

Oxlumo® (Lumasiran)

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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

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 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
 - Patient has not received a liver transplant; **and**
 - Oxlumo is prescribed by, or in consultation with, a specialist (e.g., geneticist, nephrologist, urologist) with expertise in the treatment of PH1; **and**
 - Oxlumo dosing is in accordance with the United States Food and Drug Administration approved labeling; **and**
 - Initial authorization will be for no more than 6 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**

- Oxlumo is prescribed by, or in consultation with, a specialist (e.g., geneticist, nephrologist, urologist) with expertise in the treatment of PH1; **and**
- Oxlumo 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

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). Glycolate oxidase (GO) is an enzyme responsible for the metabolism of glycolate to glyoxylate and glyoxalate to oxalate. Lumasiran reduces levels of GO enzyme 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. As the GO enzyme is upstream of the deficient alanine:glyoxylate aminotransferase (AGT) enzyme that causes PH1, the mechanism of action of lumasiran is independent of the underlying AGXT gene mutation. Lumasiran is not expected to be effective in primary hyperoxaluria type 2 (PH2) or type 3 (PH3) because its mechanism of action does not affect the metabolic pathways causing hyperoxaluria in PH2 and PH3.

In patients with PH, the increased urinary excretion of oxalate results in an oversaturated urine for calcium oxalate, which leads to urolithiasis and nephrocalcinosis. Recurrent stones and progressive nephrocalcinosis cause renal parenchymal inflammation and fibrosis, and if persistent, may progress to ESRD. As renal function deteriorates, plasma oxalate exceeds 30 micromol/L (the plasma supersaturation threshold for calcium oxalate), because of reduced urinary oxalate excretion. This leads to calcium oxalate deposition into nonrenal tissues including the retina, myocardium, vessel walls, skin, bone, and the central nervous system (systemic oxalosis). 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.

Clinical Evidence

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).

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 a 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.

References

1. Oxlumo [package insert] Cambridge MA, Alnylam Pharmaceuticals, Inc. September 2023.
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3. Hoppe B, Beck BB, Milliner DS. The primary hyperoxalurias. *Kidney Int* 2009; 75:1264.
4. Niaudet P. Primary Hyperoxaluria. In: UpToDate, Mattoo TK, Kim MS, (Ed), UpToDate, Waltham, MA, 2020.
5. A Phase 1/2 Trial Of Lumasiran (ALN-GO1), An Investigational RNA Interference (RNAi) Therapeutic, For Primary Hyperoxaluria Type 1. ESPN Annual Meeting. Antalya, Turkey. 4 October 2018.
6. A Study to Evaluate Lumasiran in Children and Adults With Primary Hyperoxaluria Type 1 (ILLUMINATE-A). Clinicaltrials.gov website <https://clinicaltrials.gov/ct2/show/NCT03681184?term=lumasiran&draw=2&rank=4> Accessed December 1, 2020.
7. A Study of Lumasiran in Infants and Young Children With Primary Hyperoxaluria Type 1 (ILLUMINATE-B). Clinicaltrials.gov website <https://clinicaltrials.gov/ct2/show/NCT03905694?term=lumasiran&draw=2&rank=2> Accessed December 1, 2020.
8. A Study to Evaluate Lumasiran in Patients With Advanced Primary Hyperoxaluria Type 1 (ILLUMINATE-C). Clinicaltrials.gov website <https://clinicaltrials.gov/ct2/show/NCT04152200?term=lumasiran&draw=2&rank=1> Accessed October 11, 2022.

Policy History/Revision Information

Date	Summary of Changes
12/01/2023	Supporting Information <ul style="list-style-type: none">Updated <i>References</i> section to reflect the most current informationArchived previous policy version IEXD0102.05

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.