic defects in pathways of glyoxylate metabolism that result in enhanced oxalate production. PH type 1 (approximately 80 percent of cases) is due to mutations of hepatic peroxisomal enzyme alanine:glyoxylate aminotransferase (AGT).). Liver transplantation is the only curative intervention for PH type 1 as it corrects the underlying enzymatic defect due to mutations of the AGXT gene.

Lumasiran reduces levels of glycolate oxidase (GO), an enzyme responsible for the metabolism of glycolate to glyoxylate and glyoxalate to oxalate, by targeting the hydroxyacid oxidase 1 (HAO1) messenger ribonucleic acid (mRNA) in hepatocytes through RNA interference. Decreased GO enzyme levels reduce the amount of available glyoxylate, a substrate for oxalate production.

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, thereby reducing subsequent oxalate burden.

Clinical Evidence

Lumasiran

The efficacy of lumasiran was established in a pivotal placebo-controlled and open-label clinical studies (ILLUMINATE-A, ILLUMINATE-B, and a phase 1/2 study) in 77 patients with PH1 (including 56 pediatric patients). Patients ranged in age from 4 months to 61 years at first dose. The median duration of exposure was 9.1 months (range 1.9 to 21.7 months). Overall, 58 patients were treated for at least 6 months, and 18 patients for at least 12 months.

A phase 1/2 study evaluated lumasiran at multiple doses in a single blind, randomized, placebo-controlled trial in 20 patients with PH1. Patients were randomized 3:1 to receive lumasiran and all patients received lumasiran in the open-label extension phase. After a median of 7 months on lumasiran, patients experienced a 66% mean reduction of urinary oxalate content from baseline. Among patients receiving 3.0 mg/kg monthly or quarterly doses of lumasiran, 10/12 (83%) achieved urinary oxalate levels within the normal range.

ILLUMINATE-A was a randomized, double-blind trial comparing lumasiran and placebo in 39 patients ≥ 6 years of age with PH1 and an eGFR ≥ 30 mL/min/1.73 m2 (ILLUMINATE-A; NCT03681184). Patients received 3 loading doses of 3 mg/kg lumasiran (n = 26) or placebo (n = 13) administered once monthly, followed by quarterly maintenance doses of 3 mg/kg lumasiran or placebo. The primary endpoint from ILLUMINATE A was the percent reduction from baseline in 24-hour urinary oxalate excretion corrected for BSA averaged over months 3 through 6. The LS mean percent change from baseline in 24-hour urinary oxalate in the lumasiran group was -65% (95% CI: -71, -59) compared with -12% (95% CI: -20, -4) in the placebo group, resulting in a between-group LS mean difference of 53% (95% CI: 45, 62; p < 0.0001). By Month 6, 52% (95% CI: 31, 72) of patients treated with lumasiran achieved a normal 24-hour urinary oxalate corrected for BSA (≤ 0.514 mmol/24 hr/1.73 m2) compared to 0% (95% CI: 0, 25) placebo-treated patients (p = 0.001).

ILLUMINATE-B was a single-arm study in 18 patients < 6 years of age with PH1 and an eGFR > 45 mL/min/1.73 m2 for patients ≥ 12 months of age or a normal serum creatinine for patients < 12 months of age (ILLUMINATE-B; NCT03905694). The median age was 47 months (range 4 to 74 months). The primary endpoint was the percent reduction from baseline in spot urinary oxalate:creatinine ratio averaged over months 3 through 6. Patients treated with lumasiran achieved a reduction in spot urinary oxalate:creatinine ratio from baseline of 71% (95% CI: 65, 77).

The approval of lumasiran for the expanded indication to include lowering of plasma oxalate levels was based on ILLUMINATE-C, a single-arm study in 21 patients with PH1, including patients on hemodialysis. Cohort A included 6 patients who did not require dialysis at the time of study enrollment. Cohort B included 15 patients who were on a stable regimen of hemodialysis. The primary endpoint was the percent change in plasma oxalate from baseline to month 6 for Cohort A and the percent change in pre-dialysis plasma oxalate from baseline to month 6 for Cohort B. The percent change from baseline to month 6 in plasma oxalate levels in Cohort A was a least-squares (LS) mean difference of -33% (95% CI: -82, 15) and in Cohort B it was -42% (95% CI: -51, -34).

Nedosiran

The efficacy of nedosiran was established in a randomized, double-blind trial (PHOX2) comparing nedosiran and placebo in patients aged 6 years or older with PH1 or PH2 and an eGFR ≥ 30 mL/min/1.73 m2 (NCT03847909). Too few PH2 patients were enrolled to evaluate efficacy in the PH2 population. Therefore, nedosiran is only indicated for patients with PH1. Patients received monthly doses of nedosiran (n = 23) or placebo (n = 12). The nedosiran dose for patients at least 12 years of age weighing at least 50 kg was 160 mg, for patients at least 12 years of age weighing less than 50 kg was

128 mg, and for children 6 to 11 years of age was 3.3 mg/kg (to a maximum of 128 mg). The median age was 20 years (range 9 - 46 years), 51% were female, 71% were White, 17% were Asian, 83% had PH1, and 17% had PH2. At baseline, mean 24-hour urinary oxalate excretion, normalized by 1.73 m2 BSA in patients less than 18 years of age, was 1547 μmol/24-hour. Mean plasma oxalate was 8.2 μmol/L, 43% of patients had an eGFR ≥ 90 mL/min/1.73 m2, 34% had an eGFR 60 to < 90 mL/min/1.73 m2, 23% had an eGFR 30 to < 60 mL/min/1.73 m2, 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 (95% CI: -5025, -1947) in the nedosiran group compared to 1490 (95% CI: 781, 3761) in the placebo group, for a between group difference of 4976 (95% CI: 2803, 7149; p < 18 years of age) averaged over Days 90, 120, 150 and 180, was -37% (95% CI: -53%, -21%) in the nedosiran 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%).

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

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Oxlumo (lumasiran) is an HAO1-directed small interfering ribonucleic acid (siRNA) indicated for the treatment of primary hyperoxaluria type 1 (PH1) to lower urinary and plasma oxalate levels in pediatric and adult patients.

Rivfloza (nedosiran) is an LDHA-directed small interfering RNA (siRNA) indicated 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, e.g., eGFR ≥ 30 mL/min/1.73 m2.

References

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11. Long term extension study in patients with primary hyperoxaluria (PHYOX3). ClinicalTrials.gov website Accessed March 6, 2024.

Policy History/Revision Information

Date	Summary of Changes
07/01/2025	**Coverage Rationale** • Revised coverage criteria for initial therapy for Rivfloza; replaced criterion requiring "the patient is at least ***9*** years of age and older" with "the patient is at least ***2*** years of age and older" **Supporting Information** • Updated *FDA* and *References* sections to reflect the most current information • Archived previous policy version IEXD0102.08

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard benefit plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. UnitedHealthcare Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.