Medical Policy Bulletin
Title:
Lumasiran (Oxlumo®)
Policy #:
MA08.131a

The Company makes decisions on coverage based on the Centers for Medicare and Medicaid Services (CMS) regulations and guidance, benefit plan documents and contracts, and the member's medical history and condition. If CMS does not have a position addressing a service, the Company makes decisions based on Company Policy Bulletins. Benefits may vary based on contract, and individual member benefits must be verified. The Company determines medical necessity only if the benefit exists and no contract exclusions are applicable. Although the Medicare Advantage Policy Bulletin is consistent with Medicare's regulations and guidance, the Company's payment methodology may differ from Medicare.

When services can be administered in various settings, the Company reserves the right to reimburse only those services that are furnished in the most appropriate and cost-effective setting that is appropriate to the member's medical needs and condition. This decision is based on the member's current medical condition and any required monitoring or additional services that may coincide with the delivery of this service.

This Policy Bulletin document describes the status of CMS coverage, medical terminology, and/or benefit plan documents and contracts at the time the document was developed. This Policy Bulletin will be reviewed regularly and be updated as Medicare changes their regulations and guidance, scientific and medical literature becomes available, and/or the benefit plan documents and/or contracts are changed.

Policy

Coverage is subject to the terms, conditions, and limitations of the member's Evidence of Coverage.

MEDICALLY NECESSARY

INITIAL APPROVAL

Lumasiran (Oxlumo®) is considered medically necessary and, therefore, covered for the treatment of primary hyperoxaluria type 1 (PH1) to lower urinary oxalate levels in pediatric and adult individuals when ALL of the following criteria are met:

- Diagnosis of PH1 confirmed by identification of biallelic pathogenic variants in alanine:glyoxylate aminotransferase (*AGT or AGXT*) gene OR liver biopsy demonstrating AGT deficiency.
- Presence of one of the following, which are associated with clinical presentation of PH1
    - Elevated urine oxalate excretion (body surface area–normalized daily urine oxalate excretion output ≥0.7 mmol/1.73 m2)
    - Elevated plasma oxalate concentration >20 µmol/L or >1.76 mg/L
    - Urine oxalate excretion:creatinine ratio above age-specific upper limit of normal
- Individual has not received a liver transplant.
- Prescribed by or in consultation with a nephrologist, urologist, geneticist, or any healthcare provider with expertise in treating PH1.

CONTINUATION OF TREATMENT

Continuation of lumasiran (Oxlumo®) is considered medically necessary and, therefore, covered when ALL of the following requirements are met:

- Individual continues to meet the initial treatment criteria cited above.
- Documented evidence to support clinically meaningful response to therapy from pretreatment baseline (e.g., decreased urinary oxalate concentrations, decreased urinary oxalate:creatinine ratio, decreased plasma oxalate concentrations, improvement, stabilization or slowed worsening of nephrocalcinosis, renal stone events, renal impairment or systemic calcinosis).
- Does not exceed US Food and Drug Administration–approved maintenance dose.

NOTE: Evio has been selected by the Company to administer clinical outcomes monitoring for patients receiving certain high-cost drug therapies. Lumasiran (Oxlumo®) is included in the portfolio of high-cost drug therapies for which Evio will be tracking clinical outcomes. If a patient meets all medical policy provisions and is approved to

receive treatment, the requesting professional provider or member must attest and agree to providing clinical outcomes data and information via Evio's secure web portal as requested.

EXPERIMENTAL/INVESTIGATIONAL

Lumasiran (Oxlumo®) is considered experimental/investigational and, therefore, not covered when the above criteria are not met and for all other indications unless the indication is supported as an accepted off-label use, as defined in the Company medical policy on off-label coverage for prescription drugs and biologics.

REQUIRED DOCUMENTATION

The individual's medical record must reflect the medical necessity for the care provided. These medical records may include, but are not limited to: records from the professional provider's office, hospital, nursing home, home health agencies, therapies, and test reports.

The Company may conduct reviews and audits of services to our members, regardless of the participation status of the provider. All documentation is to be available to the Company upon request. Failure to produce the requested information may result in a denial for the drug.

Guidelines

BENEFIT APPLICATION

Subject to the terms and conditions of the applicable Evidence of Coverage, lumasiran (Oxlumo®) is covered under the medical benefits of the Company's Medicare Advantage products when the medical necessity criteria listed in this medical policy are met.

US FOOD AND DRUG ADMINISTRATION (FDA)

On November 23, 2020, lumasiran (Oxlumo) was approved by the FDA for the treatment of primary hyperoxaluria type 1 to lower urinary oxalate levels in pediatric and adult patients.

On October 6, 2022, the FDA approved a new label expansion to lower urinary oxalate and plasma oxalate levels in pediatric and adult patients. The approval was based on the results of A Study to Evaluate Lumasiran in Patients With Advanced Primary Hyperoxaluria Type 1 (ILLUMINATE-C) Phase 3 trial in patients with severe renal impairment, including individuals on hemodialysis.

DOSAGE AND FREQUENCY

The recommended dose of lumasiran (Oxlumo®) is weight-based and given as a subcutaneous injection. All maintenance doses begin 1 month after the last loading dose.

- For individuals weighing less than 10 kg: Loading dose is 6 mg/kg once monthly for 3 doses followed by a maintenance dose of 3 mg/kg once monthly.
- For individuals weighing 10 kg to less than 20 kg: Loading dose is 6 mg/kg once monthly for 3 doses followed by a maintenance dose of 6 mg/kg once every 3 months (quarterly).
- For individuals weighing 20 kg and above: Loading dose is 3 mg/kg once monthly for 3 doses followed by a maintenance dose of 3 mg/kg once every 3 months (quarterly).

For individuals on hemodialysis, lumasiran (Oxlumo®) is administered after hemodialysis if administered on dialysis days.

High-dose pyridoxine has been shown to be effective in reducing urinary oxalate levels in individuals with primary hyperoxaluria type 1, particularly those with homozygous p.Gly170Arg or p.Phe152Ile variant. In the pivotal trials of lumasiran (Oxlumo), background use of pyridoxine was allowed. About 50% and 61% of participants in the lumasiran (Oxlumo)-treated arm in ILLUMINATE-A and ILLUMINATE-B received background pyridoxine treatment.

Description

PRIMARY HYPEROXALURIA TYPE 1 (PH1)

Primary hyperoxalurias (PHs) are rare inborn errors of glyoxylate metabolism characterized by the overproduction of oxalate, which is poorly soluble and is deposited as calcium oxalate in various organs (including the bones, eyes, heart, and kidney). Primary hyperoxaluria is caused by mutations in one of the three genes that encode enzymes involved in glyoxylate metabolism. Primary hyperoxaluria type 1 (PH1; about 80% of cases) is caused by mutations of hepatic peroxisomal enzyme alanine-glyoxylate aminotransferase (AGT); it is the most common and severe type, affecting an estimated one to three individuals per million in Europe and North America. Because oxalate is primarily excreted in the urine, the kidney is the prime target for oxalate deposition, which leads to end-stage renal disease (ESRD) in many cases. Individuals with PH1 produce excessive oxalate, which can combine with calcium to cause kidney stones and deposits in the kidneys. Individuals can experience progressive kidney damage, which can lead to kidney failure and the need for dialysis. As kidney function worsens, oxalate can build up and damage other organs (Cochat and Rumsby, 2013; Niaudet, 2022).

Liebow et al. (2017) stated that PH1 arises from mutations in the enzyme AGT; and the resulting deficiency in this enzyme leads to abnormally high oxalate production resulting in calcium oxalate crystal formation and deposition in the kidney and many other organs, with systemic oxalosis and ESRD being common outcomes. Although a small subset of individuals can manage the disease with vitamin B6 treatments, the only effective treatment for most is a combined liver-kidney transplant. These researchers discussed the development of ALN-GO1, an investigational RNA interference (RNAi) therapeutic targeting glycolate oxidase, to deplete the substrate for oxalate synthesis. Subcutaneous administration of ALN-GO1 resulted in potent, dose-dependent, and durable silencing of the mRNA encoding glycolate oxidase and increased serum glycolate concentrations in wild-type mice, rats, and nonhuman primates. Furthermore, ALN-GO1 increased urinary glycolate concentrations in normal nonhuman primates and in a genetic mouse model of PH1. Notably, ALN-GO1 reduced urinary oxalate concentration up to 50% following a single dose in the genetic mouse model of PH1, and up to 98% after multiple doses in a rat model of hyperoxaluria. The authors concluded that these findings showed the ability of ALN-GO1 to reduce oxalate production in preclinical models of PH1 across multiple species and provided a clear rationale for clinical trials with this compound.

McGregor et al. (2020), by sequencing autozygous human populations, identified a healthy adult woman with lifelong complete knockout of HAO1 (expected about 1 in 30 million outbred people). HAO1 (glycolate oxidase) silencing is the mechanism of lumasiran, an investigational RNAi therapeutic for PH1. Lumasiran acts by lowering oxalate production. The individual's plasma glycolate levels were 12 times, and urinary glycolate six times, the upper limit of normal observed in healthy reference individuals (n=67). Plasma metabolomics and lipidomics (1871 biochemicals) revealed 18 markedly elevated biochemicals (>5 standard deviations outliers vs n=25 controls) suggesting additional HAO1 effects. Comparison with lumasiran pre-clinical and clinical trial data suggested she had less than 2% residual glycolate oxidase activity. Cell line p.Leu333SerfsTer4 expression showed markedly reduced HAO1 protein levels and cellular protein mislocalization. The authors concluded that in this individual, lifelong HAO1 knockout is safe and without clinical phenotype, de-risking a therapeutic approach and informing therapeutic mechanisms. Unlocking evidence from the diversity of human genetic variation can facilitate drug development.

LUMASIRAN

Lumasiran, a HAO1-directed small interfering ribonucleic acid (siRNA), is available as the brand Oxlumo (Alnylam Pharmaceuticals, Inc.). Per the label for Oxlumo, lumasiran (Oxlumo®) reduces levels of glycolate oxidase (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 AGT enzyme that causes PH1, the mechanism of action of lumasiran (Oxlumo®) is independent of the underlying AGXT gene mutation. Lumasiran (Oxlumo®) 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 (Alnylam, 2022).

The most common adverse reaction (reported in 20% or more of individuals) is injection site reactions. Lumasiran (Oxlumo®) acts by lowering oxalate production. It was examined in two studies in individuals with PH1: a randomized, placebo-controlled trial in individuals 6 years and older and an open-label study in individuals younger than 6 years.

STUDIES

A STUDY TO EVALUATE LUMASIRAN IN PATIENTS WITH ADVANCED PRIMARY HYPEROXALURIA TYPE 1 (ILLUMINATE-A)

ILLUMINATE-A was a randomized double-blind trial comparing lumasiran (Oxlumo®) and placebo in 39 individuals 6 years of age and older with PH1 and an eGFR greater than or equal to 30 mL/min/1.73 m2 (ILLUMINATE-A; NCT03681184). Individuals received three loading doses of 3 mg/kg lumasiran (Oxlumo®) (N=26) or placebo (N=13) administered once monthly, followed by quarterly maintenance doses of 3 mg/kg lumasiran (Oxlumo®) or placebo. The median age was 15 years (range, 6–61 years), 67% were male, and 77% were White. At baseline, the median 24-hour urinary oxalate excretion corrected for body surface area (BSA) was 1.7 mmol/24 h/1.73 m2, the median plasma oxalate level was 13.1 µmol/L, 33% of individuals had eGFR greater than or equal to 90 mL/min/1.73 m2, 49% had eGFR of 60 to less than 90 mL/min/1.73 m2, and 18% had eGFR 30 to less than 60 mL/min/1.73 m2, 56% were on pyridoxine, and 85% reported a history of symptomatic kidney stone events.

The primary endpoint 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 (Oxlumo®) group was −65% (95% CI, −71 to −59) compared with −12% (95% CI, −20 to −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 individuals treated with lumasiran (Oxlumo®) 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 individuals (*P*=0.001).

ILLUMINATE-B

ILLUMINATE-B was a single-arm study in 18 individuals less than 6 years of age with PH1 and an eGFR greater than 45 mL/min/1.73 m2 for individuals 12 months of age or older, or a normal serum creatinine for individuals younger than 12 months of age (ILLUMINATE-B; NCT03905694). Efficacy analyses included the first 16 individuals who received 6 months of treatment with lumasiran (Oxlumo®). Dosing was based on body w
eight.

SUMMARY

PHs are a group of rare genetic diseases. There are three subtypes, each resulting in the overproduction of oxalate by the liver. Type 1 is the most common type, which accounts for approximately 80% of cases and occurs as a result of a genetic defect in the alanine:glyoxylate aminotransferase (AGXT) gene that encodes the enzyme alanine glyoxylate aminotransferase. A defect in the enzyme results in overproduction of oxalate, which leads to deposition of calcium oxalate crystals in the kidneys and urinary tract. The result is the formation of painful and recurrent nephrolithiasis (renal stones), nephrocalcinosis, and renal failure. Compromised renal function exacerbates the disease as the excess oxalate can no longer be effectively excreted, resulting in subsequent accumulation and crystallization in bones, eyes, skin, and heart, leading to severe illness and death. Lumasiran (Oxlumo®) is a subcutaneously administered RNA interference (RNAi) therapeutic that silences the HAO1 gene, which encodes for a glycolate oxidase enzyme. By silencing the HAO1 gene, levels of glycolate oxidase are depleted, decreasing production of oxalate, the metabolite that directly contributes to the pathophysiology of primary hyperoxaluria type 1.

For individuals with PH1, evidence includes one phase 3 randomized controlled trial (RCT) (ILLUMINATE-A) in individuals 6 years and older and two single-arm prospective studies (ILLUMINATE-B and ILLUMINATE-C). Relevant outcomes are symptoms, quality of life, disease-specific survival, change in disease status, treatment-related morbidity, and treatment-related mortality. In ILLUMINATE-A and ILLUMINATE-B, individuals with preserved renal function were enrolled (estimated glomerular filtration rate [eGFR] >30 mL/min/1.73 m2), while in ILLUMINATE-C, individuals with moderately or severely reduced GFR including individuals with kidney failure on hemodialysis were enrolled. In ILLUMINATE-A, 39 individuals were randomly assigned 2:1 to lumasiran (Oxlumo®)or placebo for 6 months. The primary endpoint was the percent change in 24-hour urinary oxalate excretion from baseline to month 6. The percent reduction in 24-hour urinary oxalate from baseline to month 6 was −65% and −12% in the lumasiran (Oxlumo®) and placebo groups, respectively, with a between-group mean difference of 53% (95% CI, 45%–62%; *P*<0.0001). A similar effect was seen in individuals with high baseline urinary oxalate values, and approximately half of individuals who received lumasiran (Oxlumo®) achieved normal urinary oxalate values by month 6. In ILLUMINATE-B, 18 individuals were treated with lumasiran (Oxlumo®). The primary endpoint was the percent change in spot urinary oxalate-to-creatinine ratio from baseline to month 6. Lumasiran (Oxlumo®) demonstrated a percent reduction in spot urinary oxalate-to-creatinine ratio from baseline of –71% (95% CI, –77% to –65%) at 6 months. Results at 1 year follow-up showed that treatment effects were sustained. The magnitude of the reduction and the time course were consistent with findings in ILLUMINATE-A. In ILLUMINATE-C, 21 individuals were treated with lumasiran (Oxlumo®). The primary endpoint was the percent change in plasma oxalate levels from baseline to month 6. Lumasiran (Oxlumo®) demonstrated a percent reduction in plasma oxalate levels of –33% (95% CI, –82% to 15%) and –42% (95% CI, –51% to –34%) in individuals who did not require dialysis at the time of study enrollment and individuals who were on a stable regimen of hemodialysis. The major limitation is the lack of data on health outcomes such as renal stones, nephrocalcinosis, and renal failure, since neither trial was powered to assess these health outcomes. However, use of urinary oxalate as a surrogate for health outcomes in the pivotal trials may be

justified based on the knowledge of the pathophysiology of the disease and the causal role of urinary oxalate in kidney stone formation, nephrocalcinosis, and loss of kidney function. Further, the consistency and size of treatment effect across three trials are indicative of the potential for a clinical benefit over the long term. Lumasiran was generally well tolerated in all three studies.

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Coding

Inclusion of a code in this table does not imply reimbursement. Eligibility, benefits, limitations, exclusions, precertification/referral requirements, provider contracts, and Company policies apply.

The codes listed below are updated on a regular basis, in accordance with nationally accepted coding guidelines. Therefore, this policy applies to any and all future applicable coding changes, revisions, or updates.

In order to ensure optimal reimbursement, all health care services, devices, and pharmaceuticals should be reported using the billing codes and modifiers that most accurately represent the services rendered, unless otherwise directed by the Company.

The Coding Table lists any CPT, ICD-10, and HCPCS billing codes related only to the specific policy in which they appear.

CPT Procedure Code Number(s)
N/A

ICD - 10 Procedure Code Number(s)
N/A

ICD - 10 Diagnosis Code Number(s)
E72.53 Primary hyperoxaluria

HCPCS Level II Code Number(s)
J0224 Injection, lumasiran, 0.5 mg

Revenue Code Number(s)
N/A

Policy History

Revisions From MA08.131a:

03/28/2025	This version of the policy will become effective 03/28/2025. This policy has been updated to communicate the Company's coverage position and criteria for lumasiran (Oxlumo®). A note has been added to the Policy Section regarding Evio, wihch has been selected by the Company to administer clinical outcomes monitoring for patients receiving certain high-cost drug therapies.

MA08.079j

03/28/2025	This policy has been reissued in accordance with the Company's annual review process.
05/07/2024	The following new policy has been developed to communicate the Company's coverage criteria for Lumasiran (Oxlumo®). The policy will become effective on 05/07/2024.

Version Effective Date:
03/28/2025
Version Issued Date:
03/28/2025
Version Reissued Date:
N/A