Pharmacotherapy for primary hyperoxaluria Type 1 (PH1)

Policy # 00746
Original Effective Date: 05/10/2021
Current Effective Date: 05/13/2024

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider lumasiran (Oxlumo™)‡ or nedosiran (Rivfloza™)‡ for the treatment of primary hyperoxaluria type 1 (PH1) to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for lumasiran (Oxlumo™)‡ and nedosiran (Rivfloza™)‡ will be considered when the following criteria are met:

- For lumasiran (Oxlumo) requests:
  - Initial
    - Patient has a diagnosis of PH1 confirmed by BOTH of the following:
      - ONE of the following:
        - Genetic confirmation of *AGXT* gene mutation; OR
        - Liver biopsy demonstrating absent or significantly reduced alanine:glyoxylate aminotransferase (AGT) activity; AND
      - ONE of the following:
        - Elevated urine oxalate (UOx) excretion as measured by body surface area-normalized daily UOx output greater than the upper limit of normal; OR
        - Elevated UOx excretion as measured by UOx:Creatinine ratio above age-specific upper limit of normal; OR
        - Elevated plasma oxalate (POx) concentration greater than the upper limit of normal; AND

- Patient does not have secondary causes of hyperoxaluria (e.g., diet with excessive intake of oxalate, gastric bypass surgery, intestinal disorders, etc.); AND
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*
- Patient has NOT had a liver transplant; AND
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*
- Patient will NOT use in combination with nedosiran (Rivfloza™); AND
- Dose will not exceed the FDA-labeled dose as described below:

Body weight	Loading dose	Maintenance Dose (begin 1 month after last loading dose)
Less than 10 kg	6 mg/kg once monthly for 3 doses	3 mg/kg once monthly
10 kg to less than 20 kg	6 mg/kg once monthly for 3 doses	6 mg/kg once every 3 months
20 kg and above	3 mg/kg once monthly for 3 doses	3 mg/kg once every 3 months

- Continuation
  - Patient has received an initial authorization for Oxlumo; AND
  - Liver transplantation has not occurred since previous authorization; AND
    *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*
  - Patient has responded to therapy as demonstrated by a reduction of urine or plasma oxalate levels relative to pre-treatment baseline or improvement, stabilization, or slowed worsening of one or more clinical manifestations of PH1 (e.g., nephrocalcinosis, renal stone events, renal impairment, systemic oxalosis); AND

*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*

- Patient will NOT use in combination with nedosiran (Rivfloza™); AND
- Dose will not exceed the FDA-labeled dose as described below:

Body weight	Maintenance Dose
Less than 10 kg	3 mg/kg once monthly
10 kg to less than 20 kg	6 mg/kg once every 3 months
20 kg and above	3 mg/kg once every 3 months

- For nedosiran (Rivfloza) requests:
  - Initial (6 months)
    - Patient has a diagnosis of PH1; AND
    - Diagnosis has been verified by documentation of ONE of the following:
      - Genetic testing confirming *AGXT* gene mutation; OR
      - Liver biopsy demonstrating absent or significantly reduced alanine:glyoxylate aminotransferase (AGT) enzyme activity; AND
    - Patient is 9 years of age or older; AND
    - Patient has documentation of ONE of the following:
      - 24-hour urinary oxalate (UOx) excretion ≥ 0.7 mmol normalized to 1.73 m^2 BSA; OR
      - Plasma oxalate (POx) level ≥ 20 µmol/L; AND
    - Patient's estimated glomerular filtration rate (eGFR) is ≥30 mL/min/1.73 m^2; AND
    - Patient has NOT received a kidney or liver transplant; AND
      *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*
    - Patient will NOT use in combination with lumasiran (Oxlumo); AND
    - Patient will use Rivfloza in combination with pyridoxine (vitamin B6) unless patient is determined to be a non-responder to pyridoxine therapy

(non-responsive is defined as less than or equal to a 30% decrease in urine oxalate after 3 months of treatment with maximally tolerated pyridoxine).
*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*

- Continuation
  - Patient has received an initial authorization for Rivfloza; AND
  - Liver or kidney transplantation has not occurred since previous authorization; AND
    *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*
  - Patient has responded to therapy as demonstrated by a reduction of urine or plasma oxalate levels relative to pre-treatment baseline OR improvement, stabilization, or slowed worsening of one or more clinical manifestations of PH1 (e.g., nephrocalcinosis, renal stone events, renal impairment, systemic oxalosis); AND
    *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*
  - Patient will NOT use in combination with lumasiran (Oxlumo); AND.
  - Patient will use the requested medication in combination with pyridoxine (vitamin B6) unless the patient is determined to be a non-responder to pyridoxine therapy (non-responsive is defined as less than or equal to a 30% decrease in urine oxalate after 3 months of treatment with maximally tolerated pyridoxine).
    *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*

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When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of lumasiran (Oxlumo) when the patient has a secondary cause of hyperoxaluria or has received a liver transplant to be **not medically necessary.****

Based on review of available data, the Company considers the continued use of lumasiran (Oxlumo) when the patient has not responded to therapy or has received a liver transplant to be **not medically necessary.****

Based on review of available data, the Company considers the use of nedosiran (Rivfloza) when the patient has received a kidney or liver transplant or will NOT use Rivfloza in combination with pyridoxine (vitamin B6) unless the patient is determined to be a non-responder to pyridoxine therapy to be **not medically necessary.****

Based on review of available data, the Company considers the continued use of nedosiran (Rivfloza) when the patient has received a kidney or liver transplant, has not responded to therapy, or will NOT use Rivfloza in combination with pyridoxine (vitamin B6) unless the patient is determined to be a non-responder to pyridoxine therapy to be **not medically necessary.****

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of lumasiran (Oxlumo) or nedosiran (Rivfloza) when patient selection criteria are not met (except those denoted above as **not medically necessary****) to be **investigational.***

Background/Overview

Oxlumo is a small interfering RNA indicated for the treatment of patients with primary hyperoxaluria type 1 (PH1), a rare condition caused by a genetic mutation that results in buildup of oxalate. It works by targeting messenger RNA for the *hydroxyacid oxidase 1* (*HAO1*) gene to reduce the production of glycolate oxidase and ultimately, oxalate. The dosing of Oxlumo is weight-based

and consists of loading doses for the first 3 doses followed by maintenance doses either monthly or quarterly. It is administered as a subcutaneous injection by a healthcare professional.

Rivfloza, the second FDA-approved treatment for PH1, is also a small interfering RNA therapy which reduces levels of hepatic lactate dehydrogenase (LDH) via the degradation of lactate dehydrogenase A (LDHA) messenger ribonucleic acid (mRNA) in hepatocytes through RNA interference. The reduction of hepatic LDH by Rivfloza reduces the production of oxalate by the liver, thereby reducing subsequent oxalate burden. Rivfloza is administered subcutaneously once a month by a healthcare professional, caregiver, or patient, and the dose is weight based.

Primary hyperoxalurias are rare autosomal recessive inborn errors of glyoxylate metabolism that result in the overproduction of oxalate, primarily by the liver. PH1 is the most common form of primary hyperoxaluria with an estimated prevalence of 1-3 cases per 1 million individuals in the population with fewer than 1000 individuals affected in the US. Each type of primary hyperoxaluria is caused by a different enzyme deficiency resulting from a specific mutation. PH1 results from mutations in the *AGXT* gene that encodes for a hepatic- specific peroxisomal enzyme, AGT. Clinical signs and symptoms of PH1 are caused by the buildup of oxalate and include progressive renal damage from tubular oxalate toxicity, nephrocalcinosis, and renal obstruction by stones, which are often accompanied by infection and inflammation. Ultimately, the patient's eGFR declines and the kidney becomes incapable of excreting all of the oxalate being produced. Plasma oxalate levels then rise and oxalate is deposited into a variety of tissues causing a range of effects depending on the tissue where the oxalate is deposited. Diagnosis is established by identification of biallelic pathogenic variants in *AGXT* on molecular genetic testing or via a liver biopsy to assay the activity of the AGT enzyme. Before Rivfloza was approved, Oxlumo was the first specific treatment for PH1. Prior to these therapy options, patients were encouraged to maintain a high fluid intake and limit oxalate-rich foods. Additional treatment options include oral potassium citrate or sodium citrate to alkalinize the urine and prevent calcium oxalate crystallization and pyridoxine supplementation to reduce oxalate synthesis.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
Oxlumo was approved in November 2020 for the treatment of primary hyperoxaluria type 1 (PH1) to lower urinary oxalate levels in pediatric and adult patients.

Rivfloza was approved in September of 2023 to lower urinary oxalate levels in children 9 years of age and older and adults with primary hyperoxaluria type 1 (PH1) and relatively preserved kidney function (e.g. estimated glomerular filtration rate [eGFR] ≥30 mL/min/ 1.73 m2).

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Oxlumo
The safety and efficacy of Oxlumo was established based on three trials: ILLUMINATE-A, ILLUMINATE-B, and ILLUMINATE-C.

ILLUMINATE-A was a randomized, double-blind trial comparing Oxlumo and placebo in 39 patients 6 years of age and older with PH1 and an eGFR≥30 mL/min/1.73m^2. Patients received 3 loading doses of 3 mg/kg Oxlumo (n=26) or placebo (n=13) administered once monthly, followed by quarterly maintenance doses of 3 mg/kg Oxlumo or placebo. The primary endpoint in the study 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 Oxlumo 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).

ILLUMINATE-B was a single-arm study in 18 patients <6 years of age with PH1 and an eGFR>45 mL/min/1.73 m^2 or a normal serum creatinine for patients <12 months of age. Efficacy analyses included the first 16 patients who received 6 months of treatment with Oxlumo. Dosing was based on body weight. The primary endpoint was the percent reduction from baseline in spot urinary

oxalate:creatinine ratio averaged over months 3 through 6. Patients treated with Oxlumo achieved a reduction in spot urinary oxalate:creatinine ratio from a baseline of 71%.

ILLUMINATE-C enrolled a total of 21 patients in a multi-center, single-arm study in patients with PH1 and an eGFR ≤ 45 mL/min/1.73 m^2 in patients 12 months of age and older or an elevated serum creatinine for age in patients less than 12 months of age, including patients on hemodialysis. ILLUMINATE-C included 2 cohorts. 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 hemodialysis regimen was to remain stable in these patients for the first 6 months of the study. Patients received the recommended dosing regimen of Oxlumo based on body weight. Patients requiring peritoneal dialysis were excluded. For Cohort A, the median plasma oxalate level was 58 µmol/L. For Cohort B, the median pre-dialysis plasma oxalate level was 104 µmol/L. The primary endpoint was the percent change in plasma oxalate from baseline to Month 6 (average from Month 3 to Month 6) for Cohort A (N=6) and the percent change in pre-dialysis plasma oxalate from baseline to Month 6 (average from Month 3 to Month 6) for Cohort B (N=15). The percent change from baseline to Month 6 in plasma oxalate levels in Cohort A was an LS mean difference of -33% (95% CI: -82, 15) and in Cohort B was -42% (95% CI: -51, -34). Mean plasma oxalate decreased from 65 µmol/L (95% CI: 21, 108) at baseline to 33 µmol/L (95% CI: 10, 56) at Month 6 in Cohort A, and from 108 µmol/L (95% CI: 92, 125) at baseline to 62 µmol/L (95% CI: 51, 72) at Month 6 in Cohort B.

Rivfloza

PHYOX2 was a randomized, double-blind trial comparing Rivfloza and placebo in patients aged 6 years or older with PH1 or PH2 and an eGFR ≥ 30 mL/min/1.73 m^2. Because too few PH2 patients were enrolled to evaluate efficacy in the PH2 population, Rivfloza is only indicated for patients with PH1. Unless otherwise noted, data are presented for the complete study population (PH1 and PH2). Patients received monthly doses of Rivfloza (N=23) or placebo (N=12). Patients at least 12 years of age weighing at least 50 kg, received Rivfloza 160 mg, and for patients at least 12 years of age weighing less than 50 kg, the dose was 128 mg. Children 6 to 11 years of age received a dose of 3.3 mg/kg (to a maximum of 128 mg). 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 LS mean AUC24-hour Uox was -3486 (95% CI: -5025, -1947) in the Rivfloza group compared to 1490 (95% CI: 781, 3761) in the placebo group, for a between group difference of 4976 (95% CI: 2803, 7149; p<0.0001). The LS mean percent change from baseline in 24-hour urinary

oxalate excretion (corrected for BSA in patients < 18 years of age) averaged over Days 90, 120, 150 and 180, was -37% (95% CI: -53%, -21%) in the Rivfloza 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%).

References

1. Oxlumo [package insert]. Alnylam Pharmaceuticals. Cambridge, MA. Updated October 2023.
2. Oxlumo Drug Evaluation. Express Scripts. Updated December 2020.
3. Rivfloza [package insert]. Novo Nordisk. Lexington, MA. Updated November 2020.
4. Rivfloza Drug Evaluation. Express Scripts. Updated October 2023.
5. Rivfloza New Drug Review. IPD Analytics. Updated October 2023.

Policy History

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04/01/2021	Medical Policy Committee review
04/14/2021	Medical Policy Implementation Committee approval. New policy.
04/07/2022	Medical Policy Committee review
04/13/2022	Medical Policy Implementation Committee approval. No change to coverage. Coding update
04/06/2023	Medical Policy Committee review
04/12/2023	Medical Policy Implementation Committee approval. No change to coverage.
04/04/2024	Medical Policy Committee review
04/10/2024	Medical Policy Implementation Committee approval. Changed title from "lumasiran (Oxlumo)' to 'Pharmacotherapy for primary hyperoxaluria Type 1 (PH1)." Added new criterion to Oxlumo to prevent using in combination with Rivfloza, removed GFR requirement due to findings from ILLUMINATE C trial, and updated applicable sections of the policy. Added the new drug Rivfloza to the policy with relevant criteria, background information, and rationale.

Next Scheduled Review Date: 04/2025

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Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2023 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No codes
HCPCS	J0224 Add codes effective 05/01/2024: J3490, C9399
ICD-10 Diagnosis	All related diagnoses

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*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.