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CADTH Reimbursement Recommendation

Lumasiran (Oxlumo)

Indication: For the treatment of primary hyperoxaluria type 1 to lower urinary oxalate levels in pediatric and adult patients

Sponsor: Alnylam Netherlands B.V.

Recommendation: Reimburse with conditions

CADTH

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Oxlumo?

CADTH recommends that Oxlumo be reimbursed by public drug plans for the treatment of primary hyperoxaluria type 1 (PH1) to lower urinary oxalate levels in pediatric and adult patients if certain conditions are met.

Which Patients Are Eligible for Coverage?

Oxlumo should only be covered to treat those with a genetically confirmed diagnosis of PH1 and whose urine oxalate excretion is not normalized with standard of care therapy (including 3 to 6 months of vitamin B6).

What Are the Conditions for Reimbursement?

Oxlumo should only be reimbursed if its cost is reduced and it is initially prescribed by a nephrologist or metabolic diseases specialist experienced in the diagnosis and management of PH1.

Why Did CADTH Make This Recommendation?

- One clinical trial demonstrated that Oxlumo reduced 24-hour urinary oxalate levels in patients 6 years or older compared to placebo. Two clinical trials provided evidence of Oxlumo lowering urinary and plasma oxalate levels for patients who were aged younger than 6 years and for those with kidney disease with or without hemodialysis.
- Oxlumo may meet some of the needs identified by patients, such as reducing oxalate formation, but evidence was lacking to suggest that Oxlumo prevents kidney stones or end-stage kidney disease (ESKD), improves health-related quality of life (HRQoL), or delays the need for organ transplant.
- Based on CADTH's assessment of the evidence, Oxlumo does not represent good value to the health care system at the public list price; a price reduction is required.
- Based on public list prices, Oxlumo is estimated to cost the public drug plans approximately $122 million over the next 3 years. However, the actual budget impact is uncertain as the total number of patients with PH1 who are eligible for funding of Oxlumo is unknown.

Additional Information

What Is PH1?

PH1 is caused by a genetic error that allows oxalate to build up in the body and form crystals, such as kidney stones, that are difficult for the kidneys to remove from the body. The accumulating oxalate crystals cause permanent damage to tissues, specifically the kidneys, leading to loss of function. Though prevalence in Canada is unknown, it is between 1 and 3 per million people in Europe.

Unmet Needs in PH1

Patients with PH1 need effective treatments that prevent further kidney damage, decrease oxalate accumulation throughout the body, and prevent the need for dialysis or organ transplant.

How Much Does Oxlumo Cost?

Treatment with Oxlumo is expected to cost approximately $581,132 for pediatric patients and $1,743,495 for adults in the first year, and $387,421 for pediatric patients and $1,162,263 for adults in subsequent years.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that lumasiran be reimbursed for the treatment of PH1 to lower urinary oxalate levels in pediatric and adult patients only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One multicentre, double-blind (DB), phase III, randomized controlled trial (RCT) (ILLUMINATE-A; N = 39) that enrolled patients who had documented or confirmed PH1 who were 6 years or older, had a mean 24-hour urinary oxalate excretion of at least 0.70 mmol/24 hour/1.73 m^2, and were on a stable dose of vitamin B6 demonstrated that, compared to placebo, 6 months of lumasiran was associated with a statistically significant reduction in 24-hour urinary oxalate levels, where the between-group difference from baseline to the average of months 3 to 6 was −53.55 mmol/24 hour/1.73 m^2 (95% confidence interval [CI], −62.31 to −44.78 mmol/24 hour/1.73 m^2). In addition, compared to placebo, lumasiran was associated with a statistically significant reduction in percent and absolute changes in plasma oxalate levels compared to the average in months 3 to 6. Moreover, 84% (95% CI, 64% to 95%) of patients in the lumasiran group had a 24-hour urine oxalate measure at month 6 that was at or less than 1.5 times the upper limit of normal [ULN] compared to no patients in the placebo group with a between-group difference in proportions of 0.84 (95% CI, 0.55 to 0.94; $P < 0.001$). Also, results from 2 multicentre, single-arm, phase III trials that enrolled patients with PH1 who were on a stable dose of vitamin B6 and were younger than 6 years with a urinary oxalate:creatinine ratio greater than the ULN based on age (ILLUMINATE-B; N = 18) or were any age with an estimated glomerular filtration rate (eGFR) of 45 mL/min/1.73 m^2 or lower with or without stable hemodialysis (ILLUMINATE-C; N = 21) were generally consistent with those observed in the ILLUMINATE-A trial for the outcomes of change from baseline in the 24-hour urine oxalate and plasma oxalate measures.

Patients identified a need for treatment options that effectively maintain kidney function; decrease the likelihood of kidney stones, oxalosis, and the need for renal dialysis and kidney and/or liver transplant; and improve the physical challenges and emotional burden of managing PH1. CDEC concluded that that the evidence for lumasiran appears to address some of the needs identified by patients; however, no definitive conclusions could be made regarding the effects of lumasiran on prevention of kidney stones, prevention of progression to ESKD, improvement of HRQoL, or preventing or delaying the need for organ transplant.

Using the sponsor-submitted price for lumasiran and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio for lumasiran was $2,165,926 per quality-adjusted life-year (QALY) gained compared with established clinical management. At this incremental cost-effectiveness ratio, lumasiran is not cost-effective at a $50,000 per QALY willingness-to-pay threshold for patients with PH1; a price reduction is required for lumasiran to be considered cost-effective at a $50,000 per QALY threshold.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Patients must have a genetically confirmed diagnosis of PH1.	Patients enrolled in the ILLUMINATE trials must have had documented or confirmed diagnosis of PH1 by genetic testing.	—
2. Patients in whom urinary oxalate can be measured must be unable to normalize urine oxalate excretion while staying compliant with standard of care therapy, including vitamin B6 for a duration of 3 to 6 months.	This condition will help select patients who are in need of treatment such as lumasiran to normalize urine oxalate excretion despite receiving standard of care therapy. The clinical experts noted to CDEC that vitamin B6 therapy may be able to lower oxalate levels in a small subset of patients; however, not all patients achieve normalization of oxalate levels. Patients enrolled in the ILLUMINATE-A trial who were receiving therapeutic vitamin B6 were on a stable regimen for at least 90 days before screening and maintained the regimen for at least 6 months during the trial. All had increased urine oxalate excretion at the time of enrolment.	The clinical experts noted to CDEC that urine oxalate measures are not helpful for patients with ESKD or those who are on dialysis and instead should have predialysis plasma oxalate levels measured.
Discontinuation		
3. Treatment with lumasiran must be discontinued if the patient has received a liver transplant with or without a kidney transplant.	The clinical experts noted that transplant of a healthy liver restores enzyme function, making lifelong treatment with lumasiran unnecessary.	—
4. Treatment should be stopped if there is evidence of no response (where response is defined as lowering 24-hour urine oxalate to less than 1.5 times the ULN, for patients in whom urinary oxalate can be measured), or loss of response.	The clinical experts indicated that it would be reasonable to stop treatment if there was no response to lumasiran, or loss of response. The proportion of patients with a 24-hour urine oxalate measure at month 6 that was at or less than 1.5 times the ULN was a secondary end point in the ILLUMINATE-A trial.	The clinical experts noted to CDEC that children who are not continent could be assessed using spot oxalate:creatinine ratios, and that a 30% reduction in the oxalate:creatinine ratio is considered a response to treatment. Measurements of the oxalate:creatinine ratio must be taken at least twice per year to monitor therapeutic response. The clinical experts noted to CDEC that for patients with ESKD or who are on dialysis, a 15% reduction in plasma oxalate levels after 1 year of treatment is considered a response. The clinical experts noted to CDEC that an increase in plasma oxalate levels or an increase in urine oxalate levels to pretreatment baseline after an initial improvement would be considered a loss of response. CDEC noted that there is

Reimbursement condition	Reason	Implementation guidance
		variability in the oxalate measurements from day to day and that test assay, time of day, food, and activity may affect the results of oxalate levels in plasma and urine. CDEC also noted that repeated measurement and interpretation of urine and plasma oxalate levels is part of the expert management of patients with PH1 and their disease's responsiveness to treatment. CDEC noted that patients who progress to dialysis despite treatment could continue treatment unless they meet any of the discontinuation criteria. It was also noted that for patients who progress to dialysis, a baseline plasma level would be required and used to assess treatment response thereafter.
Prescribing		
5. Lumasiran must be initially prescribed by a nephrologist or metabolic diseases specialist with experience in the diagnosis and management of PH1.	Accurate diagnosis and management of patients with PH1 is important to ensure that lumasiran is prescribed to appropriate patients.	—
6. Subsequent renewal of prescriptions following the initial prescription can be through a pediatrician instead of nephrologist or metabolic diseases physician.	Including pediatricians among appropriate prescribers for renewal of lumasiran would help provide equitable access for patients in communities without access to nephrologists or metabolic disease specialists. Pediatricians have the expertise necessary to determine whether renewal is appropriate given the objective outcomes of laboratory tests.	—
Pricing		
7. A reduction in price	The ICER for lumasiran is $2,165,926 per QALY gained when compared with established clinical management. A price reduction of at least 95% would be required for lumasiran to be able to achieve an ICER of $50,000 per QALY compared to established clinical management.	—
Feasibility of adoption		
8. The feasibility of adoption of lumasiran must be addressed.	At the submitted price, the incremental budget impact of lumasiran is expected to be greater than $40 million in year 1. Furthermore, the magnitude of uncertainty in the budget impact must be addressed to ensure	—

Reimbursement condition	Reason	Implementation guidance
	the feasibility of adoption, given the difference between the sponsor's estimate and CADTH's estimate.	

CDEC = CADTH Canadian Drug Expert Committee; ESKD = end-stage kidney disease; ICER = incremental cost-effectiveness ratio; PH1 = primary hyperoxaluria type 1; QALY = quality-adjusted life-year; ULN = upper limit of normal.

Discussion Points

- The sponsor requested a minor reconsideration of the initial draft recommendation to reimburse lumasiran for the treatment of PH1 to lower urinary oxalate levels in pediatric and adult patients. The CDEC committee subpanel discussed each of the issues identified by the sponsor in their request for reconsideration.
- During the reconsideration meetings, the CDEC committee subpanel discussed that in the ILLUMINATE-C study, which evaluated the efficacy and safety of lumasiran in patients with PH1 and advanced kidney disease, including a cohort of patients undergoing hemodialysis, lumasiran resulted in reductions in plasma oxalate levels within 6 months of therapy initiation, where the least squares mean (LSM) percent change from baseline to the average of months 3 to 6 was −33.33% (95% CI, −81.82% to 15.16%) for patients who were not receiving hemodialysis and −42.43% (95% CI, −50.71% to −34.15%) for patients who had begun stable hemodialysis. CDEC recognizes that these were group means but noted that the clinical experts indicated that most patients would show a timely positive response and that assessment at 12 months provided sufficient opportunity to demonstrate responsiveness.
- CDEC discussed that current standard of care treatments for PH1 leave patients with many unmet needs such as challenges with compliance, and treatments being burdensome, not addressing the underlying issue of hepatic oxalate overproduction, and having limited or no impact on the long-term complications of PH1. CDEC also discussed that while liver (or combined liver-kidney) transplant is the only cure for patient with PH1, it is associated with high morbidity and mortality, lifelong immunosuppression, and limited survival of the allograft; in addition, there is limited availability of liver-kidney transplant in Canada for patients with PH1.
- The clinical experts noted to CDEC the importance of preserving kidney function and preventing progression to ESKD in patients with PH1. CDEC discussed that based on the available evidence from the ILLUMINATE trials, it is unclear how lumasiran affects kidney function in the long-term and that there is a need for long-term data, ideally from more patients, to better understand what effect lumasiran has on eGFR and delaying dialysis or kidney failure. CDEC also discussed that the available evidence does not clearly demonstrate that lumasiran will improve long-term morbidity and mortality in patients with PH1.
- CDEC discussed that it is unclear if lumasiran conveys a benefit over placebo in reducing kidney stone events over time. It is also not clear if or how lumasiran impacts HRQoL for patients with PH1.
- CDEC discussed the need for assessing response and continual response to treatment. In the ILLUMINATE-A trial, the ULN was defined as a 24-hour urinary oxalate measurement corrected for body surface area (BSA) of 0.514 mmol/24 hour/1.73 m^2. The clinical experts

noted to CDEC that a full response is defined as normalization of urine and plasma oxalate. It was also noted that patients with systemic oxalosis would want to see an improvement in symptoms like clearance of skin deposits, normal cardiac ejection fraction, and improvement in musculoskeletal and vascular issues.

- CDEC discussed the uncertainty of using surrogate outcomes for measuring treatment efficacy in PH1, which has severe consequences if left untreated and in which early intervention is valuable.
- CDEC discussed that, due to their complex kinetic states, measurements of plasma and urine oxalate levels may not reflect true outcomes for some time after the hepatic overproduction of oxalate is being reduced with lumasiran. It was noted that plasma levels may not change during early treatment with lumasiran as the oxalate stored in tissues is remobilizing and replacing that which is lost through urine or dialysis; therefore, the potential magnitude of benefit of lumasiran may not be immediately apparent based on measuring only plasma oxalate. The clinical experts noted to CDEC that patients with substantial systemic oxalate burden who receive liver transplant or who are receiving lumasiran may require years to experience normalized urinary excretion as the body is slowly clearing stored oxalate.
- CDEC discussed that patients should be treated with lumasiran before and after kidney transplant to lower both plasma and urine oxalate levels.
- CDEC discussed the uncertainty in the economic analysis, specifically that if lumasiran is not 100% effective in preventing ESKD, or if more children are started on therapy before disease manifestation (due to screening), a greater reduction in price is likely required. Furthermore, estimates of the budget impact may be underestimated due to PH1 being underdiagnosed in the adult population, as well as the current absence of routine PH1 screening in neonates in Canada.

Background

PH1 is a rare, autosomal recessive metabolic condition caused by a pathogenic variant of the *AGT* gene. There is considerable heterogeneity with PH1 in the age of onset, severity of disease, residual enzyme activity, and genotype. Oxalate binds to calcium-producing insoluble calcium oxalate salts that are difficult for the body to eliminate. Once kidney function declines to an eGFR of less than 30 mL/min/1.73 m^2 to 45 mL/min/1.73 m^2, the kidneys become unable to excrete excess oxalate. Elevated plasma oxalate levels lead to systemic oxalosis where oxalate builds up in tissues throughout the body. Patients often progress to ESKD, which, combined with complications of systemic oxalosis, results in early death. The incidence of PH1 has been estimated to be between 0.4 and 1 per 100,000 live births in different populations. The prevalence has been estimated to be between 1 and 3 per million in European countries with higher rates among countries with consanguinity. No Canadian data for prevalence or incidence have been identified from the literature. It is suggested that the best form of management is to reduce hepatic oxalate production as this is the main cause of PH1. An estimated 30% of patients have a form of PH1 that is sensitive to high-dose vitamin B6, though while therapeutic doses of vitamin B6 may be able to lower oxalate levels in some patients, not all patients achieve normalization of oxalate levels. Citrate supplementation to inhibit crystal formation and hyperhydration (2 L/m^2 per day to 3 L/m^2 per day) are also used to treat PH1 and preserve kidney function, but both can be burdensome for patients and are associated with compliance issues. Moreover, pediatric patients may

require a gastrostomy tube to ensure adequate hydration throughout the day. Patients may also undergo medical procedures to treat kidney stones. New therapeutics consisting of a small interfering ribonucleic acid, such as lumasiran and nedosiran, have been developed to treat types of primary hyperoxaluria. While hemodialysis can remove oxalate from the blood, oxalate production often exceeds clearance and plasma oxalate levels may only be lowered transiently, with a return to supersaturated levels within a few hours of dialysis treatment. The clinical experts consulted by CADTH stated that current standard of care treatments require lifelong adherence, are noncurative, and only partially alleviate the oxalate burden in patients. Liver-kidney transplant is considered the only cure for PH1 as it corrects *AGT* function and restores kidney function; however, it is associated with high morbidity, mortality, and lifelong immunosuppression.

Lumasiran is a small interfering ribonucleic acid that has been approved by Health Canada for the treatment of PH1 to lower urinary oxalate levels in pediatric and adult patients. It is available as a solution of 94.5 mg lumasiran/0.5 mL for subcutaneous injection with weight-based loading and maintenance dosing. The product monograph recommends a loading dose of 6 mg/kg once monthly for 3 doses and a maintenance dose of 3 mg/kg once monthly for patients weighing less than 10 kg; a loading dose of 6 mg/kg once monthly for 3 doses and a maintenance dose of 6 mg/kg once every 3 months for patients weighing 10 kg to less than 20 kg; and a loading dose of 3 mg/kg once monthly for 3 doses and a maintenance dose of 3 mg/kg once every 3 months for patients weighing 20 kg or more.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 1 RCT and 2 single-arm trials in adults and children with PH1, including patients with an eGFR of 45 mL/min/1.73 m^2 or lower who were either not receiving hemodialysis or had begun stable hemodialysis
- patients' perspectives gathered by 2 patient groups, the Oxalosis and Hyperoxaluria Foundation (OHF) and the Canadian Organization for Rare Disorders (CORD)
- input from public drug plans that participate in the CADTH review process
- input from 2 clinical specialists with expertise in diagnosing and treating patients with PH1
- a review of the pharmacoeconomic model and report submitted by the sponsor
- a review of relevant ethical issues related to PH1 and lumasiran
- information submitted as part of the request for minor reconsideration (described in the following).

Stakeholder Perspectives

Patient Input

Two patient groups (OHF and the Canadian Organization for Rare Disorders) provided input as a joint submission to the CADTH review of lumasiran for the treatment of PH1. The responses

were collected through an online survey and a virtual focus group with caregivers and patients. In total, 43 respondents completed the entire survey, while 16 individuals from the online survey and 2 children from the focus group reported having experience with lumasiran. Patients reported the greatest burden of PH1 being the physical toll (e.g., frequent dialysis, multiple hospitalizations, fractures) and emotional stress (e.g., worry over kidney failure, liver-kidney transplant, no approved treatment). Respondents also highlighted issues with getting appropriate and timely care as well as misdiagnoses. Patients and caregivers described the challenges associated with treatment, such as gastrostomy tube insertion for infants and children, surgery to remove kidney stones, vitamin B6 losing effect over time, noncompliance, and intensive dialysis. Patients who have received lumasiran described experiencing an improvement in PH1 management and quality of life. Survey participants responded that current treatments and dialysis are insufficient and therapies that decrease the likelihood of kidney stones, need for kidney and/or liver transplant, kidney failure, and oxalosis are critical. Patients and their families emphasized the need for access to treatments that improve physical well-being, which would also mitigate stress and anxiety for the entire family. The respondents described how the physical, emotional, and financial challenges associated with PH1 have profound impacts on their quality of life, which are further compounded by a lack of knowledge among clinicians as well as access and affordability issues to treatments.

Clinician Input

Input From the Clinical Experts Consulted by CADTH

The clinical experts consulted by CADTH emphasized the need for a PH1 treatment that effectively lowers hepatic oxalate production, reduces kidney stone formation, and prevents the development of ESKD. The experts stated that current treatments are noncurative and do not lower hepatic oxalate production or total oxalate burden in patients. The clinical experts also noted that there is a small subset of patients whose PH1 is partially or completely vitamin B6 sensitive, but vitamin B6 therapy only partially alleviates oxalate accumulation in these patients. Two therapies, lumasiran and nedosiran, were identified by the clinicians as being possible pharmacotherapies for PH1. The experts expected lumasiran to cause a shift in the current treatment paradigm, becoming the first-line treatment for patients with PH1 and specifically for patients who are insensitive or only partially sensitive to vitamin B6 therapy. The clinicians noted that treatment with lumasiran is expected to be lifelong or until the patient receives a liver transplant; they also stated the importance of continuing current standard of care treatments along with lumasiran. Per the clinical experts, patients with PH1 would typically be identified based on clinical symptoms, laboratory testing of oxalate levels, and a diagnosis confirmed by genetic testing.

The clinical experts stated that patients would be candidates for lumasiran if they have genetically confirmed PH1 and are unable to normalize urine oxalate excretion. The clinicians were uncertain if or when lumasiran would be used for patients who are sensitive to vitamin B6 therapy and are able to normalize urine oxalate excretion, but suggested it may be reasonable to begin treatment if these patients showed signs of disease progression. The experts felt that early intervention and treatment with lumasiran would be reasonable for all patients who still have kidney function and indicated that they would not wait for eGFR to decline as early treatment would help reduce kidney stone formation and slow the progression of kidney function impairment. The clinical experts indicated that patients with little or no urine oxalate excretion who are relying solely on dialysis to remove oxalate from the body are at a very high risk of systemic oxalosis and would benefit from lumasiran. The clinical experts noted that lumasiran may be effective in avoiding the need for liver transplant

in patients with ESKD and that it would be reasonable to treat patients with lumasiran before and after a kidney transplant to lower both plasma and urine oxalate levels.

The clinical experts noted that urine oxalate excretion and plasma oxalate levels are surrogate markers for oxalate production in patients with PH1 and there is no widely accepted method for measuring total body oxalate, which makes it difficult to assess how effective a treatment is. Per the clinical experts, patients in earlier stages of PH1 may be monitored for urine oxalate excretion, plasma oxalate levels, kidney function (eGFR), and nephrocalcinosis via radiological imaging. As patients in later stages of PH1 and on dialysis would not have reliable urine oxalate measures, clinicians would instead measure predialysis plasma oxalate levels every 1 to 3 months. The clinical experts stated that patients who have received a kidney or combined liver-kidney transplant may have plasma oxalate levels measured initially on a daily basis, transitioning to weekly, then monthly as levels stabilize. The clinicians expected that there would be a noticeable improvement after an initial 6-month treatment duration, but this is unlikely to be long enough to see normalization of oxalate levels. The experts suggested that treatment success must take into account disease severity before treatment and that it might be reasonable to treat a patient for at least 12 months (total) before deciding to whether to continue lumasiran. According to the clinical experts, renewal of lumasiran would depend on adequate response to treatment as well as an assessment of potential treatment issues (e.g., adverse events [AEs], antidrug antibodies [ADAs], compliance). The clinical experts stated that patients who have received a liver transplant would not be treated with lumasiran as the new liver has functional enzyme. Other possible reasons for stopping treatment were a lack of treatment response or severe untreatable or intolerable AEs.

The clinical experts agreed that a specialist (e.g., nephrologist or metabolic physician) should monitor patients with PH1 and that lumasiran can be administered by a health care professional in a community setting. One clinical expert suggested the potential for the patient or caregiver to self-administer lumasiran at home given that subcutaneous injections can be routinely performed for other medications, but the other clinical experts did not expect lumasiran to be self-administered.

According to the experts, it is unlikely that treatment would exceed the Health Canada–recommended dose for most patients but a higher dose may be warranted in infants due to their larger liver surface area to BSA ratio or to overcome potential neutralizing ADAs. The latter was based on experience with other drugs and has been suggested in the literature, though there is a lack of clinical evidence to support higher doses of lumasiran at this time. The clinical experts identified the need for additional consideration of patients who have limited access to health care resources (e.g., those living in remote areas, those with no primary care physician or access to specialists, and those lacking health insurance). The clinical experts also indicated that other ethical issues were the burden of knowing there is a treatment for PH1 but not being able to access it, especially given the severity of the disease, inadequacy of current treatments, and overall burden of care on patients and families.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a CADTH recommendation for lumasiran:

- relevant comparators
- considerations for initiation of therapy

- considerations for continuation or renewal of therapy
- considerations for discontinuation of therapy
- considerations for prescribing of therapy
- generalizability of trial populations to the broader populations in the jurisdictions
- care provision issues
- system and economic issues.

The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs, these are presented in Table 2.

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Relevant comparators	
There are no approved pharmacological treatments for PH1. Other treatments for management of PH1 include dietary or over-the-counter measures that may not be covered by drug plans: • oxalate-controlled diet • oral hyperhydration • citrate supplementation • vitamin B6 • dialysis • combined or sequential liver-kidney transplant.	CDEC noted that none of the current treatments prevent the renal complications of PH1, though some patients may have improvement and delay of ESKD with high-dose vitamin B6. Dialysis treats a consequence of the disease and not the metabolic abnormality. CDEC recognizes that liver transplant is a relevant comparator and is considered a cure for PH1, though it requires lifelong immunosuppressive therapy. CDEC also noted that there is limited availability of liver-kidney transplant in Canada for patients with PH1.
Considerations for initiation of therapy	
PH1 is a rare disease with an estimated prevalence of 1 to 3 per million. PH1 is a genetic disorder of oxalate metabolism that leads to manifestations such as recurrent kidney stones, nephrocalcinosis, progressive renal failure that can lead to ESKD, and multiorgan damage due to systemic deposition of toxic oxalate crystals. Diagnosis of PH is determined by genetic testing. Is there potential for newborn screening?	The clinical experts noted to CDEC that they do not expect there will be newborn screening for PH1 at this time and there are limitations with newborn screening that will have to be addressed before it can be implemented. CDEC noted that newborn screening of PH1 would likely help with diagnosis of infants with PH1.
Health Canada has authorized use for pediatric patients who are younger than 18 years of age; however, there is limited data for patients younger than 2 years and weighing less than 10 kg. Would patients with PH1 who are younger than 2 years or who weigh less than 10 kg be treated with lumasiran?	CDEC agreed with the clinical experts that infants with PH1 who are younger than 2 years and weigh less than 10 kg could be treated with lumasiran despite the limited evidence. CDEC also noted that early intervention will have greater benefit. The adherence to existing therapies is difficult to achieve in young children and the renal effects is devastating.
Considerations for continuation or renewal of therapy	
The primary end points in the clinical trials are reduction in urine oxalate excretion corrected for BSA averaged over months 3 to 6 (the ILLUMINATE-A trial), percent reduction from baseline in spot urine oxalate:creatinine ratio averaged over months 3 to 6 (the ILLUMINATE-B trial), and percent change in plasma oxalate levels from baseline to month 6,	CDEC agreed with the clinical experts that the end points used in the ILLUMINATE trials are not perfect surrogates for PH1 complications and it is important to consider the population being assessed and the patient's PH1 disease severity. The clinical experts described the clinical progression many patients experience and how early in PH1, patients will have

Implementation issues	Response
which was measured as predialysis plasma oxalate levels in patients on dialysis (the ILLUMINATE-C trial). How do these outcomes relate to complications associated with PH1, such as recurrent kidney stones, nephrocalcinosis, progressive renal failure, ESKD, and multiorgan damage?	normal kidney function and plasma oxalate, but increased urine oxalate excretion. As the disease progresses, eGFR declines, plasma oxalate levels increase, and urine oxalate levels remain high. Once a patient reaches ESKD and starts hemodialysis, urine oxalate excretion will decline to normal or even below normal. The clinical experts stated that there is no single biomarker that will be useful in all stages of this disease. The experts agreed that early in the disease course, when patients have preserved kidney function, urine oxalate level is a satisfactory marker, but measurement of plasma oxalate levels should be initiated as kidney function falls. The experts noted that urine oxalate measurement is not helpful for patients with ESKD or who are on dialysis and that these patients should have predialysis plasma oxalate levels measured instead. The experts suggested that plasma oxalate levels may be a better assessment for systemic outcomes, especially in patients with ESKD, as it is readily measurable and likely predicts clinical outcomes; however, they noted that there is currently a lack of data to support this theory.
The provincial lab (in 1 jurisdiction) confirmed that it can do urine (24 hour) oxalate tests, though it was suggested this is not very practical for patients. The studies used an average over 3 to 6 months. How would this be done in a real-world setting and how would it translate to demonstration of efficacy of drug treatment?	The clinical experts noted that measurement of 24-hour urine oxalate excretion is routinely done for continent patients, though children who are not continent can be assessed using spot oxalate:creatinine ratios, which is considered an imperfect substitute. The clinicians would look for a progressive lowering of urine oxalate on timed or spot urine, while accounting for age-specific changes, and suggested measurements be taken at least twice per year to monitor therapeutic response.
Random urine oxalate testing is also an option for measuring the oxalate:creatinine ratio; however, it would be difficult to determine an average over 3 to 6 months, unless testing was performed frequently. Can CDEC and the clinical experts comment on how response should be monitored or reported for patients receiving this therapy?	One clinical expert noted that the urine oxalate:creatinine ratio, while simpler to collect, is less accurate, and that measurement of 24-hour urine oxalate excretion is preferred. Other clinical experts, who treat pediatric patients, stated that spot urine oxalate:creatinine is monitored approximately every 1 to 3 months (more frequently at the beginning of therapy) and at least every 6 months. These experts also noted that the measurements must be compared to normal ranges for oxalate:creatinine ratio based on age.
Considerations for discontinuation of therapy	
The disease appears to be progressive over time, which may make stopping treatment difficult. Can CDEC and the clinical experts define what loss of response or absence of clinical benefit would look like?	The clinical experts noted to CDEC that a loss of response would present as a failure to lower predialysis plasma oxalate levels in a patient on dialysis or a failure to show a progressive reduction in urine oxalate excretion over time in patients with preserved kidney function. One expert explained that the latter response could take an extended time if there was a high tissue oxalate burden that was being slowly released. Furthermore, the expert would expect normalization of elevated plasma oxalate levels in patients with normal kidney function. Lastly, the experts stated that an increase of plasma oxalate or increase in urine oxalate after an initial improvement would also be a loss of response. If a patient

Implementation issues	Response
	appeared to show a lack of response, the clinical experts stated that it would be important to check if the patient was receiving treatment (or if they had missed any doses), had developed neutralizing ADAs, was taking vitamin C (which increases oxalate production), or if eGFR has declined, which would likely result in a rise in plasma oxalate. As there are many factors that can influence plasma oxalate levels, the experts emphasized that a rise in plasma oxalate alone would not be sufficient to indicate a lack of treatment response and other reasons would need to be investigated. The clinical experts also stated that it may be reasonable to stop treatment with lumasiran if there was documented failure to respond, serious untreatable or intolerable side effects, or the patient received a liver transplant. CDEC noted that lumasiran is a lifelong treatment, and that treatment with lumasiran should be discontinued in patients who achieve no response (where response is defined as lowering 24-hour urine oxalate measure to less than 1.5 times the ULN), or in patients whose disease does not maintain response.
Considerations for prescribing of therapy	
For all patients, the first 3 doses are administered monthly. The maintenance regimen should start 1 month after the last loading dose. After the first 3 doses, the dosing regimen is different for patients weighing less than 10 kg and those weighing more than 10 kg: • For patients weighing less than 10 kg, doses are administered monthly. • For patients weighing more than 10 kg, doses are administered quarterly.	The dosing schedule is consistent with that outlined in the Health Canada product monograph as well as that used in the ILLUMINATE trials. CDEC has not reviewed any evidence of the efficacy and safety of lumasiran outside of the recommended dosing schedule.
Lumasiran is administered via subcutaneous injection. The product monograph notes that a health care professional will administer the product. Who would be the main prescribers of this drug (e.g., nephrologists)? Would they also be administering the drug?	CDEC agreed with the clinical experts that nephrologists or genetic or metabolic specialists would both prescribe and supervise the administration of lumasiran. CDEC also noted that pediatricians can renew and supervise the administration of lumasiran for subsequent prescriptions following the initial prescription. One clinician suggested it is possible, but less likely, that a urologist would prescribe or supervise administration of lumasiran. One clinical expert stated that given the limited information regarding adverse effects of lumasiran, the drug should be administered by a health care professional and not self-administered by the patient. Another clinical expert suggested that lumasiran could be administered in a hospital outpatient clinic; an injection facility; or at home by a visiting nurse, the patient, or a caregiver. This clinician further noted that it would be unlikely that the prescriber would do the administration as subcutaneous injections are typically done by registered nurses or by the patient at home. CDEC noted that administration of treatment can be conducted by any health care provider, not specifically the prescriber.

Implementation issues	Response
Generalizability	
Certain relevant populations were not included or only minimally included in the trial.	CDEC recognizes that PH1 is a rare condition and has considered that in its recommendation.
Care provision issues	
Weight should be measured and dose should be calculated before each dose being administered. Dispensing of product may be delayed until a weight and dose are determined for each patient; otherwise, wastage or insufficient dosing may result. Could the clinical expert explain: • more about the prescribing and administration process • other care requirements for providers or informal caregivers • challenges or limitations on access to testing necessary to use drug.	One clinical expert noted to CDEC that if lumasiran were administered at an injection facility (e.g., Innomar) or hospital, the patient's weight would be assessed at the time of the injection and the dose calculated based on their current weight. Alternatively, if administered at home, the patient's weight could be taken on a reliable scale in the home, with dosing based on their current weight. A clinical expert who treats pediatric patients noted that a weight within 1 week for an infant, 2 weeks for a child, and 1 month for an adult would likely be acceptable if done in a doctor's office. One clinician stated that, for adults, weight can be checked every 3 to 6 months to adjust drug dosage. According to the product monograph, dosing is determined based on mg/kg of body weight, which the clinical expert noted is a simple calculation once the weight is obtained. CDEC noted that wastage is more likely to happen due to the vial size rather than changes in body weight.
System and economic issues	
The price of lumasiran is $96,855.33 per single-use vial (94.5 mg/0.5 mL as a single-use vial). The anticipated national budget impact is expected to be $61 million over 3 years. The sponsor states that a significant portion of this budget impact will be offset by cost savings from a reduction in dialysis costs of $5.8 million over 3 years. Savings realized through a reduction in the need for dialysis are not direct savings to drug programs.	This was a comment from the drug programs to inform CDEC's deliberations.
Wastage might be a consideration for patients of certain weights. Dosage is weight based and the product is formulated as a single-use 94.5 mg of lumasiran per 0.5 mL vial. Given that the dosage is weight based and the product is formulated as a single-use 94.5 mg of lumasiran per 0.5 mL vial, do you expect there will be wastage for patients of certain weights?	CDEC agreed with the clinical experts that wastage would be inevitable given the current available formulation and that multiple vial sizes would allow for use of the closest combination of vials to minimize wastage.

ADA = antidrug antibody; BSA = body surface area; CDEC = CADTH Canadian Drug Expert Committee; ESKD = end-stage kidney disease; eGFR = estimated glomerular filtration rate; PH = primary hyperoxaluria; PH1 = primary hyperoxaluria type 1.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

The 3 included studies (ILLUMINATE-A, ILLUMINATE -B, and ILLUMINATE-C) are ongoing phase III trials investigating the efficacy and safety of lumasiran in patients with PH1. All patients received the study drug based on weight-based loading and maintenance dosing schedules that are consistent with the Health Canada product monograph. The 3 trials were structured similarly with a 6-month primary analysis period followed by a 54-month extension period (3-month blinded extension and 51-month open-label extension in ILLUMINATE-A).

ILLUMINATE-A (N = 39) is a placebo-controlled, DB, RCT that included patients who were 6 years and older. Patients were randomized 2:1 to receive lumasiran or placebo. During the 6-month DB period, patients received the study drug (lumasiran 3 mg/kg or matching placebo) as a subcutaneous injection once per month for the first 3 months (loading doses) followed by a single administration of the study drug 1 month later (maintenance dose for the next 3 months). At month 6, patients entered the 3-month blinded treatment extension period where all patients received active treatment (i.e., patients switched from placebo to lumasiran). At month 9, the 51-month open-label extension began, and all patients were on the maintenance dosing schedule. The primary end point was percent change in 24-hour urinary oxalate excretion from baseline to month 6 corrected for BSA. The secondary end points were absolute change in urinary oxalate at month 6, percent change in urinary oxalate:creatinine ratio at month 6, percent and absolute changes in plasma oxalate levels at month 6, proportion of patients with urinary oxalate level near normal (at or below 1.5 times the ULN) and normal (at or below the ULN) at month 6, and change in eGFR at month 6. At baseline, patients had a mean age of 18.1 years (standard deviation [SD] = [redacted] years; median = 14.0 years; range, 6 years to 60 years) and most were male (66.7%) and white (76.9%). Baseline mean 24-hour urine oxalate excretion corrected for BSA was 1.82 mmol/24 hour/1.73 m^2 (SD = 0.62 mmol/24 hour/1.73 m^2).

ILLUMINATE-B (N = 18) is a single-arm trial that included patients who were younger than 6 years. The primary end point was percent change in urinary oxalate excretion from baseline to month 6. The secondary end points were proportion of patients with urinary oxalate near normal and normal, plasma oxalate levels, and eGFR levels. At baseline, patients had a mean age of [redacted] months (SD = [redacted] months; median = 50.1 months; range, 3 months to 72 months) and most were female (55.6%) and white (88.9%). Baseline mean spot urine oxalate:creatinine ratio was 0.63 mmol/mmol (SD = 0.43 mmol/mmol).

ILLUMINATE-C (N = 21) is a single-arm trial that included patients who had an eGFR of 45 mL/min/1.73 m^2 or lower and were either not receiving hemodialysis (cohort A) or had begun stable hemodialysis (cohort B). The primary end point was percent change in plasma oxalate levels from baseline to month 6 (predialysis for cohort B). The secondary end points were plasma oxalate level area under the curve between dialysis sessions (cohort B), urinary oxalate excretion, urinary oxalate:creatinine ratio, pediatric quality of life (PedsQL) and kidney disease quality of life questionnaire (KDQOL) scores, and eGFR. At baseline, patients had a mean age of [redacted] years (SD = [redacted] years; median = 8.0 years; range, 0 years to 59 years) and most were male (57.1%) and white (76.2%). Mean baseline plasma oxalate levels were [redacted] µmol/L (SD = [redacted] µmol/L) for cohort A and [redacted] µmol/L (SD = [redacted] µmol/L) for cohort B. Median baseline

plasma oxalate levels were 57.9 µmol/L (range = 22.7 µmol/L to 134.0 µmol/L) for cohort A and 103.7 µmol/L (range = 56.3 µmol/L to 167.0 µmol/L) for cohort B.

Efficacy Results

Statistical testing was conducted based on a gate-keeping procedure in the ILLUMINATE-A trial and the primary and secondary outcomes (except for eGFR) were controlled for multiplicity.

Kidney Function

During the 6-month DB period of the ILLUMINATE-A study, eGFR declined from study baseline by a mean of 2.57 mL/min/1.73 m^2 (SD = 10.65 mL/min/1.73 m^2) in the lumasiran group and 0.11 mL/min/1.73 m^2 (SD = 6.49 mL/min/1.73 m^2) in the placebo group. Data at month 18 of extended lumasiran treatment showed that eGFR increased from the study baseline by a mean of [redacted] mL/min/1.73 m^2 (SD = [redacted] mL/min/1.73 m^2) in the lumasiran followed by lumasiran treatment group and decreased from study baseline by a mean of [redacted] mL/min/1.73 m^2 (SD = [redacted] mL/min/1.73 m^2) in the placebo followed by lumasiran treatment group.

In the ILLUMINATE-B trial, eGFR declined from the study baseline by a mean of 0.26 mL/min/1.73 m^2 (SD = 15.38 mL/min/1.73 m^2) for all patients during the first 6 months of treatment. By month 12 of treatment with lumasiran, eGFR increased by a mean of [redacted] mL/min/1.73 m^2 (no SD) for 1 patient weighing less than 10 kg and decreased by a mean of [redacted] mL/min/1.73 m^2 (SD = [redacted] mL/min/1.73 m^2) and mean of [redacted] mL/min/1.73 m^2 (SD = [redacted] mL/min/1.73 m^2) in the groups of patients weighing between 10 kg and 20 kg and those weighing more than 20 kg, respectively.

In the ILLUMINATE-C trial, eGFR declined from the study baseline by a mean of [redacted] mL/min/1.73 m^2 (SD = [redacted] mL/min/1.73 m^2) for patients in cohort A during the first 6 months of treatment.

Loss of kidney function over time and prevention of dialysis and/or liver-kidney transplant were not assessed in the trials.

Kidney Stone Events

During the DB period of the ILLUMINATE-A trial, 5 (19.2%) and 2 (15.4%) patients in the lumasiran and placebo groups experienced 13 and 4 kidney stone events, respectively. Some events ([redacted]% for the lumasiran group and [redacted]% for the placebo group) were graded as [redacted] severity and the rest were [redacted]. The rate of events was 0.30 and 0.18 events per 100 person-days for the lumasiran and placebo groups, respectively. The rate of events generally appeared to decrease in the lumasiran followed by lumasiran treatment group from 1.09 events per person-year (95% CI, 0.63 to 1.88 events per person-year) between day 1 and month 6 to [redacted] events per person-year (95% CI, [redacted] to [redacted] events per person-year) between months 18 (placebo to lumasiran) and 24 (lumasiran to lumasiran) of lumasiran treatment. In the placebo followed by lumasiran treatment group, rates appeared to fluctuate over the same period and remained fewer than 1 event per person-year.

In the ILLUMINATE-B trial, [redacted] had [redacted] kidney stone [redacted] each ([redacted] from each weight group) and all events were graded as [redacted]. The rate of events was 0.11 renal stone events per person-year for the whole group.

In the ILLUMINATE-C trial, [redacted] in cohort A had a total of [redacted] kidney stone events and all events were graded as [redacted]. The rate of events was 1.52 renal stone events per person-year for cohort A.

Health-Related Quality Of Life

In the ILLUMINATE-A trial, results from the KDQOL, PedsQL, 5-level EQ-5D 5 Levels, EQ-5D Youth, and visual analogue scale generally showed [redacted] from baseline to month 6 and during extended lumasiran treatment. Data at month 18 showed mean scores [redacted] and were [redacted] the results from the DB period.

HRQoL was not assessed in the ILLUMINATE-B study and results were very limited due to small patient numbers and short treatment duration in the ILLUMINATE-C study.

Urine Oxalate Excretion Corrected for BSA

In the ILLUMINATE-A trial, the LSM percent change from baseline to the average of months 3 to 6 for urine oxalate excretion was −65.39% (95% CI, −71.32% to −59.45%) for the lumasiran group and −11.84% (95% CI, −19.53% to −4.15%) for the placebo group. The treatment difference between groups was −53.55% (95% CI, −62.31% to −44.78%; P < 0.001). For absolute change, the LSM treatment difference between groups was −0.98 mmol/24 hour/1.73 m^2 (95% CI, −1.18 mmol/24 hour/1.73 m^2 to −0.77 mmol/24 hour/1.73 m^2; P < 0.001). For patients who achieved near normalization (at or below 1.5 times the ULN), the difference in proportions was 0.84 (95% CI, 0.55 to 0.94; P < 0.001). For patients who achieved normalization (at or below the ULN), the difference in proportions was 0.52 (95% CI, 0.23 to 0.70; P = 0.0010). Data from extended treatment on lumasiran indicated decreases in 24-hour urine oxalate excretion at month 6, which appeared to be maintained for both the lumasiran followed by lumasiran and placebo followed by lumasiran treatment groups to month 18.

In the ILLUMINATE-B trial, urine oxalate assessments were based on urine oxalate:creatinine ratios and are described in a later section. In cohort A of the ILLUMINATE-C trial, the LSM absolute change from baseline to the average of months 3 to 6 was −0.53 mmol/24 hour/1.73 m^2 (95% CI, −0.89 mmol/24 hour/1.73 m^2 to −0.18 mmol/24 hour/1.73 m^2). The LSM percent change from baseline to the average of months 3 to 6 was −10.56% (95% CI, −31.99% to 10.87%).

Plasma Oxalate

In the ILLUMINATE-A trial , for absolute change, the treatment difference between groups for plasma oxalate level was −8.71 µmol/L (95% CI, −11.45 µmol/L to −5.98 µmol/L; P < 0.001) for the DB period. For percent change, the treatment difference between groups was −39.48% (95% CI, −50.10% to −28.87%; P < 0.001) for the DB period.

In the ILLUMINATE-B trial , the mean absolute change from baseline was −5.03 µmol/L (SD = [redacted] µmol/L), while the mean percent change from baseline was −32.06% (SD = [redacted]) at month 6. In the ILLUMINATE-B trial, the LSM absolute change from baseline to the average of months 3 to 6 was −5.2 µmol/L (95% CI, −6.2 µmol/L to −4.2 µmol/L), while the LSM percent change was −31.7% (95% CI, −39.5% to −23.9%). Data from the extension period indicated that decreases in plasma oxalate at month 6 appeared to be [redacted] for patients [redacted].

In the ILLUMINATE-C trial, the LSM percent change from baseline to the average of months 3 to 6 was −33.33% (95% CI, −81.82% to 15.16%) for cohort A and −42.43% (95% CI, −50.71% to −34.15%) for cohort B. The LSM absolute change from baseline to the average of months

3 to 6 was −35.28 µmol/L (95% CI, −56.32 µmol/L to −14.24 µmol/L) for cohort A and −48.33 µmol/L (95% CI, −55.85 µmol/L to −40.80 µmol/L) for cohort B.

Urine Oxalate:Creatinine Ratio

In the ILLUMINATE-A trial, for percent change, the treatment difference between groups for urine oxalate:creatinine ratio was −51.77% (95% CI, −64.27 to −39.28%; P < 0.001). Data from extended treatment on lumasiran indicated that decreases at month 6 appeared to be maintained for both the lumasiran followed by lumasiran and placebo followed by lumasiran treatment groups.

In the ILLUMINATE-B trial, the LSM percent change from baseline to the average of months 3 to 6 for all patients was −71.97% (95% CI, −77.52% to −66.42%). At month 6, 9 (50.0%) patients had achieved near normalization, while 1 (5.6%) patient had achieved normalization. Data from the extension period indicated decreases in spot urine oxalate:creatinine ratio by month 6 that appeared to be [redacted] for patients [redacted]. Additionally, [redacted] of the [redacted] patients who had data at that time point achieved near normalization and [redacted] patients achieved normalization.

In the ILLUMINATE-C trial, the LSM absolute change from baseline to the average of months 3 to 6 was −0.19 mmol/mmol (95% CI, −0.23 mmol/mmol to −0.15 mmol/mmol). The LSM percent change from baseline to the average of months 3 to 6 was −39.51% (95% CI, −64.13 to −14.90%).

Harms Results

During the primary analysis period in the ILLUMINATE-A trial, a larger proportion of patients in the lumasiran group reported an AE compared to the placebo group (84.6% versus 69.2%). All patients in the ILLUMINATE-B trial reported at least 1 AE. In the ILLUMINATE-C trial, the percentage of patients reporting an AE was similar between the groups (83.3% for no dialysis and 86.7% for dialysis). The most frequently reported AEs were injection site reaction (in the ILLUMINATE-A and ILLUMINATE-C trials), headache (in the ILLUMINATE-A trial), and pyrexia (in the ILLUMINATE-B and ILLUMINATE-C trials) with injection site reaction occurring only among patients treated with lumasiran. During the overall period of receiving lumasiran treatment, injection site reaction (defined by system organ class and preferred term) ([redacted]), abdominal pain ([redacted]), and headache ([redacted]) were the most frequently reported AEs in the ILLUMINATE-A trial. In the ILLUMINATE-B trial, pyrexia (8 patients) and vomiting (5 patients) were the most frequently reported AEs.

During the primary analysis period, there were no serious adverse events (SAEs) in the ILLUMINATE-A trial. One patient who weighed more than 20 kg (33.3%) in the ILLUMINATE-B trial reported a viral infection SAE. In the ILLUMINATE-C trial, [redacted] reported an SAE: [redacted] ([redacted]%) [redacted] not on dialysis and [redacted] ([redacted]%) [redacted] on dialysis. [redacted] and device-related infection were reported in 2 patients for each SAE (all patients were on dialysis). All other SAEs were single-patient events. During the overall period of receiving lumasiran treatment, [redacted] reported SAEs of [redacted], urosepsis, and [redacted] in the ILLUMINATE-A trial, while 1 patient reported a viral infection in the ILLUMINATE-B trial.

During the primary analysis period, 1 patient who was receiving lumasiran in the ILLUMINATE-A trial stopped treatment due to an AE (fatigue and disturbance in attention), while [redacted] in the ILLUMINATE-C trial [redacted]. There were no new reports of patients stopping treatment due to AEs during the extended treatment period for

either of the ILLUMINATE-A or ILLUMINATE-B trials. No deaths were reported for any patients during the 6-month primary analysis period for any of the 3 studies or during the extension periods up to the data cut-off dates.

Notable Harms

Complications from systemic oxalosis were not reported in the clinical study reports at the given cut-off dates.

Injection site reactions were reported among 6 patients receiving lumasiran in the ILLUMINATE-A trial, 3 patients (2 patients weighing between 10 kg and 20 kg, 1 patient weighing more than 20 kg) in the ILLUMINATE-B trial, and 5 patients (4 patients on dialysis, 1 patient not on dialysis) in the ILLUMINATE-C trial. During the overall period of receiving lumasiran treatment, [redacted] in the ILLUMINATE-A trial and 3 patients in the ILLUMINATE-B trial reported an injection site reaction with the most common symptom being erythema.

Kidney stone events were captured as an efficacy outcome and were not reported as harms. All renal events were single-patient events and were generally infrequent: [redacted] in the ILLUMINATE-A trial, [redacted] in the ILLUMINATE-B trial, and [redacted] in the ILLUMINATE-C trial. During the overall period of receiving lumasiran treatment, [redacted] in the ILLUMINATE-A trial reported renal events with the most frequent events being [redacted] ([redacted]) and [redacted] ([redacted]). In the ILLUMINATE-B trial, [redacted] reported [redacted].

Six patients reported headache in the ILLUMINATE-A trial (3 patients each on placebo and lumasiran), 2 patients reported headache in the ILLUMINATE-B trial ([redacted]), and no patients reported headache in the ILLUMINATE-C trial. During the overall period of receiving lumasiran treatment, [redacted] in ILLUMINATE-A and [redacted] in the ILLUMINATE-B trial reported headache.

Four patients reported rhinitis in the ILLUMINATE-A trial (2 patients each on placebo and lumasiran), 4 patients reported rhinitis in the ILLUMINATE-B trial (1 patient weighing less than 10 kg and 3 patients weighing between 10 kg and 20 kg), and no patients reported rhinitis in the ILLUMINATE-C trial. During the overall period of receiving lumasiran treatment, 4 patients in the ILLUMINATE-A trial and 4 patients in the ILLUMINATE-B trial reported rhinitis.

Four patients reported upper respiratory tract infection in the ILLUMINATE-A trial (2 patients each on placebo and lumasiran), 4 patients reported upper respiratory tract infection in the ILLUMINATE-B trial (1 patient weighing less than 10 kg, 2 patients weighing between 10 kg and 20 kg, and 1 patient weighing more than 20 kg), and [redacted] in the ILLUMINATE-C trial reported upper respiratory tract infection ([redacted] each not receiving dialysis and on dialysis). During the overall period of receiving lumasiran treatment, 4 patients reported upper respiratory tract infection each in the ILLUMINATE-A and ILLUMINATE-B trials.

One patient receiving lumasiran in the ILLUMINATE-A trial reported a hypersensitivity reaction. Hypersensitivity reactions were not reported in the ILLUMINATE-B or ILLUMINATE-C trials. There were no additional reports in the ILLUMINATE-A trial during extended lumasiran treatment.

One patient tested positive for ADAs in the ILLUMINATE-A trial and 3 patients tested positive for ADAs in the ILLUMINATE-B trial. The sponsor concluded that the ADAs did not appear to impact efficacy or safety results for these patients. No patients tested positive for ADAs in the ILLUMINATE-C trial. During the overall period of receiving lumasiran treatment in the

ILLUMINATE-A trial, 1 patient originally randomized to placebo tested positive for ADAs. There were no additional reports of patients testing positive for ADAs in the ILLUMINATE-B trial during extended lumasiran treatment.

Critical Appraisal

The ILLUMINATE-A trial appeared to have appropriate methods for blinding of treatment assignment, randomization, and adequate power, and the primary and secondary outcomes (except eGFR) were controlled for multiplicity. The primary and key secondary outcomes were objective in nature, centrally assessed, relevant to PH1, and supported by regulatory agencies, which reduces bias in the results. The ILLUMINATE-B and ILLUMINATE -C trials' sample sizes were based on feasibility considerations rather than power calculations, they were single-arm trials, and their end points were not controlled for multiplicity. The sponsor noted that patient heterogeneity, disease heterogeneity, rarity of PH1, lack of available approved therapies, objectively measured end points, and the sponsor's feasibility results justified the use of a single-arm trial design. Baseline characteristics were mostly balanced in the ILLUMINATE-A trial, which suggests that randomization was generally successful, and it is possible that the imbalances were due to the small number of patients included. There were imbalances in sex, race, patients' medical history, specifically for PH1-related symptoms, and vitamin B6 use, which may have introduced bias, though the magnitude and direction of the bias are uncertain. More specifically, the proportion of patients using vitamin B6 varied among treatment groups in the trials and because it may also lower oxalate levels, it is unclear how much of the treatment effect could be attributed to vitamin B6 compared to lumasiran. Subgroup analyses of baseline vitamin B6 use (yes versus no) did not indicate a clear difference between the groups, though limitations of the subgroup analyses prevent firm conclusions from being made. As patients in the ILLUMINATE-B and ILLUMINATE-C trials were not randomized to their treatment group (rather, they were categorized based on body mass and use of dialysis, respectively), imbalances between groups are likely to occur. During the 6-month primary analysis periods, few patients discontinued lumasiran during the trials and few withdrew from the trials, which suggests there was little risk of attrition bias. Due to the small amount of missing data among the 3 trials and sensitivity analyses supporting the primary outcomes, the risk of bias due to missing data appears to be low. One of the main limitations is the small number of patients in each trial (N = 39, 18, and 21 in the ILLUMINATE-A, ILLUMINATE -B, and ILLUMINATE-C trials, respectively), though consideration must be given for the rarity of PH1. The small number of patients in each treatment group makes it challenging to interpret the results and to estimate how meaningful they are. Although there are data for up to 24 months of lumasiran treatment in the ILLUMINATE-A trial, a second major limitation is the relatively short duration of evidence available given that the clinical experts expect lumasiran to be a lifelong treatment (unless liver transplant occurs). The short duration makes it difficult to be certain if the efficacy and safety results will persist long-term. A third limitation is the lack of minimal important differences for patients with PH1 identified from the literature for all outcomes in the trials. Without published minimal important differences, there is uncertainty around how meaningful the absolute and percent changes from baseline were. The sponsor performed analyses for the proportion of patients who achieved near normalization or normalization for 24-hour urine oxalate levels in the ILLUMINATE-A trial and spot urine oxalate:creatinine ratio in the ILLUMINATE-B trial, but not for plasma oxalate levels in the ILLUMINATE-C trial. According to the clinical experts, normalization of elevated oxalate levels may result in clinical benefits, but it is unclear if achieving near normalization prevents long-term kidney damage, and long-term evidence will be needed to support this.

Given the lack of details for screening failures for all 3 trials, it is unknown if this biased results or how this limits the generalizability to the entire population of patients in Canada who could receive lumasiran. Patients enrolled in the 3 ILLUMINATE trials included both adult and pediatric patients (age range, 0 years to 60 years) with a range of kidney function (eGFR range, 8.61 mL/min/1.73 m^2 to 174.06 mL/min/1.73 m^2 and included patients on dialysis) and presenting symptoms related to PH1. Patients with possible hepatic impairment (alanine aminotransferase or aspartate aminotransferase readings greater than 2 times the ULN for age or total bilirubin greater than 1.5 times the ULN), history of kidney transplant, evidence of systemic oxalosis (in the ILLUMINATE-A or ILLUMINATE-B trials), or receiving peritoneal dialysis (in the ILLUMINATE-C trial) were excluded. Thus, treatment with lumasiran is uncertain in patients with these characteristics. Aside from these limitations, the clinical experts generally felt that the trial results could be generalized to the population of people in Canada with PH1. The clinical experts confirmed that the trial outcomes, all of which are surrogate measures, were typical measures used when assessing and managing patients with PH1. However, it is unclear how the main outcomes of the trials lead to treatment goals such as prevention of kidney stones and progression to ESKD, and the clinical experts emphasized the need for long-term data to better understand how the surrogate outcomes are related to clinical benefit.

Other Relevant Evidence

Description of Studies

ALN-GO1-001 was a phase I and II study conducted in 2 parts: single ascending dose (part A) in 32 healthy adult volunteers who were between 18 and 64 years of age and multiple ascending dose (part B) in 20 patients with PH1 who were at least 6 years of age and had relatively preserved kidney function (eGFR at least 45 mL/min/1.73m^2). ALN-GO1-002 is a phase II, multicentre, open-label extension study meant to evaluate the long-term safety and efficacy of lumasiran in patients with PH1 who have completed part B of the ALN-GO1-001 trial. Patients received lumasiran according to their initiation dosing regimen in part B of the ALN-GO1-001 trial for up to 54 months.

Efficacy Results

Results are presented for baseline of the ALN-GO1-001B trial and postbaseline for the ALN-GO1-002 trial. Mean eGFR was 77.34 mL/min/1.73 m^2 (SD = 22.11 mL/min/1.73 m^2) at baseline, [redacted] mL/min/1.73 m^2 (SD = [redacted] mL/min/1.73 m^2) at month 30, and appeared to be stable throughout the study. Three (15%) patients had at least 1 kidney stone event during the study period and the rate of kidney stone events per person-year during treatment was 0.06 (95% CI, [redacted] to [redacted]). No data on HRQoL were reported in the clinical study reports. Mean 24-hour urinary oxalate corrected for BSA was 2.24 mmol/24 hour/1.73 m^2 (SD = [redacted] mmol/24 hour/1.73 m^2) at baseline, [redacted] mmol/24 hour/1.73 m^2 (SD = [redacted] mmol/24 hour/1.73 m^2) at month 30, and appeared to be stable after the first 6 months. At any postbaseline visit, 100% and [redacted]% of patients achieved near normal and normal 24-hour urinary oxalate corrected for BSA levels, respectively. Mean plasma oxalate level was 15.28 µmol/L (SD = [redacted] µmol/L) at baseline, [redacted] µmol/L (SD = [redacted] µmol/L) at month 30, and appeared to be stable after the first 6 months. Mean 24-hour urinary oxalate:creatinine ratio was 0.28 mmol/mmol (SD = [redacted] mmol/mmol) at baseline, and [redacted] mmol/mmol (SD = [redacted] mmol/mmol) at month 30 and appeared to be stable after the first 6 months.

Harms Results

All patients in the ALN-GO1-002 trial experienced at least 1 AE. The most commonly reported AEs were injection site reaction (40%), vomiting (20%), headache (15%), limb injury (15%), and oropharyngeal pain (15%). Four (20%) patients reported SAEs of increased blood creatinine, pyelonephritis, renal colic, and ureterolithiasis (1 event for each patient). One patient experienced 2 SAEs, a craniocerebral injury and bone (i.e., rib) contusion from road traffic accidents. There were no withdrawals due to AEs, no patients discontinued treatment due to AEs, and there were no deaths reported during the study.

Of the notable harms identified in the CADTH systematic review protocol, 40% of patients reported injection site reaction. Three (15%) patients experienced kidney and urinary disorders, such as nephrolithiasis, renal colic, and ureterolithiasis. Headache, [redacted], and [redacted] were reported by 3, [redacted], and [redacted] patients, respectively. Complications caused by systemic oxalosis and hypersensitivity were not reported during the study period. [redacted]

Critical Appraisal

The limitations for the ALN-GO1-002 trial are similar to those for the ILLUMINATE trials. ALN-GO1-002 was a phase II, open-label extension study and statistical analyses, with adjustments for multiplicity, and imputations for missing data points were not performed. As vitamin B6 may help to reduce oxalate levels, it is unclear how much of the effect seen in this trial could be attributed to the concomitant treatment. The sample size was not determined using a power calculation and was likely too small to make definitive conclusion about safety and efficacy. Considering the wide range of clinical manifestations with PH1, it is uncertain if the sample population adequately represents patients with PH1 in Canada, which limits the generalizability of the results. Additionally, none of the trial sites were in Canada. The follow-up time may be sufficient for observing an immediate treatment effect (the mean duration of exposure was 28.8 months) as the clinical experts stated that 2 to 3 years are deemed appropriate in kidney disease–related clinical trial settings. However, it is unlikely that the duration of exposure is long enough to draw long-term conclusions for lumasiran treatment given that it is expected to be a lifelong treatment. Although the safety data suggest that lumasiran is safe for the first 30 months of treatment, the clinical experts emphasized that longer-term data for efficacy and safety are warranted.

Economic Evidence

Table 3: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target populations	Pediatric and adult patients with PH1
Treatment	Lumasiran plus ECM

Component	Description
Dose regimen	• ≤ 10 kg: loading dose of 6 mg/kg monthly for 3 doses and a maintenance dose of 3 mg/kg monthly • 10 kg to 20 kg: loading dose of 6 mg/kg monthly for 3 doses and a maintenance dose of 6 mg/kg once every 3 months • ≥ 20 kg: loading dose of 3 mg/kg monthly for 3 doses and a maintenance dose of 3 mg/kg once every 3 months
Submitted price	Lumasiran: $96,855.33 per vial
Treatment cost	Maintenance phase annual cost of $387,421 for pediatric patients and $1,162,263 for adults
Comparator	ECM (consisting of oxalate-controlled diet, hyperhydration, vitamin B6, and oral citrate supplements)
Perspective	Canadian publicly funded health care payer
Outcomes	LYs QALYs
Time horizon	Lifetime
Key data sources	ILLUMINATE-A, ILLUMINATE-B, and ILLUMINATE-C
Key limitations	• The sponsor assumed lumasiran was 100% effective in halting CKD progression based on observations of plasma oxalate levels and the rate of eGFR loss. However, the nature of the relationship is speculative. CADTH deemed the assumption of halting CKD progression as overly optimistic, as benefits in CKD progression have not been confirmed in clinical trials. • The rate of combined liver-kidney transplants used to inform the model were underestimated. Clinical experts consulted by CADTH indicated that patients with PH1 approaching ESKD are prioritized (even more so for pediatric populations) for transplant given that an earlier liver transplant will significantly improve health outcomes. • The sponsor assumed high-intensity dialysis would be given to patients with stage 4 CKD and ESKD on ECM. According to the clinical experts consulted by CADTH, adult patients with stage 4 CKD are unlikely to start dialysis, and intensive dialysis that uses both peritoneal dialysis and hemodialysis are not typically used. • A caregiver disutility decrement of [redacted] was applied to stage 4 CKD and ESKD health states for both pediatric and adult patients. Parental disutilities (parents of children aged 6 to 17) were applied to all patients in the model; a high degree of uncertainty exists in the sponsor's calculation, as source EQ-5D data for caregiver disutility was not provided. Regarding health state utilities, the inclusion of disutilities from multiple events resulted in negative utility values (worse than death) for some health states, which was deemed implausible by clinical experts.
CADTH reanalysis results	• Changes to derive a CADTH base case included decreasing dialysis costs and excluding adults with stage 4 CKD on dialysis; increasing liver-kidney transplant rates to more realistic values; using higher baseline utilities for patients with stage 4 CKD and ESKD and removing caregiver disutility; and altering the distribution of baseline CKD status to reflect the ILLUMINATE trials. • In the CADTH base case, the ICER for lumasiran + ECM compared to ECM was $2,171,687 per QALY (incremental costs = $29,818,424; incremental QALYs = 13.77). • To achieve a mean ICER of $50,000 per QALY, a price reduction of 95% is required for lumasiran.

CKD = chronic kidney disease; ECM = established clinical management; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; ICER = incremental cost-effectiveness ratio; LY = life-year; PH1 = primary hyperoxaluria type 1; QALY = quality-adjusted life-year.

Budget Impact

CADTH identified the following key limitations with the sponsor's budget impact analysis: the total number of patients with PH1 eligible for funding of lumasiran is unknown, and the sponsor-estimated proportion of pediatric patients is likely an overestimate and would

underestimate the 3-year budget impact of reimbursing lumasiran; the expected market share of lumasiran was underestimated; and the use of treatment adherence rate to estimate the lumasiran drug cost is inappropriate. The CADTH reanalysis updated the market shares for lumasiran to reflect an update of 80%, 85%, and 88% in year 1, year 2, and year 3, respectively, and used a treatment adherence rate of 100%. In the CADTH base case, the budget impact of reimbursing lumasiran is expected to be $46,922,574 in year 1, $36,344,252 in year 2, and $38,660,077 in year 3. The 3-year total budget impact was $121,926,903.

Ethical Considerations

Patient, clinical expert, and drug program input gathered for the CADTH review, as well as relevant literatures were reviewed to identify ethical considerations relevant to the use of lumasiran for the treatment of PH1 in pediatric and adult patients.

Ethical considerations in the context of PH1 included challenges of diagnosis for this rare disease, as well as equity and access challenges related to diagnosis and treatment. The severity of PH1 was noted, as was the burdensome nature of current treatment options. Given the ongoing need for liver and kidney transplants for the treatment of PH1, considerations arise related to the allocation of scarce organs.

Ethical considerations arising in the evidence used to support lumasiran indicated that several evidentiary uncertainties exist, particularly related to the long-term safety and efficacy of this drug, and the use of surrogate end points in clinical trials, as well as their representativeness of this population in Canada.

Patients and clinical experts reported improvements in PH1 with the use of lumasiran, but uncertainties remain about efficacy and challenges in prescribing and dispensing.

Ethical considerations for health systems related to the implementation of lumasiran included the challenges of funding decisions, population screening, and issues related to high-cost drugs for rare diseases.

Request for Minor Reconsideration

The sponsor filed a request for minor reconsideration for the draft recommendation for lumasiran for the treatment of PH1 to lower urinary oxalate levels in pediatric and adult patients, in which they requested the following:

- Modify the following implementation guidance: "The clinical experts noted to CDEC that an increase in plasma oxalate or an increase in urine oxalate after an initial improvement would be considered as loss of response" to state "The clinical experts noted to CDEC that a sustained increase in plasma oxalate or a sustained increase in urine oxalate to pretreatment baseline, after an initial improvement, would be considered as loss of response."
- Modify the following implementation guidance: "The clinical experts noted to CDEC that for patients with ESKD or on dialysis, a 15% reduction in plasma oxalate levels after 1 year of

treatment is considered as response." to state "The clinical experts noted to CDEC that for patients with ESKD or on dialysis, a 15% reduction in plasma oxalate levels after 2 years of treatment is considered as response."

In the meeting to discuss the sponsor's request for minor reconsideration, CDEC committee subpanel considered the following information:

- feedback from the sponsor
- information from the initial submission relating to the issues identified by the sponsor
- feedback from 2 clinical specialists with expertise in the management of patients with PH1
- feedback from the public drug plans
- feedback from 1 patient group: OHF.

All stakeholder feedback received in response to the draft recommendation from the patient group and the public drug programs is available on the CADTH website.

CDEC Information

Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed

Meeting date: September 28, 2022

Regrets: Two expert committee members did not attend.

Conflicts of interest: None

Minor reconsideration CDEC Committee Subpanel meeting date: January 25, 2023