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Lumasiran

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Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current generally accepted standards of care developed by: nonprofit professional association(s) for the relevant clinical specialty, third-party entities that develop treatment criteria, or other federal or state governmental agencies. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and generally accepted standards of medical care. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of

American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated, and coverage is not required for non-formulary drugs.

Coverage

Lumasiran (Oxlumo™) **may be considered medically necessary** when the individual has primary hyperoxaluria type 1 (PH1) **AND ALL** of the following criteria:

- Diagnosis confirmed by identification of biallelic pathogenic variants in alanine:
  a. Genetic testing demonstrating glyoxylate aminotransferase (*AGT* or *AGXT*) gene; or
  b. Liver biopsy demonstrating AGT deficiency; **AND**
- Presence of ONE of the following clinical signs and symptoms of PH1:
  a. Elevated urinary oxalate excretion (body surface area-normalized daily urine oxalate excretion output ≥ 0.7 mmol/24 hr/1.73 m^2); or
  b. Elevated plasma oxalate concentration (E.G., greater than the upper limit of normal; **AND**
- Individual has not received a liver transplant.

Lumasiran (Oxlumo™) **is considered experimental, investigational and/or unproven** for all other non-Food and Drug Administration approved indications.

Policy Guidelines

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-treated arm in ILLUMINATE-A and ILLUMINATE-B received background pyridoxine treatment. In ILLUMINATE-

C, participants currently receiving pyridoxine therapy were required to be on a stable regimen for at least 90 days.

Description

Primary Hyperoxaluria

Primary hyperoxaluria is a rare disorder of glyoxylate metabolism characterized by the overproduction of oxalate, which is poorly soluble and deposited as calcium oxalate in the kidneys and urinary tract, leading to 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.

There are 3 types of primary hyperoxaluria. Each of these is caused by a defect in a gene that governs the production of a different hepatic enzyme, and each result in the overproduction of oxalate by the liver. The 3 types are summarized in Table 1. Type 1 is the most common type, which accounts for approximately 80% of cases. (1) Homozygous or compound heterozygous alanine:glyoxylate aminotransferase (*AGXT)* variants lead to hepatic deficiency of alanine glyoxylate aminotransferase, which converts glyoxylate into pyruvate and glycine. (2) Absent or deficient levels lead to accumulation of oxalate and its deposition as calcium oxalate.

Table 1. Primary Hyperoxaluria Types (1)

PH Type	Gene[a]	Affected Enzyme	Prevalence	Distinctive Diagnostic Features
Type 1	*AGXT*	Alanine glyoxalate aminotransferase (AGT)	80% of cases	• Elevated urinary glycolate excretion. • Definitive diagnosis testing that demonstrates a variant in the *AGXT* gene. • If no variant detected, liver biopsy demonstrating absent or significantly reduced AGT activity. (3)
Type 2	*GRHPR*	Glycolate reductase hydroxy pyruvate reductase	10% of cases	• Elevated urinary oxalate and L-glycerate (>28 mmol/mol creatinine), which is pathognomonic for type 2 disease. (4) • Definite diagnosis by genetic testing. First

				step involves sequence analysis of exons 2 and 4 to detect the 2 most common mutations, c.103delG (40%) in exon 2 and c.403_405+2 del AAGT (16%) in exon 4. If these variants are not detected, complete sequencing is performed. (5)
Type 3	*HOGA1*	4-hydroxy 2-ketoglutarate aldolase	10% of cases	• Elevated urinary hydroxy-oxo-glutarate.

[a] Approximately 5% of individuals with primary hyperoxaluria do not have identifiable genetic mutations of the *AGXT*, *GRHPR*, or *HOGA1* gene.

Primary hyperoxaluria type 1 is a heterogeneous disorder with high variability in age and severity of symptoms at the time of presentation. Kidney stones are the most common manifestation that lead to the diagnosis of primary hyperoxaluria type 1. Individuals can present from birth to adulthood with clinical presentation ranging from kidney stones to end stage renal disease (ESRD). A summary from 2 case series comprising 78 infants (6) and 155 individuals (from 129 unrelated families) (7) diagnosed with primary hyperoxaluria type 1 is presented in Table 2. Young individuals present with more severe complications than adults since they have premature kidneys and develop rapid progression to ESRD. (2) An analysis of 247 individuals with primary hyperoxaluria type 1 from the Rare Kidney Stone Consortium Registry showed that 20% of individuals developed ESRD by approximately age 20 years while 50% developed ESRD by age 35 years. By age 60 years, nearly 90% of all individuals progressed to ESRD. (8)

Table 2. Clinical Manifestations of Primary Hyperoxaluria Type 1 by Age (6, 7)

Type	**Average age of onset (range)[a]**	**Clinical Presentation**	**Prevalence**
Early onset	5.5 months (3 weeks to 9 months)	Majority of infants present with failure to thrive because of renal failure	26% of cases
Pediatric onset	7.9 years (1 to 17 years)	High variability in presentation. Recurrent symptomatic nephrolithiasis with a normal to moderate decline in kidney function	30% of cases
Adult onset	29.4 years (19 to 45 years)	Majority of individuals experience recurrent kidney stones for years before diagnosis	21% of cases

[a] Approximately 10% of individuals were diagnosed on post-transplant recurrence of kidney stones and 13% were diagnosed during family screening.

Primary hyperoxaluria type 1 is considered a rare disease with an estimated prevalence of 1 to 3 per million people worldwide (mainly based on estimates from Europe). (9) The incidence in Europe has been estimated at 1 in 120,000 live births per year. (9) Estimating the prevalence and incidence is difficult owing to the wide variability in its clinical presentation and age of clinical onset. Individuals often experience a considerable diagnostic delay; approximately 20% to 50% of individuals have advanced chronic kidney disease, or even ESRD at the time of diagnosis. (9) Data regarding prevalence and incidence is summarized in Table 3.

Table 3. Estimated United States and European Union Prevalence of Primary Hyperoxaluria Type 1[a]

	Per million in the U.S./EU	**Total Number in the U.S./EU[b]**
Variant Prevalence (8)	~4.3	~3600
Diagnosed Prevalence (10-12)	~1.5 to 2.5	~1300 to 2100
Diagnosed and Non Transplanted	~1.2 to 2.0	~1000 to 1700

EU: European Union; U.S.: United States.

[a] Assumed indication is for the treatment of primary hyperoxaluria type 1 in pediatric and adult individuals regardless of stage of disease.

[b] United States population= 328 million; European Union population including the United Kingdom= 513 million.

Diagnosis

Diagnosis of primary hyperoxaluria type 1 is often delayed because of the rarity of the condition and general lack of awareness of the disease. Diagnosis generally involves 3 steps:

1. Clinical suspicion based on symptoms and radiographic features such as recurrent renal stones, nephrocalcinosis associated with decreased glomerular filtration rate (GFR), renal failure of unknown cause, presence of oxalate crystals in any biological fluid or tissue.
2. Metabolic screening for urinary oxalate levels. Normal urinary oxalate excretion is less than 0.5 mmol/1.73 m^2 per day or 45 mg/1.73 m^2 per day. (13) Levels greater than this are strongly supportive of the diagnosis of primary hyperoxaluria type 1.
3. Diagnosis is confirmed by molecular genetic testing that demonstrates a variant of the *AGXT* gene.

Current Treatment

The initial medical management approaches, which are aimed to delay progressive renal decline, include use of pyridoxine, calcium oxalate crystallization inhibitors, hyperhydration, and dietary restrictions.

Treatment with pyridoxine (vitamin B6) has been shown to decrease urine oxalate excretion in about 10% to 30% of individuals, particularly those with homozygous p.Gly170Arg or p.Phe152lle variants. (14) As a result, a trial of pyridoxine that lasts at least 3 months is warranted in all individuals with type 1 primary hyperoxaluria. (15) A positive response is defined as a reduction greater than 30% in urinary oxalate excretion. Observational data

suggest that in individuals who are responsive to pyridoxine, continued treatment is beneficial in most individuals (15, 16) and should be continued indefinitely or until liver transplantation is performed. Large doses of pyridoxine may induce sensory neuropathy.

Certain medication such as potassium citrate, orthophosphates, and thiazides prevent crystallization of calcium oxalate in the kidneys. (14) Hyperhydration (fluid intake greater than 3 L/day per 1.73 m^2) is an effective therapy to decrease tubular fluid oxalate concentration and diminish intratubular oxalate deposition. However, it is problematic in young children, as a gastric tube or a percutaneous gastrostomy may be necessary to maintain this high urine flow around the clock including both day and nighttime. While avoidance of foods with high oxalate content, such as tea, chocolate, spinach, and rhubarb is generally advocated, most oxalate is of an endogenous source and as such dietary measures are of little help. (17)

As the disease progresses, individuals may require interventions for renal stone removal, dialysis, and renal/liver transplant. However, with conventional hemodialysis and peritoneal dialysis, the rate of oxalate removal is often less than the endogenous production of oxalate (18, 19) and plasma oxalate returns to 80% of the predialysis value within 24 hours and 95% within 48 hours after dialysis. (20) As a consequence, despite standard maintenance dialysis therapy, plasma oxalate typically exceeds the supersaturation threshold of 30 µmol/L during a substantial amount of time between dialysis treatments, thereby increasing the risk and progression of systemic oxalosis.

Liver transplantation is the only curative intervention as it corrects the underlying enzymatic defect due to mutations of the *AGXT* gene. In individuals with significant chronic renal disease, renal transplant may also be required. Currently, multiple transplantation strategies are in use and include combined liver-renal transplantation, sequential liver and renal transplantation, isolated liver transplantation, and isolated renal transplantation. However, the optimal transplantation type or sequence remains uncertain. (21) Complications include those due to immunosuppressive therapy (e.g., infections or adverse drug effects), secondary malignancy, and failure of allograft.

Regulatory Status

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

On October 6, 2022, the U.S. 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 the ILLUMINATE-C phase 3 trial in patients with severe renal impairment, including individuals on hemodialysis.

On September 9, 2023, nedosiran (Rivfloza) was approved by the U.S. FDA to lower urinary oxalate levels in children 2 years of age and older and adults with primary hyperoxaluria type 1

and relatively preserved kidney function. This drug is not reviewed as it is outside the scope of this policy.

Rationale

Medical policies assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function, including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Primary Hyperoxaluria Type 1

Clinical Context and Therapy Purpose

The purpose of lumasiran in individuals who have primary hyperoxaluria type 1 is to provide a treatment option that is an improvement on existing therapies. Potential benefits of this therapy may include the following:

- A novel mechanism of action or approach that provides an additional treatment option for many individuals who have failed or have yielded a sub-optimal response to existing treatments.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with primary hyperoxaluria type 1.

Interventions

The therapy being considered is lumasiran, an RNA interference (RNAi) therapy. It silences the *HAO1* gene that encodes for the enzyme glycolate oxidase. Decreased production of

glycolate oxidase reduces hepatic oxalate production. Treatment is administered in an outpatient setting. The recommended dose of lumasiran 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).

Comparators

The following therapies are currently being used to manage individuals with primary hyperoxaluria type 1.

The initial medical management approaches, which are aimed to delay progressive renal decline, include use of pyridoxine, calcium oxalate crystallization inhibitors, hyperhydration, and dietary restrictions. As the disease progresses, individuals may require interventions for renal stone removal, dialysis, and renal/liver transplant. Despite standard maintenance dialysis therapy, plasma oxalate typically exceeds the supersaturation threshold of 30 µmol/L during a substantial amount of time between dialysis treatments, thereby increasing the risk and progression of systemic oxalosis. Liver transplantation is the only curative intervention as it corrects the underlying enzymatic defect due to mutations of the alanine:glyoxylate aminotransferase (*AGXT)* gene. In individuals with significant chronic renal disease, renal transplant may also be required. Currently, multiple transplantation strategies are in use and include combined liver-renal transplantation, sequential liver and renal transplantation, isolated liver transplantation, and isolated renal transplantation. However, the optimal transplantation type or sequence remains uncertain. (21) Complications include those due to immunosuppressive therapy (e.g., infections or adverse drug effects), secondary malignancy, and failure of allograft.

Outcomes

The general outcomes of interest are quality of life, disease-specific survival, change in disease status, resource utilization, treatment-related mortality, and treatment-related morbidity.

Relevant outcome measures in alphabetical order are summarized in Table 4.

Table 4. Health Outcome Measures Relevant to Primary Hyperoxaluria Type 1

Outcome	Description	Relevance
Kidney stones	Kidney stone event rates can be measured in multiple ways including visits to a healthcare provider because of a renal stone, medications for renal colic, stone passage, macroscopic hematuria due to	Kidney stone events may be considered a direct health outcome measure as it is a direct reflection of

	renal stones, development of new stones, and change in the size or shape of existing stones.	underlying disease pathophysiology.
Nephrocalcinosis	Nephrocalcinosis is characterized by the deposition of calcium in the kidney parenchyma and tubules. It can be graded on a standardized 4-point scale by renal ultrasound as grade 0, no echogenicity; grade 1, mild echogenicity around medullary pyramid borders; grade 2, moderate echogenicity around and inside pyramids; and grade 3, severe echogenicity of entire pyramids. (22) Outcomes were categorized as bilateral improvement, unilateral improvement, stabilized, or worsened in the clinical trials of lumasiran.	Outcomes related to the severity of nephrocalcinosis may be considered a direct health outcome measure as it is a direct reflection of underlying disease pathophysiology.
Urinary oxalate excretion	Urinary oxalate excretion is considered a surrogate measure. It may not be useful in CKD stage 3b to 5 as kidney function declines, urine oxalate excretion decreases, and the urinary oxalate estimation becomes inaccurate. (23) It is typically measured from a 24-hour urine sample. Normal urinary oxalate excretion: <0.5 mmol/1.73 m^2 per day. (13) Levels >1 mmol/1.73 m^2 per day are indicative of PH1. Some individuals excrete as much as 1.5 to 3 mmol/1.73 m^2 per day. (15) In younger individuals, obtaining a 24-hour urine collection is difficult, especially in infants and small children who are not toilet trained. An alternative measure is molar oxalate: creatinine ratio in spot urine samples. Normative values for spot oxalate: creatinine (mmol/mmol) vary by age and the assay method, the generally acceptable normal values	The optimal target would be close to normal levels (i.e., <0.5 mmol/1.73 m^2).

	based on age used to screen for hyperoxaluria are: (13, 15) • < 6 months: <0.32 to 0.36 • 6 months and 2 years: <0.13 to 0.17 • 2 and 5 years: <0.098 to 0.1 • 6 and 12 years: <0.07 to 0.08. A retrospective analysis of registry data of 297 individuals that included all types of primary hyperoxaluria (65% PH1) showed that individuals with higher baseline urine oxalate excretion were at the highest risk of developing kidney failure. The hazard ratio for kidney failure was 3.4 (95% CI, 1.4 to 7.9) for individuals with an oxalate excretion rate in the highest 4th quartile compared to those in quartiles 1 to 3. The 20-year kidney survival was 96% for those with an oxalate excretion rate of 1.11 mmol/1.73 m^2 per 24 hours in contrast to 42% for those with excretions ≥2.45 mmol/1.73 m^2 per 24 hours at the time of diagnosis. Further, the risk of kidney failure increases with increasing urine oxalate levels with a hazard ratio of 1.8 (95% CI, 1.2 to 2.5) per 1 mmol/1.73 m^2 per 24-hour increase. (24)	
Plasma oxalate levels	Plasma oxalate level is considered a surrogate measure. Plasma oxalate concentration remains normal as long as the GFR is higher than 40 mL/min per 1.73 m^2. Plasma oxalate levels may be more accurate in individuals with advanced CKD. (14, 25) When GFR is well preserved (>60 mL/min per 1.73 m^2), plasma oxalate levels are normal/modestly increased (2 to 10 mmol/L; normal is 1 to 3 mmol/L with most assays). In individuals with CKD stage	In individuals with preserved GFR (CKD stage 1 to 3a), the role of plasma oxalate in disease progression has not been studied due to the small number of laboratories performing plasma oxalate measurements, differences in measurement methods, and infrequent measurement of plasma oxalate in earlier stages of CKD. (12)

	5, plasma oxalate levels increase markedly (>90 to 100 mmol/L). (9, 15, 26) Plasma oxalate concentrations that exceed the supersaturation threshold for calcium oxalate are typically observed in individuals with primary hyperoxaluria with a GFR ≤30 to 40 mL/min per 1.73 m^2 (CKD stage 3b to 5). (26, 27)	Evidence relating to a decrease in plasma oxalate reducing the risk or severity of subsequent systemic oxalosis is limited to anecdotal experience with intensive dialysis regimens and the resolution of disease manifestations after transplantation. Plasma oxalate has been shown to decrease rapidly after liver transplantation, (21) with gradual resolution of oxalosis. (28) Studies of treatment response to plasma oxalate reduction in individuals with primary hyperoxaluria who have CKD stages 1 to 3a are lacking. The magnitude of change in plasma oxalate in CKD stages 3b to 5 that is likely to predict clinical benefit requires further study. (12)

CI: confidence interval; CKD: chronic kidney disease; GFR: glomerular filtration rate; PH1: primary hyperoxaluria type 1; mL/min: milliliters per minute; m:meters.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

The clinical development program for lumasiran includes 3 prospective trials. These trials enrolled individuals with primary hyperoxaluria type 1 with varying levels of renal function, with age groups ranging from infant to adult. ILLUMINATE-A (NCT03681184) enrolled individuals aged 6 years and older with an estimated glomerular filtration rate [eGFR] ≥30 mL/min/1.73 m^2,

ILLUMINATE-B (NCT03905694) enrolled individuals aged less than 6 years old with an eGFR >45 mL/min/1.73 m^2 (if ≥12 months old) and ILLUMINATE-C (NCT04152200) enrolled individuals with advanced primary hyperoxaluria type 1 irrespective of age with an eGFR ≤30 mL/min/1.73 m^2. A dose-finding phase-I first-in-human study (NCT02706886) was not included in the review of evidence. (29)

Randomized Controlled Trials

ILLUMINATE-A is the pivotal phase 3 randomized, double-blind, placebo-controlled trial. (30) The study consists of 2 parts: an initial 6-month, double-blind treatment period followed by a 54-month extension period in which placebo individuals had an option to switch to lumasiran. The study characteristics are summarized in Table 5. Results with 6-month follow-up are available and summarized in Table 6. At 6 months, the percent change in 24-hour urinary oxalate excretion from baseline to month 6 in the lumasiran group was -65% compared to -12% in the placebo group, resulting in a between-group least square (LS) mean difference of 53% (95% confidence interval [CI], 45% to 62%; p<.0001). The proportion of individuals who achieved a 24-hour urinary oxalate level at or below the upper limit of normal (ULN) at month 6 was 52% in the lumasiran group versus 0% in the placebo group (p=.001). The absolute change in 24-hour urinary oxalate levels in the lumasiran group was -1.24 (95% CI, -1.37 to -1.12) compared to -0.27 (95% CI, -0.44 to -0.10) in the placebo group with a difference of -0.98 (95% CI, -1.18 to -0.78) mmol/24 hr/1.73 m^2. (31) Urinary oxalate excretion is a surrogate health outcome and, while it is directly related to the pathophysiology of the disease, ILLUMINATE-A was not powered to assess hard endpoints associated with hyperoxaluria such as renal stones, nephrocalcinosis, and renal failure. Renal stone events was a composite outcome and included at least 1 of the following: visit to healthcare provider because of a renal stone, medication for renal colic, stone passage, or macroscopic hematuria due to a renal stone. Overall, 8 individuals (31%) in the lumasiran group and 3 (23%) in the placebo group experienced stone events during the 6-month, placebo-controlled period (13 vs. 4 stone events, respectively). Evidence of a treatment effect on kidney stone events was not expected given that calcium oxalate stones are slow to form and pass. The proportion of individuals with self-reported stone events at baseline was greater in the lumasiran group versus the placebo group (89% vs. 77%).

At 36-month follow-up, mean reductions in 24-hour urinary oxalate from baseline were 63% and 58% in the respective treatment groups. A total of 76% and 92% of individuals achieved 24-hour urinary oxalate excretion levels ≤1.5 times the upper limit of normal. Estimated glomerular filtration rate remained stable throughout the treatment period. The incidence of kidney stone events declined from 2.31 events per person-year (95% CI: 1.88-2.84) in the 12 months prior to study enrollment to 0.60 events (95% CI: 0.46-0.77) during treatment with lumasiran. Medullary nephrocalcinosis was generally stable or showed improvement, with approximately one-third of individuals in both groups demonstrating complete resolution. (32)

Table 5. Summary of ILLUMINATE-A Characteristics

Study	ILLUMINATE-A (31, 33)
Study Type	DBRCT
Country	Global

Dates	2018-ongoing
Participants	*Inclusion criteria* • Individuals with PH1 aged 6 years and older • Confirmed *AGXT* gene variants • eGFR ≥30 mL/min/1.73 m^2 • Urinary oxalate excretion ≥0.7 mmol/24 hr/1.73 m^2 *Exclusion criteria* • History of kidney or liver transplant • History of alcohol abuse; hepatitis B or C, or HIV *Patient characteristics* • Median age: 15 years (range, 6 to 61) • Male: 67% • Pyridoxine use: 56% • Nephrocalcinosis grade 1: 78% • Lifetime history of renal stones: 85% • History of renal stones in last 12 months: 39%
Treatment	• 6-month double-blind treatment period[a] • Lumasiran/placebo every month for first 3 months then every 3 months[a] • Lumasiran (n=26) • Placebo (n=13)
Follow-Up	60 months (results at 6 months are reported)

AGXT: alanine glyoxylate aminotransferase; DBRCT: double-blind randomized controlled trial; eGFR: estimated glomerular filtration rate; HIV: human immunodeficiency virus; hr: hour; PH1: primary hyperoxaluria type 1.

[a] Treatment arms were stratified at randomization based upon mean 24-hr urinary oxalate from the first 2 valid samples collected during screening (≤1.70 mmol/24 hr/1.73 m^2 vs. >1.70 mmol/24 hr/1.73 m^2).

Table 6. Summary of ILLUMINATE-A Results

Study	**LSM % Change in 24-hr Urinary Oxalate Excretion[a]**	**% of Individuals with Normal 24-hr Urinary Oxalate Excretion corrected for BSA (≤0.514 mmol/24 hr/1.73 m^2)**	**Renal Stones Events[b] n/N(%)**
ILLUMINATE-A (30, 31, 33)	N=39	N=39	N=39
6 months			
Lumasiran	-65% (95% CI, -71% to -59%)	52% (95% CI, 31% to 72%)	• Overall: 8/26 (31%) • In individuals without event in preceding year: 1/15 (7%)

			• In individuals with event in preceding year: 7/11 (64%)[c] • Number of stone events: 13
Placebo	-12% (95% CI, -20% to -4%)	0% (95% CI, 0% to 25%)	• Overall: 3/13 (23%) • In individuals without event in preceding year: 1/9 (11%) • In individuals with event in preceding year: 2/4 (50%)[c] • Number of stone events: 4
Between Group LSM Difference	53% (95% CI, 45% to 62%; p<.0001)	p=.001	-

BSA: body surface area; CI: confidence interval; LSM: least square mean.

[a] 24-hr urinary oxalate levels were measured as mmol/24 hr/1.73 m^2.

[b] A renal stone event was defined as an event that includes at least 1 of the following: visit to healthcare provider because of a renal stone, medication for renal colic, stone passage, or macroscopic hematuria due to a renal stone. Randomization was not stratified by renal stone events at baseline.

[c] Patient-reported history of renal stone events.

Single Arm Prospective Trials

ILLUMINATE-B is the pivotal single-arm trial in infants and children younger than 6 years. The study consists of 2 parts: (a 6-month primary analysis period followed by a 54-month extension period). The study characteristics and results are summarized in Tables 7 and 8 with 6-months follow-up. (34) At 6 months, the percent change in spot urinary oxalate:creatinine ratio from baseline was -72% in lumasiran-treated individuals. When stratified by weight, the percent reduction was 84%, 67%, and 71% among individuals <10 kg (n=3), 10 to <20 kg (n=11), and ≥20 kg (n=2), respectively. Data reported at 12-month (35) and 30-month (36) follow-up report durability of treatment effect on spot urinary oxalate:creatinine ratio. eGFR remained stable through month 30. In 14 individuals (86%) with nephrocalcinosis at baseline, nephrocalcinosis grade improved at month 24 in 12; no patient worsened. In the 4 individuals without baseline nephrocalcinosis, nephrocalcinosis was absent at month 24. Kidney stone event rates were ≤0.25 per person-year through month 30. While ILLUMINATE-B lacked a concurrent control, the magnitude of reduction in urinary oxalate and time course were generally consistent with the findings in ILLUMINATE-A.

ILLUMINATE-C is the pivotal single-arm trial in pediatric and adult individuals with moderately or severely reduced GFR (eGFR ≤45 mL/min/1.73 m^2 or pediatric individuals <12 months of age with serum creatinine above the ULN for age) including individuals with kidney failure on hemodialysis. The primary endpoint was the percent change in plasma oxalate levels from baseline to month 6. The study consisted of 2 cohorts: cohort A included 6 individuals who did

not require dialysis at the time of study enrollment while cohort B included 15 individuals who were on a stable regimen of hemodialysis; the hemodialysis regimen was to remain stable in these individuals for the first 6 months of the study. The study characteristics and results are summarized in Tables 7 and 8 with 6-month follow-up. At 6 months, the percent change from baseline in plasma oxalate levels in cohort A was a LS mean difference of -33% (95% CI, -82% to 15%) and in cohort B was -42% (95% CI, -51% to -34%). (33, 37)

Safety

A safety analysis included pooled data from 98 individuals (including 71 pediatric individuals and 15 individuals on hemodialysis) from placebo-controlled and open-label clinical studies. Overall, 92 individuals were treated for at least 6 months, 78 individuals for at least 12 months, and 29 individuals for at least 24 months. In ILLUMINATE-A, the most common (≥20%) adverse reaction reported was injection site reaction. Injection site reactions occurred throughout the study period and included erythema, pain, pruritus, and swelling. These symptoms were generally mild, resolved within 1 day of the injection, and did not lead to discontinuation of treatment. The safety profile in ILLUMINATE-B and ILLUMINATE-C was similar to that seen in ILLUMINATE-A. As with all oligonucleotides, there is a concern for development of anti-drug antibodies that may neutralize the therapeutic effect of a drug. A U.S. Food and Drug Administration data analysis from across all clinical studies in the lumasiran development program, including individuals with primary hyperoxaluria type 1 and healthy volunteers exposed to lumasiran, 7 of 120 (6%) lumasiran-treated individuals with a mean follow-up duration of 8.9 months tested positive for anti-drug antibodies. No clinically significant differences in the safety, pharmacokinetic, or pharmacodynamic profiles of lumasiran were observed in individuals who tested positive for an anti-lumasiran antibody.

Table 7. Summary of Single Arm Trial Characteristics

Study	ILLUMINATE-B (33, 34)	ILLUMINATE-C (33, 37)
Study Type	Single arm prospective cohort[a]	Single arm prospective cohort
Country	Global	Global
Dates	2019-ongoing	2020-ongoing
Participants	*Inclusion criteria* • Infants and children with PH1 aged 6 years and younger • Confirmed *AGXT* gene variants • eGFR >45 mL/min/1.73 m^2 if ≥12 months old; non elevated serum creatinine if <12 months old *Exclusion criteria* • Abnormal serum creatinine levels at screening for infants who are less than 1 year old • Does not have relatively preserved kidney function	*Inclusion criteria* • Individuals with PH1 with confirmed AGXT gene variants • GFR ≤45 mL/min/1.73 m^2 (if age ≥12 months) or increased serum creatinine level (if age <12 months), and plasma oxalate ≥20 µmol/L at screening • Individuals receiving pyridoxine therapy were required to have been receiving a stable regimen for at least 90 days • Individuals undergoing

	• Clinical evidence of systemic oxalosis • History of kidney or liver transplant *Patient characteristics* • Median age: 47 months (range, 4 to 74) • Male: 44% • Mean spot UOx:Cr ratio, mmol/mmol: 0.47	hemodialysis were required to have been receiving a stable hemodialysis regimen for at least 4 weeks before the screening plasma oxalate assessment and to maintain this regimen through the 6-month visit *Exclusion criteria* • Individuals receiving peritoneal dialysis alone or combined hemodialysis/peritoneal dialysis. *Patient characteristics* • Median age: 9 years (range, 0 to 59) • Male: 57% • White: 76%
Treatment	Weight based dosing lumasiran (n=18) • <10 kg: 6.0 mg/kg every month for 3 months followed by 3.0 mg/kg every month • ≥10 kg to <20 kg: 6.0 mg/kg every month for 3 months followed by 6.0 mg/kg every 3 months • ≥20 kg: 3.0 mg/kg every month for 3 month followed by 3.0 mg/kg every 3 months	Weight based dosing lumasiran (n=21) • <10 kg: 6.0 mg/kg every month for 3 months followed by 3.0 mg/kg every month • ≥10 kg to <20 kg: 6.0 mg/kg every month for 3 months followed by 6.0 mg/kg every 3 months • ≥20 kg: 3.0 mg/kg every month for 3 month followed by 3.0 mg/kg every 3 months
Follow-Up	60 months (results at 6 months are reported)	60 months (results at 6 months are reported)

AGXT: alanine glyoxylate aminotransferase; DBRCT: double-blind randomized controlled trial; eGFR: estimated glomerular filtration rate; GFR: glomerular filtration rate; PH1: primary hyperoxaluria type 1; UOx:Cr: urinary oxalate creatinine ratio.

[a] Treatment arms were stratified at randomization based upon mean 24-hr urinary oxalate from the first 2 valid samples collected during screening (≤1.70 mmol/24 hr/1.73 m^2 vs. >1.70 mmol/24 hr/1.73 m^2).

Table 8. Summary of Single Arm Trial Results

Study	**% Reduction in Spot Urinary Oxalate: Creatinine Ratio**	
ILLUMINATE-B	N=18	
6-month results (33, 34)	71% (95% CI, 65% to 77%)	
12-month results (35)	72% (95% CI not reported)	
ILLUMINATE-C (33, 37)	**Plasma Oxalate Levels (µmol/L) at Baseline**	**Plasma Oxalate Levels (µmol/L) at 6 Months**

Cohort A[a]	65 (95% CI, 21 to 108)	33 (95% CI, 10 to 56)
LS mean difference	33% (95% CI, 82% to 15%)	
Cohort B[b]	108 (95% CI, 92 to 125)	62 (95% CI, 51 to 72)
LS mean difference	42% (95% CI, 51% to 34%)	

CI: confidence interval; LS: least squares.

[a] For Cohort A, the baseline is defined as the mean of all plasma oxalate samples collected prior to the first dose of lumasiran.

[b] For Cohort B, the baseline is defined as the last 4 pre-dialysis plasma oxalate samples collected prior to the first dose of lumasiran. In Cohort B, only pre-dialysis samples were utilized.

The purpose of limitations tables is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of the evidence supporting the position statement. Identified limitations in study relevance and study design/conduct are summarized in Tables 9 and 10. The major limitation is the lack of data on clinical outcomes, such as nephrolithiasis and related complications and loss of kidney function, and individual reported outcomes such as quality of life. Given the rarity of the disease and its slow progression, it would be challenging to detect treatment effects on clinical events in a clinical trial. Use of urinary oxalate as a surrogate for clinical outcomes in the pivotal trials can 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. Epidemiologic data demonstrates an association between urinary oxalate and loss of kidney function, particularly in individuals with high levels of urinary oxalate. (8, 24, 38) Further observational data from individuals treated with pyridoxine or a liver transplant show associations between reductions in urinary oxalate and preservation of kidney function. (28, 39, 40) Further, the consistency and size of treatment effect (more than half of individuals receiving lumasiran achieved normal urinary oxalate levels at 6 months of treatment in ILLUMINATE-A) in clinical trials are indicative of the potential for a clinical benefit over the long term.

Table 9. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
ILLUMINATE-A (30, 31, 33)				2. Physiologic measures (oxalate levels), not validated surrogates	
ILLUMINATE-B (33, 34)				2. Physiologic measures (oxalate levels), not validated surrogates	
ILLUMINATE-C (33, 37)				2. Physiologic measures	1. Not sufficient

				(oxalate levels), not validated surrogates	duration for benefits 2. Not sufficient duration for harms

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.

[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported.

[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 10. Study Design and Conduct Limitations

Study	ILLUMINATE-A (30, 31, 33)	ILLUMINATE-A (33, 34)	ILLUMINATE-A (33, 37)
Allocation[a]		1. Participants not randomly allocated 2. Allocation not concealed 3. Allocation concealment unclear	1. Participants not randomly allocated 2. Allocation not concealed 3. Allocation concealment unclear
Blinding[b]		1. Not blinded to treatment assignment	1. Not blinded to treatment assignment
Selective Reporting[c]			
Data Completeness[d]			
Power[e]			
Statistical[f]			

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Section Summary: Primary Hyperoxaluria Type 1

The evidence for lumasiran for individuals with primary hyperoxaluria consists of 1 phase 3 RCT (ILLUMINATE-A) in individuals 6 years and older and 2 single arm prospective studies (ILLUMINATE-B and ILLUMINATE-C). In ILLUMINATE-A and ILLUMINATE-B, individuals with preserved renal function were enrolled (eGFR >30 mL/min/1.73 m^2) 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 randomized 2:1 to lumasiran 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 and placebo groups, respectively, with a between-group mean difference of 53% (95% CI, 45% to 62%; p<.0001). A similar effect was seen in individuals with high baseline urinary oxalate values, and approximately half of individuals receiving lumasiran achieved normal urinary oxalate values by month 6. In ILLUMINATE-B, 18 individuals were treated with lumasiran. The primary endpoint was the percent change in spot urinary oxalate-to-creatinine ratio from baseline to month 6. Lumasiran demonstrated a percent reduction in spot urinary oxalate-to creatinine ratio from baseline of -71% (95% CI, -77% to -65%). 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. The primary endpoint was the percent change in plasma oxalate levels from baseline to month 6. Lumasiran 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 consistency and size of treatment effect across 3 trials are indicative of the potential for a clinical benefit over the long term. The most common treatment-related adverse events were injection site reactions, which were mild and transient and included erythema, pain, pruritus, or swelling at the injection site.

Summary of Evidence

For individuals with primary hyperoxaluria type 1, evidence includes 1 phase 3 randomized controlled trial (RCT) (ILLUMINATE-A) in individuals 6 years and older and 2 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 m^2) 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 randomized 2:1 to lumasiran 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 and placebo groups, respectively, with a between-group mean difference of 53% (95% confidence interval [CI], 45% to 62%; p<.0001). A similar effect was seen in individuals with high baseline urinary oxalate values, and approximately half of individuals who received lumasiran achieved normal urinary oxalate values by month 6. In ILLUMINATE-B, 18 individuals were treated with lumasiran. The primary endpoint was the percent change in spot urinary oxalate-to-creatinine ratio from baseline to month 6. Lumasiran 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. The primary endpoint was the percent change in plasma oxalate levels from baseline to month 6. Lumasiran 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. 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 3 trials are indicative of the potential for a clinical benefit over the long term. Lumasiran was generally well-tolerated in all 3 studies. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Practice Guidelines and Position Statements

National Institute for Health and Care Excellence (NICE)

On April 19, 2023, the NICE issued technology appraisal guidance on lumasiran for treating primary hyperoxaluria type 1. Lumasiran is recommended as an option for treating primary hyperoxaluria type 1 in people of all ages and the conditions laid out in the managed access agreement were followed. (41)

European Hyperoxaluria Consortium

Clinical practice recommendations for primary hyperoxaluria were published by a workgroup comprising members from OxalEurope (a network of European scientists and physicians who specialize in primary hyperoxaluria) and the metabolic workgroup of the European Rare Kidney Disease Reference Network. (42) The group formulated and graded statements relating to the management of primary hyperoxaluria on the basis of existing evidence. Recommendations are summarized in Table 11 and 12.

Table 11. Recommendations for Management of Patients With or Suspected to Have Primary Hyperoxaluria

Statement Number	Statement	Grading
41	We suggest that the benefit of RNAi therapy should always be weighed against its potential long-term risks in patients with PH1	X (strong recommendation)
42	We recommend treatment with RNAi therapy under the following conditions: 1. PH1 is genetically established in patients of any age AND 2. Patients are biochemically unresponsive to pyridoxine OR have a mutation consistent with pyridoxine unresponsiveness AND 3. Urine oxalate excretion is >1.5 times the upper reference limit AND 4. Patients demonstrate a clinical phenotype of PH1, characterized by active stone disease AND/OR nephrocalcinosis AND/OR renal impairment	B (strong recommendation)
43	We recommend treatment with RNAi therapy under the following conditions: 1. PH1 is genetically established in patients of any age with a mutation consistent with pyridoxine unresponsiveness and eGFR <30 mL/min/1.73 m^2 OR 2. Patients are suspected to have PH1 based on findings of elevated plasma oxalate and plasma glycolate levels with stage 5D CKD, but are awaiting genetic confirmation	B (strong recommendation)
44	We suggest treatment with RNAi therapy under the following conditions: 1. PH1 is genetically established in patients of any age AND 2. Partial pyridoxine responsiveness has been biochemically established up to urinary oxalate remaining >1.5 times the upper reference limit of normal AND 3. Patients demonstrate a clinical phenotype of PH1, characterized by active stone disease AND/OR nephrocalcinosis AND/OR renal impairment	B (moderate recommendation)
45	We suggest treatment with RNAi therapy under the following conditions: 1. PH1 is genetically established AND 2. Pyridoxine unresponsiveness is biochemically established OR patients have a mutation consistent with pyridoxine unresponsiveness AND 3. Urine oxalate excretion is >1.5 times the upper reference limit AND 4. Patients have no ongoing clinical disease	C (weak recommendation)

46	If RNAi therapy is not available, we suggest testing other medications that are currently under investigation (for example, stiripentol).	D (weak recommendation)
47	We do not recommend administering RNAi therapies to patients with PH who are pyridoxine-responsive and have normalization of urinary oxalate excretion	C (moderate recommendation)
48	We suggest that continuation of RNAi and other specific new therapies should be based on annual re-evaluation of biochemical and clinical efficacy	X (strong recommendation)

CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; PH: primary hyperoxaluria; RNAi: RNA interference.
Grading of recommendations was based on the American Academy of Pediatrics. (43)

Table 12. Recommended Management and Monitoring of Patients with Primary Hyperoxaluria on RNA Interference Therapy

Group[a]	**Start**	**Cessation criteria after 6 months of therapy**	**6-monthly analyses for 5 years and cessation criteria**
Group A (VB6−, eGFR >30 mL/min/1.73 m^2)	We recommend starting therapy	Uox >1.5 UL or less than a 30% reduction in Uox[b] or a deterioration of the clinical condition or evidence of a SAE[c]	SAE or deterioration in clinical condition related to RNAi therapy[c]
Group B (VB6+, eGFR >30 mL/min/1.73 m^2)	We suggest starting therapy, based on patient characteristics (not fully VB6 responsive, severe disease)	Uox >1.5 UL or <30% reduction Uoxb; or deterioration of clinical condition or evidence of a SAE[c]	SAE or deterioration in clinical condition related to RNAi therapy[c]
Group C (VB6−, eGFR <30 mL/min/1.73 m^2)	We recommend starting therapy	Decrease in Pox <20% from baseline or deterioration of clinical condition or evidence of a SAE[c]	Stop if decrease in Pox is <20%[d,e] from baseline: discuss options if the decrease in Pox is <30% from baseline[d,e]. Also stop treatment if there is evidence of an SAE OR deterioration in clinical condition related to RNAi therapy[c].

Group D (VB6+, eGFR <30 mL/min/1.73 m^2)	We suggest starting therapy based on patient characteristics (not fully VB6 sensitive, rapidly deteriorating kidney function in case of eGFR 20 to 30 mL/min/1.73 m^2)	Decrease in Pox <20% from baseline[d,f] or deterioration of clinical condition as assessed by a committee; or evidence of a SAE[c]	Stop therapy if the decrease in Pox is <20% (43, 44); discuss options if the decrease in Pox is <30%[d,f]. Also stop treatment if there is evidence of a SAE or deterioration in clinical condition related to RNAi therapy[c].
Group E (no genetic diagnosis, eGFR <30 mL/min/1.73 m^2)	We recommend starting therapy with monthly monitoring of Pox levels	Decrease Pox <20% of baseline or deterioration of clinical condition as assessed by a committee; or evidence of a SAE[c]. Also stop therapy if the suspected PH diagnosis is not confirmed genetically.	Not applicable
Group F (no ongoing clinical disease)	We suggest starting therapy in adults and recommend starting therapy in children	Uox >1.5 UL or <30% reduction Uox of baseline; or deterioration of clinical condition as assessed by a committee; or evidence of a SAE[c]	SAE or deterioration in clinical condition related to RNAi therapy[c]
Group G (full VB6+)	We do not recommend starting therapy	Not applicable	Not applicable

CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate (units: ml/min/1.73 m^2); PH: primary hyperoxaluria; Pox: plasma oxalate; RNAi: RNA interference; SAE: severe adverse event; UL: upper level reference value; Uox: urinary oxalate excretion; VB6: vitamin B6 (also known as pyridoxine).

[a] Groups are defined as follows:

Group A patients are defined as patients of any age with (genetically established) PH1; and biochemically established non-responsiveness to pyridoxine therapy or with mutation consistent with pyridoxine unresponsiveness; and urinary oxalate excretion >1.5 times the upper reference limit (based on at least 2 samples); and a clinical phenotype of PH1, characterized by active stone disease and/or nephrocalcinosis and/or renal impairment (but with eGFR >30 mL/min/1.73 m^2).

Group B patients are defined as patients of any age with genetically established PH1; and biochemically established partial responsiveness to pyridoxine therapy (that is, urinary oxalate level 1.0 to 1.5 times the upper reference limit of normal while on pyridoxine treatment); and a clinical phenotype of PH1, characterized by active stone disease and/or nephrocalcinosis and/or renal impairment (but with eGFR >30 mL/min/1.73 m^2).
Group C patients are defined as patients of any age with genetically established PH1; and a mutation consistent with pyridoxine unresponsiveness and eGFR <30 mL/min/1.73 m^2.
Group D patients are defined as patients of any age with genetically established PH1; and a mutation consistent with pyridoxine responsiveness and eGFR <30 mL/min/1.73 m^2.
Group E patients are defined as patients with clinically suspected PH1 with stage 5 CKD based on elevated plasma oxalate levels (>80 µmol/L in those with stage 5D CKD; >10 µmol/L in patients not on dialysis) and plasma glycolate levels, but awaiting genetic confirmation.
Group F patients are defined as patients of any age with genetically established PH1; and biochemically established non-responsiveness to pyridoxine therapy or with a mutation consistent with pyridoxine non-responsiveness; and urinary oxalate excretion >1.5 times the upper reference limit (based on at least 2 samples); and no ongoing clinical disease.
Group G patients are defined as patients of any age with genetically established PH1; and biochemically established full pyridoxine responsiveness (urinary oxalate less than the upper reference limit of normal while on pyridoxine treatment); and a clinical phenotype of PH1, characterized by active stone disease and/or nephrocalcinosis and/or renal impairment (but eGFR >30 mL/min/1.73 m^2).
[b] Urinary oxalate excretion per 24 h or urinary oxalate excretion-to-creatinine ratio.
[c] Deterioration should be evaluated in the context of the individual patient; recurrent attacks due to pre-existing stones are not a criterion for failure. Only consider serious adverse events that are potentially related to lumasiran.
[d] Evaluated in patients on a stable dialysis regimen or in pre-dialysis patients with a stable eGFR; otherwise discussion.
[e] In patients who do not undergo kidney transplantation during therapy course. In patients who do undergo kidney transplantation, evaluate the response to RNAi therapy on plasma oxalate levels, taking into account the expected reduction in relation to eGFR and estimation of stored oxalate. High urinary oxalate levels after kidney transplantation may be the result of oxalate release from bone.
[f] In patients who have not undergone kidney transplantation; in patients who do undergo kidney transplantation, consider stopping lumasiran 3 months after kidney transplantation if urinary oxalate levels is normalized; repeat measurement of urinary oxalate levels every month and restart lumasiran if urinary oxalate increases >1 UL.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this policy are listed in Table 13.

Table 13. Summary of Key Trials

NCT Number	Trial Name	Planned Enrollment	Completion Date
NCT04982393[a]	BONAPH1DE, A Prospective Observational Study of Patients With Primary Hyperoxaluria Type 1 (PH1)	200	Sep 2028

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	J0224

*Current Procedural Terminology (CPT®) ©2025 American Medical Association: Chicago, IL.

References

1. Hoppe B, Langman CB. A United States survey on diagnosis, treatment, and outcome of primary hyperoxaluria. Pediatr Nephrol. Oct 2003; 18(10):986-991. PMID 12920626
2. Harambat J, Fargue S, Bacchetta J, et al. Primary hyperoxaluria. Int J Nephrol. 2011; 2011:864580. PMID 21748001
3. Milliner DS. The primary hyperoxalurias: an algorithm for diagnosis. Am J Nephrol. 2005; 25(2):154-160. PMID 15855742
4. Chlebeck PT, Milliner DS, Smith LH. Long-term prognosis in primary hyperoxaluria type II (L-glyceric aciduria). Am J Kidney Dis. Feb 1994; 23(2):255-259. PMID 8311084
5. Rumsby G. Primary hyperoxaluria Type 2. Gene Reviews. Available at <https://www.ncbi.nlm.nih.gov> (accessed October 7, 2025).
6. Cochat P, Koch Nogueira PC, Mahmoud MA, et al. Primary hyperoxaluria in infants: medical, ethical, and economic issues. J Pediatr. Dec 1999; 135(6):746-750. PMID 10586179
7. Harambat J, Fargue S, Acquaviva C, et al. Genotype-phenotype correlation in primary hyperoxaluria type 1: the p.Gly170Arg AGXT mutation is associated with a better outcome. Kidney Int. Mar 2010; 77(5):443-449. PMID 20016466
8. Hopp K, Cogal AG, Bergstralh EJ, et al. Phenotype-Genotype Correlations and Estimated Carrier Frequencies of Primary Hyperoxaluria. J Am Soc Nephrol. Oct 2015; 26(10):2559-2570. PMID 25644115
9. Cochat P, Rumsby G. Primary hyperoxaluria. N Engl J Med. Aug 15 2013; 369(7):649-658. PMID 23944302
10. Cochat P, Deloraine A, Rotily M, et al. Epidemiology of primary hyperoxaluria type 1. Société de Néphrologie and the Société de Néphrologie Pédiatrique. Nephrol Dial Transplant. 1995; 10 Suppl 8:3-7. PMID 8592622
11. Kopp N, Leumann E. Changing pattern of primary hyperoxaluria in Switzerland. Nephrol Dial Transplant. Dec 1995; 10(12):2224-2227. PMID 8808215

12. van Woerden CS, Groothoff JW, Wanders RJ, et al. Primary hyperoxaluria type 1 in The Netherlands: prevalence and outcome. Nephrol Dial Transplant. Feb 2003; 18(2):273-279. PMID 12543880
13. Hoppe B. An update on primary hyperoxaluria. Nat Rev Nephrol. Jun 12 2012; 8(8):467-475. PMID 22688746
14. Bhasin B, Ürekli HM, Atta MG. Primary and secondary hyperoxaluria: Understanding the enigma. World J Nephrol. May 06 2015; 4(2):235-244. PMID 25949937
15. Hoppe B, Beck BB, Milliner DS. The primary hyperoxalurias. Kidney Int. Jun 2009; 75(12):1264-1271. PMID 19225556
16. Rumsby G, Williams E, Coulter-Mackie M. Evaluation of mutation screening as a first line test for the diagnosis of the primary hyperoxalurias. Kidney Int. Sep 2004; 66(3):959-963. PMID 15327387
17. Sikora P, von Unruh GE, Beck B, et al. [13C2]oxalate absorption in children with idiopathic calcium oxalate urolithiasis or primary hyperoxaluria. Kidney Int. May 2008; 73(10):1181-1186. PMID 18337715
18. Hoppe B, Graf D, Offner G, et al. Oxalate elimination via hemodialysis or peritoneal dialysis in children with chronic renal failure. Pediatr Nephrol. Aug 1996; 10(4):488-492. PMID 8865249
19. Marangella M, Petrarulo M, Cosseddu D, et al. Oxalate balance studies in patients on hemodialysis for type I primary hyperoxaluria. Am J Kidney Dis. Jun 1992; 19(6):546-553. PMID 1595703
20. Hoppe B, Kemper MJ, Bökenkamp A, et al. Plasma calcium oxalate supersaturation in children with primary hyperoxaluria and end-stage renal failure. Kidney Int. Jul 1999; 56(1):268-274. PMID 10411702
21. Bergstralh EJ, Monico CG, Lieske JC, et al. Transplantation outcomes in primary hyperoxaluria. Am J Transplant. Nov 2010; 10(11):2493-2501. PMID 20849551
22. Dick PT, Shuckett BM, Tang B, et al. Observer reliability in grading nephrocalcinosis on ultrasound examinations in children. Pediatr Radiol. Jan 1999; 29(1):68-72. PMID 9880623
23. Milliner DS, McGregor TL, Thompson A, et al. End Points for Clinical Trials in Primary Hyperoxaluria. Clin J Am Soc Nephrol. Jul 01 2020; 15(7):1056-1065. PMID 32165440
24. Zhao F, Bergstralh EJ, Mehta RA, et al. Predictors of Incident ESRD among Patients with Primary Hyperoxaluria Presenting Prior to Kidney Failure. Clin J Am Soc Nephrol. Jan 07 2016; 11(1):119-126. PMID 26656319
25. Cochat P, Hulton SA, Acquaviva C, et al. Primary hyperoxaluria Type 1: indications for screening and guidance for diagnosis and treatment. Nephrol Dial Transplant. May 2012; 27(5):1729-1736. PMID 22547750
26. Hoppe B, Kemper MJ, Bökenkamp A, et al. Plasma calcium-oxalate saturation in children with renal insufficiency and in children with primary hyperoxaluria. Kidney Int. Sep 1998; 54(3):921-925. PMID 9734617
27. Marangella M, Petrarulo M, Vitale C, et al. Serum calcium oxalate saturation in patients on maintenance haemodialysis for primary hyperoxaluria or oxalosis-unrelated renal diseases. Clin Sci (Lond). Oct 1991; 81(4):483-490. PMID 1657494

28. Galanti M, Contreras A. Excellent renal function and reversal of nephrocalcinosis 8 years after isolated liver transplantation in an infant with primary hyperoxaluria type 1. Pediatr Nephrol. Nov 2010; 25(11):2359-2362. PMID 20628764
29. Frishberg Y, Deschênes G, Groothoff JW, et al. Phase 1/2 Study of Lumasiran for Treatment of Primary Hyperoxaluria Type 1: A Placebo-Controlled Randomized Clinical Trial. Clin J Am Soc Nephrol. Jul 2021; 16(7):1025-1036. PMID 33985991
30. Garrelfs SF, Frishberg Y, Hulton SA, et al. Lumasiran, an RNAi Therapeutic for Primary Hyperoxaluria Type 1. N Engl J Med. Apr 01 2021; 384(13):1216-1226. PMID 33789010
31. Center for Drug Evaluation and Research. Application Number: 214103Orig1s000 Integrated Review for NDA 214103 Oxlumo (lumasiran). Available at <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm > (accessed on October 7, 2025).
32. Saland JM, Lieske JC, Groothoff JW, et al. Efficacy and Safety of Lumasiran in Patients With Primary Hyperoxaluria Type 1: Results from a Phase III Clinical Trial. Kidney Int Rep. Jul 2024; 9(7):2037-2046. PMID 39081738
33. Prescribing Label: Oxlumo (lumasiran) injection, for subcutaneous use. Available at <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm> (accessed on October 27, 2025).
34. Sas DJ, Magen D, Hayes W, et al. Phase 3 trial of lumasiran for primary hyperoxaluria type 1: A new RNAi therapeutic in infants and young children. Genet Med. Mar 2022; 24(3):654-662. PMID 34906487
35. Hayes W, Sas DJ, Magen D, et al. Efficacy and safety of lumasiran for infants and young children with primary hyperoxaluria type 1: 12-month analysis of the phase 3 ILLUMINATE-B trial. Pediatr Nephrol. Apr 2023; 38(4):1075-1086. PMID 35913563
36. 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. PMID 39355649
37. Michael M, Groothoff JW, Shasha-Lavsky H, et al. Lumasiran for Advanced Primary Hyperoxaluria Type 1: Phase 3 ILLUMINATE-C Trial. Am J Kidney Dis. Feb 2023; 81(2):145-155.e1. PMID 35843439
38. Milliner DS, Harris PC, Cogal AG, et al. Primary Hyperoxaluria Type 1. 2002 Jun 19 [Updated 2017 Nov 30]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021. Available at <https://www.ncbi.nlm.nih.gov> (accessed October 7, 2025).
39. Khorsandi SE, Samyn M, Hassan A, et al. An institutional experience of pre-emptive liver transplantation for pediatric primary hyperoxaluria type 1. Pediatr Transplant. Jun 2016; 20(4):523-529. PMID 27061278
40. Nolkemper D, Kemper MJ, Burdelski M, et al. Long-term results of pre-emptive liver transplantation in primary hyperoxaluria type 1. Pediatr Transplant. Aug 2000; 4(3):177-181. PMID 10933316
41. Lumasiran for treating primary hyperoxaluria type 1. Highly specialized technologies guidance. Reference number: HST25 Published: 19 April 2023. Available at <https://www.nice.org.uk> (accessed on April 8, 2026).

42. 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. Mar 2023; 19(3):194-211. PMID 36604599
43. American Academy of Pediatrics Steering Committee on Quality Improvement and Management. Classifying recommendations for clinical practice guidelines. Pediatrics. Sep 2004; 114(3):874-877. PMID 15342869
44. Garrelfs SF, Rumsby G, Peters-Sengers H, et al. Patients with primary hyperoxaluria type 2 have significant morbidity and require careful follow-up. Kidney Int. Dec 2019; 96(6):1389-1399. PMID 31685312

Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
09/01/2026	Document updated. The following change was made to Coverage: Added "clinical signs and symptoms of PH1" to the second bullet that currently states "Presence of ONE of the following". Added references 23, 32 and 36.
01/01/2026	Document updated. The following change was made to Coverage: Removed statement on vitamin B6 treatment as well as statement on concurrent use. Added references 1-30 and 32-41.
09/15/2024	Document updated with literature review. The following changes were made to Coverage: 1) Revised conditional coverage to remove "and potassium citrate or sodium citrate" from "Documented failure, inadequate response, contraindication, or intolerance to treatment with vitamin B6 (pyridoxine);" and 2) Removed "history of kidney transplantation or estimated glomerular filtration rate (eGFR) of less than 30 mL/min/1.73m^2." References updated.
05/15/2024	Document updated with literature review. The following changes were made to Coverage: 1) Updated conditional coverage adding: "Documented failure, inadequate response, contraindication or intolerance to treatment with vitamin B6 (pyridoxine) AND potassium citrate or sodium citrate; AND Will NOT use lumasiran concurrently with other biologics used to treat primary hyperoxaluria (e.g., nedosiran); AND"; and 2) Updated urinary

	oxalate level from “greater than 1 mmol/1.73 m2 per day [90 mg/1.73 m2 per day]” to “≥ 0.7 mmol/24 hr/1.73 m^2**”.** References updated.
10/15/2022	Reviewed. No changes.
08/01/2021	New medical document. Lumasiran (Oxlumo™) may be considered medically necessary for the diagnosis of primary hyperoxaluria type 1 (PH1) when conditional criteria are met.