5.11 LUMASIRAN,
Solution for subcutaneous injection 94.5 mg in 0.5 mL
Oxlumo®,
Medison Pharma Australia Pty Ltd

1. Purpose of submission
	1. The Category 1 submission requested a General Schedule Authority Required (Streamlined) listing for lumasiran for the treatment of primary hyperoxaluria type 1 (PH1).
	2. Listing was requested on the basis of a cost-effectiveness analysis versus best supportive care (BSC).

Table 1: **Key components of the clinical issue addressed by the submission (as stated in the submission)**

| Component | Description |
| --- | --- |
| Population | Patients with primary hyperoxaluria type 1 (PH1) |
| Intervention | Lumasiran (OXLUMO®) in addition to best supportive care (BSC)* Lumasiran is a subcutaneous injection which should be administered by a healthcare professional.
* The recommended dose of lumasiran consists of loading doses given once a month for 3 months, followed by maintenance doses starting 1 month after the last loading dose
* Dosing is based on body weight:
	+ Patients <10 kg: 6 mg/kg once monthly for 3 months (loading dose), followed by 3 mg/kg once monthly (maintenance dose)
	+ Patients 10 kg to <20 kg: 6 mg/kg once monthly for 3 months (loading dose), followed by 6 mg/kg every 3 months (maintenance dose)
	+ Patients ≥20 kg: 3 mg/kg once monthly for 3 months (loading dose), followed by 3 mg/kg every 3 months (maintenance dose)
 |
| Comparator | BSC alone (i.e. pyridoxine, oxalate-controlled diet, liver transplant with a combined/sequential kidney transplant in patients with advanced PH1, haemodialysis, hyperhydration) |
| Outcomes | * Oxalate levels
* Change in estimated glomerular filtration rate (eGFR)
* Need for liver transplant with a kidney transplant
* Mortality
* Adverse effects of treatment
* Health-related quality of life (HRQoL)
* Renal stone events
* Systemic oxalosis
 |
| Clinical claim  | Lumasiran, when used in addition to BSC, is superior in terms of effectiveness compared with BSC alone.Lumasiran, when used in addition to BSC, is comparable in terms of safety compared with BSC alone. |

Abbreviations: BSC, best supportive care; eGFR, estimated glomerular filtration rate; HRQoL, health-related quality of life; PH1, primary hyperoxaluria type 1

Source: Table 1.1, p16 of the submission and p97 of the submission.

1. Background

Registration status

* 1. Lumasiran was TGA registered on 24 June 2024 for the treatment of PH1 in all age groups.
	2. Lumasiran was approved in the European Union (EU) by the European Medicines Agency (EMA) for the treatment of PH1 in all age groups on 19 November 2020. Lumasiran was approved in the United States by the Food and Drug Administration (FDA) and in Canada by Health Canada for the treatment of PH1 to lower urinary oxalate levels in paediatric and adult patients on 23 November 2020 and 7 March 2022, respectively.
1. Requested listing

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **MEDICINAL PRODUCT****medicinal product pack** |  **Dispensed Price for Max. Qty** | **Max. qty packs** | **Max. qty units** | **№.of****Repeats** | **Available brands** |
| LUMASIRAN |
| lumasiran (as sodium) 94.5 mg/mL injection vial | Published Price $435,495.88 Effective Price$||||  | 4 | 4 | 2 | Oxlumo |
|  |
| **Indication:** Primary hyperoxaluria type 1 |
| **Treatment Phase:** Treatment initiation |
| **Clinical criteria:** |
| The condition must be primary hyperoxaluria type 1 confirmed by genetic testing |
| **AND** |
| Patient must have urinary oxalate ≥0.70 mmol/24 h/1.73 m2 measured by mean 24-h urinary oxalate excretion from a valid 24-h urine collection; ORPatient must have urinary oxalate:creatinine ratio greater than the upper limit of normal based on age on at least two of three single-void collections during screening; ORPatient must have clinical symptoms indicative of hyperoxaluria, such as nephrocalcinosis and/or renal stones and/or renal impairment and/or systemic oxalosis |
| **Treatment criteria:** |
| Must be treated by a nephrologist with experience in the management of hyperoxaluria or in consultation with a nephrologist with experience in the management of hyperoxaluria |
| **Population criteria:** |
| Patient must not have previously undergone a liver transplant for primary hyperoxaluria type 1 |
| **Prescribing Instructions:**  |
| At the time of the authority application, prescribers should request the appropriate number of vials for a single dose based on the patient's weight, as per the Product Information |
|  |
| **Treatment Phase:** Treatment continuation |
| **Clinical criteria:** |
| Patient must have previously received PBS-subsidised treatment with this drug for this condition |
| **AND** |
| Patient must continue to demonstrate clinical benefit |
| **Treatment criteria:** |
| Must be treated by a nephrologist with experience in the management of hyperoxaluria or in consultation with a nephrologist with experience in the management of hyperoxaluria |
| **Population criteria:** |
| Patient must not have previously undergone a liver transplant for primary hyperoxaluria type 1 |
| **Prescribing Instructions:**  |
| At the time of the authority application, prescribers should request the appropriate number of vials and number of repeats for a single dose based on the patient's weight, as per the Product Information |

|  |
| --- |
| **Treatment Phase:** Transitioning from non-PBS to PBS-subsidised supply - Grandfather arrangements |
| **Clinical criteria:** |
| Patient must have received treatment with this drug for this condition prior to PBS listing date |
| **AND** |
| Patient must continue to demonstrate clinical benefit |
| **Treatment criteria:** |
| Must be treated by a nephrologist with experience in the management of hyperoxaluria or in consultation with a nephrologist with experience in the management of hyperoxaluria |
| **Population criteria:** |
| Patient must not have previously undergone a liver transplant for primary hyperoxaluria type 1 |
| **Prescribing Instructions:**  |
| At the time of the authority application, prescribers should request the appropriate number of vials and number of repeats for a single dose based on the patient's weight, as per the Product Information |

* 1. The submission proposed a Special Pricing Arrangements (SPA). The submission requested an effective ex-manufacturer price (EMP) of $||| ||| per vial (published EMP: $108,873.97 per vial). The maximum per script is 4 vials for both children and adults. Calculated based on this, the published DPMQ should be $435,495.88; the effective DPMQ should be $||| |||.
	2. The requested listing was narrower than the TGA indication which includes all patients with PH1. The proposed listing was more specific, requiring patients to meet the following criteria:
1. Urinary oxalate ≥0.70 mmol/24 h/1.73 m2 measured by mean 24-hour urinary oxalate excretion from a valid 24-hour urine collection, OR
2. Urinary oxalate:creatinine (O:C) ratio greater than the upper limit of normal (based on age) on at least 2 of 3 single-void collections during screening, OR
3. Clinical symptoms indicative of hyperoxaluria, such as nephrocalcinosis and/or renal stones and/or renal impairment and/or systemic oxalosis.
	1. Criteria A and B above are aligned with the trial populations in ILLUMINATE-A and ILLUMINATE-B. The Pre-Sub-Committee Response (PSCR) noted that criterion C was necessary as patients with advanced renal disease may not be able to produce urine samples for testing and considered that the clinical symptoms proposed in the criterion were consistent with the expert consensus statement from ERKNet and OxalEurope9[[1]](#footnote-2) and advice from local clinical experts. The ESC agreed with the PSCR and considered the inclusion of criterion C was likely reasonable. While this criterion does not align with the inclusion of the clinical trials, the ESC considered that the potential for broad use (from bypassing the clinical markers in criterion A and B) was low given the additional requirement for genetically confirmed PH1, which is the gold standard for diagnosis[[2]](#footnote-3). The ESC also considered that the listed clinical symptoms in criterion C were likely to be clinically meaningful. However, the ESC and DUSC considered that ‘renal impairment’ required further clinical clarification/definition.
	2. The ILLUMINATE trials excluded patients with a history of renal or liver transplant, however the proposed restriction excluded only patients with liver transplants. The ESC considered that this was reasonable as liver transplant is curative, whereas a renal transplant is used to manage advanced chronic kidney disease (CKD) and is not curative.
	3. The proposed listing for initial treatment requires PH1 to be confirmed by genetic testing. There are MBS items to fulfill this testing requirement.
	4. The proposed listing for patient continuation requires patients to have already received PBS-subsidised lumasiran treatment and demonstrated ‘clinical benefit’ from treatment. The submission stated that due to the heterogeneous nature of the disease, the assessment of clinical benefit should be individualised, considering each patient’s outcomes and at the discretion of the treating physician. However, the submission stated that local experts had been consulted and considered a broad definition of clinical efficacy to lumasiran would be demonstrated by, but not limited to, the stabilisation of CKD and non-progression to renal failure. The submission also noted that clinical practice guidelines (ERKNet/OxalEurope) suggest that biochemical effectiveness, including urinary oxalate levels, be re-evaluated when considering clinical benefit and treatment continuation. However, the PSCR noted that patients who could not provide a urine sample due to impaired renal function could not be tested against specific biochemical markers. The PSCR considered the criterion proposed by the submission was likely appropriate for a rare, heterogeneous condition managed by clinical experts and noted that it was consistent with the PBS continuing restriction for patisiran. However, the ESC considered that it likely remained appropriate to include a definition for clinical benefit and that this definition should be developed in consultation with nephrology specialists. The DUSC also consideredthat a quantifiable measure to describe ‘clinical benefit’ should be considered for inclusion in the continuing restriction.
	5. The ESC also considered that it may be appropriate for the treatment criterion stating that patients must be treated by a nephrologist with experience in the management of hyperoxaluria or in consultation with a nephrologist with experience in the management of hyperoxaluria, to be expanded to include paediatricians and paediatric nephrologists.
	6. The ESC noted that different genotypes of PH1 respond differently to pyridoxine therapy.[[3]](#footnote-4) The PBAC is asked to consider whether patients carrying a pyridoxine responsive allele should trial pyridoxine therapy (B6) prior to treatment with lumasiran.
	7. A ‘grandfather’ listing to transition patients accessing lumasiran through a compassionate access program to PBS-subsidised supply was proposed in the submission. The submission stated that there were no patients currently being treated with lumasiran in Australia, however a compassionate access program was in development. The submission stated that a small number of patients may require access to lumasiran through such a listing.

*For more detail on PBAC’s view, see section 7 PBAC outcome.*

1. Population and disease
	1. PH1 is a potentially fatal condition that impacts oxalate metabolism. PH1 is caused by a mutation in the AGXT gene, leading to a deficiency of the enzyme alanine-glyoxylate aminotransferase (AGT). This deficiency prevents the conversion of glyoxylate to glycine, causing excess glyoxylate to accumulate and overproduction of oxalate. The accumulation of oxalate can result in kidney stones, nephrocalcinosis, progressive renal failure and systematic oxalosis which causes multi-organ damage.
	2. PH1 is present at birth but may not be diagnosed until patients become highly symptomatic, with 90% of patients becoming symptomatic in childhood or adolescence. PH1 tends to be more severe the earlier it is diagnosed such as in infantile PH1, in which there is often a rapid progression to stage 5 chronic kidney disease (CKD 5), and significantly reduced survival compared to patients with later clinical onset.
	3. There is currently minimal published epidemiological data for the prevalence and incidence of PH1 in Australia. Based on European data, the prevalence of PH1 is estimated to be 1–3 cases per million people and the incidence was estimated to be 1 in 100,000 live births[[4]](#footnote-5),[[5]](#footnote-6),[[6]](#footnote-7).
	4. At present there are no available pharmacological treatments for PH1, with current clinical management focusing on disease management strategies known as BSC. BSC aims to either reduce oxalate levels or mitigate the effects of oxalate accumulation, but it is not curative. The ESC noted that BSC constitutes of hyperhydration (3−5 litres per day), with young children often requiring a nasogastric or percutaneous enterostomy tube, and high dose pyridoxine (vitamin B6), which improves urine oxalate levels in some patients; however, can cause peripheral neuropathy. The ESC also noted BSC also includes potassium/sodium citrate supplementation, dietary oxalate restriction, and frequent (often daily) haemodialysis for CKD. The ESC noted that liver transplantation was curative and is often done in combination with a renal transplant. Lumasiran is being proposed as an addition to BSC, not a replacement.
	5. Lumasiran targets messenger ribonucleic acid (mRNA) in the HAO1 gene in hepatocytes using small interfering ribonucleic acid (siRNA)-mediated interference to reduce levels of the enzyme glycolate oxidase. The decrease in glycolate oxidase reduces the amount of glyoxylate available for oxalate production, thereby reducing the amount of oxalate being produced. This results in a reduction in plasma and urinary oxalate levels, the underlying cause of symptoms and complications associated with PH1.
	6. Details of the proposed clinical management algorithm is provided in Figure 1. The ESC noted that patients may also initially present to a general practitioner, the emergency department or a general paediatrician.

Figure 1: Proposed clinical management algorithm



Abbreviations: AGXT, alanine-glyoxylate aminotransferase; CKD, chronic kidney disease; ESKD, end-stage kidney disease; PH1, primary hyperoxaluria type 1; PBS, Pharmaceutical Benefits Scheme

Source: p29, Figure 1.5 of the submission. Based on Australian PH1 clinical expert opinion (Data on File).

*For more detail on PBAC’s view, see section 7 PBAC outcome.*

1. Comparator
	1. The submission nominated BSC as the main comparator. The submission stated that BSC may include dietary management, hyper-hydration, citrate and pyridoxine (vitamin B6) administration, urological management of kidney stones, dialysis and combined liver-kidney transplantation (LKT).
	2. Lumasiran was proposed to not replace any medicines in Australia; it was proposed to be offered in addition to BSC.
	3. The ESC considered that non-invasive measures were a reasonable main comparator for lumasiran. The ESC noted that lumasiran may reduce progression to dialysis and renal transplantation (included in BSC), and this was considered in the economic/financial models.

*For more detail on PBAC’s view, see section 7 PBAC outcome.*

1. Consideration of the evidence

Sponsor hearing

* 1. The sponsor requested a hearing for this item. The first clinician noted that patients with PH1 are often diagnosed late at an advanced stage of disease and typically experience a very difficult clinical course. The clinician emphasised the significant time, effort, and expense involved in reducing oxalate levels in individuals with PH1 and noted that current BSC places a significant burden on patients. Patients typically require 6 to 8 hours of dialysis, 6 to 7 days per week, and commonly experience recurrent kidney stones, leading to repeat hospitalisations for urological procedures and pain management. The clinician emphasised the importance of early kidney and liver transplantation and the need for reducing oxalate accumulation in the body, as transplants performed at a more advanced stage of disease, and when combined with high oxalate levels, are associated with poor outcomes. The second clinician noted that PH1 tends to be more severe when diagnosed in the first 3 years of life. The clinician also noted that urinary oxalate is typically used as a biomarker for disease activity, but plasma oxalate would be used for patients with very severe disease. The second clinician also highlighted the burden on both patients and healthcare systems in managing oxalate levels in children while they await a liver transplant. The second clinician considered that the results from the lumasiran clinical trials were encouraging and considered that integrating lumasiran into clinical practice could significantly reduce the current burden of BSC on both patients and healthcare providers. The third clinician considered that the incidence and prevalence of PH1 in Australia was similar to that reported overseas and also discussed the relationship between plasma oxalate, urinary oxalate and the progression of PH1.

Consumer comments

* 1. The PBAC noted and welcomed the input from individuals (6), health care professionals (3) and organisations (4) via the Consumer Comments facility on the PBS website. Clinicians, individuals and their caregivers and supporters described PH1 as a devastating condition that severely impacts the physical and psychological wellbeing of individuals with PH1 and their supporting caregivers and family. Comments described that current supportive therapies for PH1 impose a significant burden on patients and carers, and often include consistent and intensive dialysis, regular medications, and strict fluid intake and diet modifications. For children, adhering to complex and restrictive medical regimens can be particularly challenging, and managing them effectively can become a considerable strain for caregivers. Comments emphasised that patients who develop ESKD experience an increased risk of cardiovascular issues and have a reduced life expectancy. Patients with PH1 also face significant emotional, psychological and cognitive challenges, which impact on their ability to succeed in school and hinder their ability to navigate adult life independently. Family members and carers describe the anxiety related to developmental delays and the unknown impact PH1 will have on their child’s future health and quality of life. The comments described a range of potential benefits of treatment with lumasiran including the reduction of oxalate levels and the potential to prevent/reduce kidney stones, renal replacement therapy and transplantation, end-stage kidney failure and the sequelae related to systemic oxalosis. Caregivers describe the potential for lumasiran to reduce the significant treatment burden and provide children and all individuals with PH1 with an improved quality of life and restore some normalisation to their life and family routine.
	2. The PBAC noted the input received from the Australia and New Zealand Society of Nephrology (ANZSN), the Australian and New Zealand Paediatric Nephrology Association (ANZPNA), Kidney Health Australia and the KidGen Renal Genetics Consortium. The organisations expressed strong support for the PBS listing of lumasiran for the treatment of PH1. The advice stated that current PH1 therapy includes hyperhydration and that this represents water intake beyond what feels comfortable to consume, and younger children usually require a nasogastric tube or percutaneous enterostomy tube insertion to maintain sufficient fluid intake. If chronic kidney disease develops, intensive dialysis is necessary to mitigate oxalate accumulation in the bones, bone marrow, eyes, heart and blood vessels, skin and other tissues. It was emphasised that access to optimal management is challenging, particularly in regional areas where specialised renal genetic services are limited. Furthermore, provision of paediatric dialysis is limited to tertiary metropolitan centres, and therefore paediatric PH1 patient requiring dialysis require metropolitan relocation. The PBAC noted advice stating that intensive dialysis does not treat the underlying disease, and that liver transplantation involves long wait times, requires lifelong immunosuppression, and is associated with increased risk of morbidity and mortality. It was emphasised that lumasiran had the potential to reduce the significant healthcare burden associated with PH1 and provide patients with access to alternative therapy that is effective and generally well tolerated.

Clinical trials

* 1. The submission was based on the following clinical evidence:
* ILLUMINATE-A (N=39): A randomised, double blind, placebo-controlled trial (6 months) with an extension period with both arms receiving lumasiran (3 month blinded, 51-month open-label period). Patients were aged >6 years of age, eGFR ≥30 mL/min/1.73 m2, and have a mean 24-hour urinary oxalate excretion ≥0.70 mmol/24 h/1.73 m2 (from first two valid 24-h urine collections).
* ILLUMINATE-B (N=18): A phase 3, single-arm, open-label trial (6 month) with an extension period (54 months). Patients were between 37 weeks estimated gestational age and <6 years, eGFR ≥45 mL/min/1.73 m2 if aged ≥1 year or normal serum creatinine if aged <1 year, and urinary oxalate:creatinine ratio > upper limit of normal (ULN; ULN = 0.514 mmol/24hr/1.73 m2).
* ILLUMINATE-C (N=21): A phase 3, single-arm, open-label trial (6 month) with an ongoing extension period (52 months). Patients were ≥37 weeks estimated gestational age, eGFR ≤45 mL/min/1.73 m2, a mean plasma oxalate level during screening ≥20 μmol/L, and for patients who require dialysis (Cohort B): on a stable haemodialysis regimen for >4 weeks prior to screening plasma oxalate assessment and able to maintain this regimen through Month 6, with changes permitted only when medically indicated.
	1. Additional clinical evidence was also provided:
* ALN-GO1-001B (N=20): A phase 1/2 randomised, placebo-controlled dosing study. Patients were aged ≥6 years with PH1 with urinary oxalate ≥0.7 mmol/1.73 m2/day and eGFR >45 mL/min/1.73 m2.
* ALN-GO1-002 (N=20): A phase 2, open-label extension safety study of people previously enrolled in ALN-GO1-001B.
	1. The median age of patients included in ILLUMINATE-A was 14 years (range = 6−60 years) with 44% of patients 18 years or older with relatively preserved kidney function. The ILLUMINATE-B trial included paediatric patients with relatively preserved kidney function and the ILLUMINATE-C trial included patients ≥37 weeks gestational age with more advanced CKD. The evaluation noted that the three ILLUMINATE trials included a small number of patients with varying levels of kidney function. For this reason, the results of the 3 trials should not be interpreted within the same context.
	2. The ILLUMINATE-A and -B trials excluded patients with systemic oxalosis, which is a feature of PH1 progression. Therefore, the generalisability of the findings to these patients is uncertain.
	3. The ESC noted the rarity of PH1, and considered the availability of randomised data, though limited, was a valuable contribution to the evidence base.
	4. Details of the trial publications presented in the submission are provided in Table 2.

Table 2: Trials and associated reports presented in the submission

| Trial ID | Publication/Conference abstract/Clinical study report title | Publication type; Publication citation |
| --- | --- | --- |
| **Randomised trials** |
| ILLUMINATE-AALN-GO1-003NCT03681184 | Alnylam Pharmaceuticals. Data on File. ILLUMINATE-A (ALN-GO1-003) Clinical Study Report (CSR) 2. | CSR; 28 June 2024. |
| Alnylam Pharmaceuticals. Data on File. ILLUMINATE-1 (ALN-GO1-003) Clinical Study Report (CSR) 1. | CSR; 10 March 2020. |
| 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. | Full publication; Kidney Int Rep. 2024;9(7):2037-2046. |
| Hulton SA, Groothoff JW, Frishberg Y, et al. Randomized clinical trial on the long-term efficacy and safety of lumasiran in patients with primary hyperoxaluria type 1. | Full publication; Kidney Int Rep. 2022;7(3):494-506. |
| Garrelfs SF, Frishberg Y, Hulton S, et al. Lumasiran, an RNAi therapeutic for primary hyperoxaluria type 1. | Full publication; N Engl J Med. 2021;384:1216-1226. |
| **Non-randomised trials** |
| ILLUMINATE-BALN-GO1-004NCT03905694 | Alnylam Pharmaceuticals. Data on File. ILLUMINATE-B (ALN-GO1-004) Clinical Study Report (CSR) 2. | CSR; 18 December 2020. |
| 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. | Full publication; Pediatr Nephrol. 2023;38(4):1075-1086. |
| 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. | Full publication; Genet Med. 2022;24(3):654-662. |
| Michael M, Magen D, Hayes W, Shasha-Lavsky H, Sas D, Sellier-Leclerc AL, 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. | Conference abstract;Nieren- und Hochdruckkrankheiten. 2024;53(2):90-1. |
| ILLUMINATE-CALN-GO1-005NCT04152200 | Alnylam Pharmaceuticals. Data on File. ILLUMINATE-C (ALN-GO1-005) Clinical Study Report (CSR) 1. | CSR; 18 October 2021. |
| Michael M, Groothoff JW, Shasha-Lavsky H, et al. Lumasiran for advanced primary hyperoxaluria type 1: Phase 3 ILLUMINATE-C trial. | Full publication; Am J Kidney Dis. 2023;81(2):145-155.e141. |
| Magen D, Sellier-Leclerc AL, Shasha-Lavsky H, Simkova E, Devresse A, Michael M, et al. Lumasiran for primary hyperoxaluria Type 1 and impaired kidney function: 24-month analysis of the Phase 3 ILLUMINATE-C trial. | Conference abstract; Nieren- und Hochdruckkrankheiten. 2024;53(2):91. |
| Lieske JC, Magen D, Sellier-Leclerc ALA, Shasha-Lavsky H, Simkova E, Devresse A, et al. Lumasiran for Primary Hyperoxaluria Type 1 and Impaired Kidney Function: 24-Month Analysis of the Phase 3 ILLUMINATE-C Trial. | Conference abstract; Journal of the American Society of Nephrology. 2023;34:566. |
| Frishberg Y, Michael M, Groothoff J, Shasha-Lavsky H, Lieske JC, Simkova E, et al. Lumasiran for Patients With Primary Hyperoxaluria Type 1 and Impaired Kidney Function: 12-Month Analysis of the Phase 3 ILLUMINATE-C Trial. | Conference abstract; Journal of the American Society of Nephrology. 2022;33:416. |
| Phase 1/2ALN-GO1-001NCT02706886 | Alnylam Pharmaceuticals. Data on File. Lumasiran Phase 1/2 (ALN-GO1-001) Clinical Study Report (CSR). | CSR; 18 July 2019. |
| Frishberg Y, Deschenes G, Groothoff JW, Hulton SA, Magen D, Harambat J, et al. Phase 1/2 study of lumasiran for treatment of primary hyperoxaluria type 1 a placebo-controlled randomized clinical trial. | Full publication; Clinical Journal of the American Society of Nephrology. 2021;16(7):1025-36. |
| Phase 2 OLEALN-GO1-002NCT03350451 | Alnylam Pharmaceuticals. Data on File. Lumasiran Phase 2 Open-label Extension (ALN-GO1-002) Clinical Study Report (CSR).  | CSR; 13 February 2020. |
| Frishberg Y, Groothoff JW, Hulton SA, Harambat J, Hogan J, Anne-Laure SL, et al. Long-term treatment with lumasiran: final results from the phase 2 open-label extension study. | Conference abstract; Nephrology Dialysis Transplantation. 2024;39:i2390-i2. |
| Magen D, Groothoff J, Hulton SA, Harambat J, Hogan J, Sellier-Leclerc AL, et al. POS-438 Long-term Treatment With Lumasiran: Results From the Phase 2 Open-Label Extension Study. | Conference abstract; Kidney International Reports. 2022;7(2):S195. |

Abbreviations: CSR, clinical study report; OLE, open label extension

Source: Table 2.3, pp42-43 of the submission.

* 1. The submission primarily focused on ILLUMINATE-A, -B and -C. The submission noted that ALN-GO1-001 Part B and ALN-GO1-002 were identified in the literature search and were stated to support the extended assessment of harms for lumasiran. An additional ongoing study (BONAPH1DE) was also identified by the submission, however it was not discussed or used in the submission. Given these studies were not the primary focus of the submission, detail on these studies is not provided herein.
	2. The key features of the included trials are summarised in Table 3.

Table 3: Key features of the included evidence

| **Trial** | **N** | **Design/ duration** | **Risk of bias** | **Patient population** | **Outcome(s)** | **Use in model** |
| --- | --- | --- | --- | --- | --- | --- |
| **Lumasiran vs placebo**  |
| ILLUMINATE-A | 39 | R, DB, MC6 months + 54 months extension  | High, using criteria for RCT | Patients aged ≥6 years with PH1 and RPRF (eGFR ≥30 mL/min/1.73 m2) | Primary: 24-hour urinary oxalate (percent change)Secondary: 24-hour urinary oxalate (absolute change), 24-hour urinary oxalate:creatinine ratio (percent change), Plasma oxalate (percent change), 24-hour urinary oxalate ≤1.5 x ULN (proportion of patients), 24-hour urinary oxalate ≤ ULN (proportion of patients), Plasma oxalate (absolute change), eGFR (change from baseline) | Plasma oxalate reduction at 6 months;renal stone events; treatment-related AEs; CKD1-3b utility; time on treatment. |
| **Lumasiran (single arm)** |
| ILLUMINATE-B | 18 | OL, MC, SA6 months + 54 months extension | Moderate, using criteria for non-RCT | Patients aged <6 years with PH1 and RPRF (eGFR ≥45 mL/min/1.73 m2 or normal serum creatinine if aged <1 year) | Primary: Spot urinary oxalate:creatinine ratio (percent change)Secondary: Urinary oxalate (absolute change), Urinary oxalate ≤ the ULN and ≤ 1.5 x ULN (proportion of patients), Plasma oxalate (per cent and absolute change), eGFR (change from baseline) | Plasma oxalate reduction at 6 months; renal stone events; time on treatment. |
| ILLUMINATE-C | 21 | OL, MC, SA6 months + 54 months extension | Moderate, using criteria for non-RCT | Patients with PH1 and advanced renal disease (eGFR ≤45 mL/min/1.73 m2)Cohort A = patients not on dialysis Cohort B = patients on dialysis  | Primary: Plasma oxalate (percent change)Secondary: Plasma oxalate AUC (per cent change), Plasma oxalate (per cent and absolute change), Nephrocalcinosis (change over time), Renal stone event (frequency), Urinary oxalate (change over time), Systemic oxalosis measures (change over time) | Plasma oxalate reduction at 12 months renal stone events. |

Abbreviations: AUC, area under the curve; CKD, chronic kidney disease; DB, double blind; eGFR, glomerular filtration rate; MC, multi-centre; NA, not applicable; OL, open label; PH1, primary hyperoxaluria type 1; R, randomised; RCT, randomised controlled trial; RPRF, relatively preserved renal function; SA, single arm; ULN, upper limit of normal.

Source: Section 2.3, pp45-50 of the submission.

* 1. In ILLUMINATE-A differences between the lumasiran and placebo arms were observed for: age (mean age for lumasiran: 9.6 years; placebo: 7.9 years), race (lumasiran: 80.8% Anglo-Saxon; placebo: 69.2% Anglo-Saxon), pyridoxine use at baseline (lumasiran: 50.0%; placebo: 69.2%), and the number of renal stones 12 months prior to consent (≥1 renal stone for lumasiran: 42.3%; placebo: 30.8%). Whether or not these imbalances introduced biases to the result is unclear. The evaluation considered that due to the differences in the pyridoxine use at baseline between treatment groups (which has also been shown to reduce urinary oxalate), it is unclear whether the pyridoxine had an additional impact on participant treatment effects. The ESC noted that different genotypes of PH1 respond differently to pyridoxine therapy.[[7]](#footnote-8) The ESC also noted that the percentage of patients carrying a pyridoxine responsive allele was similar across treatment arms: 42% (11/26) of the lumasiran arm compared to 46% (6/13) in the placebo arm (p=0.89).
	2. For ILLUMINATE-A, the overall risk of bias as assessed during the evaluation, was high. A high risk of bias was assigned due to issues related to the assessment of the plasma oxalate outcomes (percent and absolute). Firstly, patients with baseline plasma oxalate levels near the lower limit of quantitation (LLOQ) (i.e., <1.5×LLOQ) were excluded from the analysis. The clinical study report (CSR) states that this was done to ensure that meaningful reductions in plasma oxalate could be evaluated for the study population. The evaluation also noted missing outcome data at baseline and at follow-up timepoints. All other outcomes were assessed as being of some concern due to imbalances in baseline characteristics. The PSCR argued that missing data for the primary and secondary endpoints were rare, with data for all 39 patients (100%) included in the full analysis set and contributing to the Mixed Model Repeated Measures (MMRM) analyses for the primary endpoint. The PSCR also noted it was necessary for the plasma oxalate endpoints to be analysed using patients with baseline plasma oxalate level ≥1.5x LLOQ to ensure meaningful evaluation without confounding from floor effects.
	3. As assessed during the evaluation, ILLUMINATE-B and -C single arm studies had a moderate level of bias. A moderate level of bias was assigned due to the lack of blinding, along with insufficient details on co-interventions (i.e. BSC), and participants entering the studies at different stages of PH1 (e.g. those on dialysis vs not on dialysis).
	4. The long-term treatment effects of lumasiran compared to placebo could not be assessed in ILLUMINATE-A, given the follow-up for the double-blind period was 6 months.
	5. The submission suggested ILLUMINATE-B and ILLUMINATE-C addressed the applicability of lumasiran in patients for whom listing is sought, but who were not included in the pivotal RCT (ILLUMINATE-A).

Comparative effectiveness

**ILLUMINATE-A — ≥6 years of age**

* 1. A summary table presenting the clinical results for ILLUMINATE-A for both the double-blind period (6 months) and extension period (60 months) is provided below.

Table 4: Primary and secondary outcomes reported in ILLUMINATE-A to 6 months and 60 months

|  |
| --- |
| **ILLUMINATE-A (double-blind period to 6 months)** |
| **Outcomes** | **Mean change** | **Mean change** | **Effect size (95% CI)** |
| **Lumasiran (n=26)** | **Placebo (n=13)** |
| Percent change in 24-h urinary oxalate excretion from baseline to Month 6, %, LSM (95% CI) | -65.39(-71.3, -59.5) | -11.84(-19.5, -4.1) | **-53.55** **(-62.3, -44.8)\*\*** |
| Absolute change in 24-h urinary oxalate from baseline to Month 6, mmol/24 h/ 1.73 m2, LSM (95% CI) | -1.24 (-1.37, -1.12) | -0.27(-0.44, -0.10) | **-0.98****(-1.18, -0.77)\*\*** |
| Percent change in 24-h urinary oxalate:creatinine ratio frombaseline to Month 6, %, LSM (95% CI) | -62.55(-70.71, -54.39) | -10.78(-21.58, 0.03) | **-51.77****(-64.27, -39.28)\*\*** |
| Proportion of patients with 24-h urinary oxalate ≤1.5×ULN at Month 6a (95% CI) | 0.84 (0.64, 0.95) | 0.00(0.00, 0.25) | **0.84** **(0.55, 0.94)\*\*** |
| Proportion of patients with 24-h urinary oxalate ≤ULN at Month 6a (95% CI) | 0.52 (0.31, 0.72) | 0.00 (0.00, 0.25) | **0.52** **(0.23, 0.70)\*\*** |
| Percent change in plasma oxalate from baseline to Month 6, %, LSMb (95% CI) | -39.80(-45.81, -33.80) | -0.32(-9.12, 8.48) | **-39.48****(-50.10, -28.87)\*\*** |
| Absolute change in plasma oxalate from baseline to Month 6, μmol/L, LSMb (95% CI) | -7.46 (-9.03, -5.90) | 1.25 (-1.04, 3.54) | **-8.71** **(-11.45, -5.98)\*\*** |
| **ILLUMINATE-A – Extension period (to 60 months)** |
| **Outcomes** | **Lumasiran/lumasiran****(n=26)** | **Placebo/lumasiran (n=13)** | **Effect size (95% CI)** |
| Percent change in 24-h urinary oxalate excretion, %c (SEM) | -53.98 (NR) | -55.57 (NR) | NA |
| Absolute change in 24-h urinary oxalate, mmol/24 h/1.73 m2c (SEM) | -1.13 (0.17) | -0.95 (0.25) | NA |
| Percent change in 24-h urinary oxalate:creatinine ratio, %, LSM (SEM) | -55.74 (7.01) | -57.19 (10.55) | NA |
| Proportion of patients with 24-h urinary oxalate ≤1.5×ULN, %a (SEM) | 0.632 (NR) | 0.667 (NR) | NA |
| Percent change in plasma oxalate, %, LSMb (SEM) | -37.13 (6.19) | -49.8 (6.40)c | NA |
| Absolute change in plasma oxalate, μmol/Lb (SEM) | -7.25 (1.73) | -9.71 (3.06) | NA |

Abbreviations: CI, confidence interval; LLOQ, lower limit of quantification; LSM, least squares mean; NA, not applicable; NR, not reported; SEM, standard error of the mean; ULN, upper limit of normal.

Notes:
Patients in the placebo group switched to lumasiran after the 6-month double-blind period, with patients in the lumasiran group remaining on lumasiran for the extension period (54 months).

Outcomes for the lumasiran/lumasiran group is baseline to 60 months, for the placebo/lumasiran it is 6 months (first dose of lumasiran) to 60 months.

\*\* P-value of <0.05 = statistically significant

a ULN=0.514 mmol/24hr/1.73m2 for 24-hour urinary oxalate corrected for body surface area (BSA)

b Plasma oxalate outcomes were analysed in the Plasma Oxalate Analysis Set, defined as those patients who received any amount of study drug and had baseline plasma oxalate level ≥1.5×LLOQ. LLOQ is 5.55 μmol/L. This included 23 patients in the lumasiran arm and 10 patients in the placebo arm.

c LSM has not been used

Source: Section 2.5.1, pp62-77 of the submission, ILLUMINATE-A Clinical Study Report 1 (Alnylam Pharmaceuticals Inc. 2020b) ILLUMINATE-A Clinical Study Report 2 (Alnylam Pharmaceuticals Inc. 2024).

* 1. The submission reported a statistically significant decrease in 24-hour urinary oxalate in the lumasiran group compared to the placebo group (least square mean [LSM] [95% confidence interval [CI]] difference: −53.6% [−62.3%, −44.8%]; p<0.001) from baseline to 6 months. Patients who remained on lumasiran (lumasiran/lumasiran) demonstrated a sustained reduction to 60 months, while patients switching from placebo to lumasiran (placebo/lumasiran) achieved a reduction in 24-hour urinary oxalate of 55.6% after 54 months of treatment. The submission reported a statistically significant reduction in absolute change in 24-hour urinary oxalate levels between lumasiran and placebo from baseline to 6 months (LSM [95% CI] difference: −0.98 [−1.18, −0.77 mmol/24 h/1.73 m2]; p<0.001). These reductions were sustained throughout the extension period for both the lumasiran/lumasiran and placebo/lumasiran treatment groups. The submission considered the percent and absolute reductions in 24-hour urinary oxalate to be clinically meaningful.
	2. Lumasiran treatment demonstrated a statistically significant reduction in percent change in 24-hour urinary oxalate:creatinine (O:C) ratio compared to placebo from baseline to 6 months (LSM [95% CI] difference: −51.8% [−64.3%, −39.3%]; p<0.001). These reductions were maintained in the lumasiran/lumasiran group (LSM [standard error of the mean; SEM] percent change: −55.7% [7.0%]) and crossover patients in the placebo/lumasiran group (LSM [SEM] percent change: −57.2% [10.6%]) exhibited sustained decreases in 24-hour urinary O:C ratio at 60 months. The submission considered the reduction in urinary O:C ratio from baseline to 6 months to be clinically meaningful.
	3. A higher proportion of patients in the lumasiran group achieved oxalate level normalisation (≤ULN) or near-normalisation (≤1.5xULN) from baseline to 6 months, with no patients in the placebo group achieving either. These findings were statistically significant, and the submission considered the oxalate level normalisation or near-normalisation to be clinically meaningful from baseline to 6 months. In the extension period, these levels remained stable in the lumasiran/lumasiran group. In patients who crossed over to placebo/lumasiran, 66.7% achieved normalisation or near-normalisation at 60 months (compared to 0% prior to crossover).
	4. For the urinary oxalate outcomes presented in ILLUMINATE-A the submission considered the findings to be clinically meaningful given that the risk of disease complications increase continuously as oxalate levels rise, any sustained lowering of hepatic oxalate production would be beneficial to PH1 patients and considered clinically meaningful. However, the submission did not nominate a minimally clinical important difference (MCID), nor could an MCID be identified (via published literature) during the evaluation to quantify what constituted a clinically meaningful difference in urinary oxalate reduction to translate into a clinically meaningful benefit to PH1 patients. The PSCR noted that the primary outcome results of the ILLUMINATE-A trial exceeded the minimum expected differences in the statistical analysis plan. The PSCR reiterated that the risk of disease complications increases continuously as oxalate levels rise, and therefore any sustained lowering of hepatic oxalate production would be beneficial to PH1 patients[[8]](#footnote-9),[[9]](#footnote-10). The PSCR argued that the oxalate-lowering efficacy of lumasiran was also shown to translate to patient-relevant outcomes, including, preservation and maintenance of renal function (eGFR), reduction of renal stone events and reversal or stabilisation of nephrocalcinosis, and therefore it is reasonable to conclude that the magnitude of effect for oxalate reduction observed is clinically meaningful.
	5. Lumasiran demonstrated statistically significant reductions in both percentage change (LSM difference [95% CI]: -39.5% [-50.1, -28.9]; p<0.001) and absolute change (LSM difference [95% CI]: -8.7 μmol/L [-11.5, -6.0]; p<0.001) in plasma oxalate levels when compared to placebo from baseline to 6 months. These reductions were maintained through the extension period for patients in the lumasiran/lumasiran group and the placebo/lumasiran treatment group had a rapid and sustained decrease in plasma oxalate (percent and absolute) after switching to lumasiran.
	6. eGFR remained stable from baseline to 6 months across both the lumasiran and placebo groups. During the extension period the eGFR remained stable in all patients from baseline to 60 months.
	7. A summary table presenting the exploratory patient reported outcome measures (PROMS) of health-related quality of life (HRQoL) from ILLUMINATE-A using EuroQol-5 dimension (EQ-5D) for both the double-blind period and extension period is provided in Table 5.

Table 5: Patient-reported outcomes reported in ILLUMINATE-A to 6 months and 54 months

|  |
| --- |
| **ILLUMINATE-A – Patient-reported outcomes (double-blind period to 6 months)** |
|  | **Mean change (SD)** |
| Outcomes | Lumasiran (n=22)a | Placebo (n=6)a |
| EQ-5D VAS, baseline to 6 months | 3.8 (18.2) | −2.0 (8.9) |
| **ILLUMINATE-A – Patient-reported outcomes (to 54 months)** |
|  | **Mean change (SD)** |
| Outcomes | Lumasiran/Lumasiran (n=22)a | Placebo/Lumasiran (n=6)a |
| EQ-5D VAS, baseline to 54 months | 6.3 (13.5) | 10.5 (12.1) |

Abbreviations: EQ-5D, EuroQol-Five Dimension; SD, standard deviation; VAS, visual analogue scale.

a Patient numbers at 6-month, 54-month and 60-month timepoint as reported in ILLUMINATE-A Clinical Study Report 2, Table 11.

Source: Section 2.5.4, p92 of the submission

* 1. The EQ-5D visual analogue scale (VAS) was used to assess overall patient-reported HRQoL, with higher scores indicating better quality of life (QoL). Mean (standard deviation; SD) change was 3.8 (18.2) in the lumasiran group and -2.0 (8.9) in the placebo group from baseline to 6 months. In the extension period, mean (SD) change was 6.3 (13.5) in the lumasiran/lumasiran treatment group and 10.5 (12.1) in the placebo/lumasiran treatment group from baseline to 54 months.
	2. HRQoL was also assessed using Kidney Disease Quality of Life Questionnaire-36 (KDQOL-36) in participants aged ≥18 years and Pediatric Quality of Life Inventory (PedsQL) in participants aged <18 years; with higher scores indicating better QoL status. The submission stated that no clinically meaningful differences between treatment groups were expected during the 6-month double-blind period. In the extension period, both groups demonstrated a trend toward improved scores and a maintenance of QoL as measured by the 12-Item short form survey (SF-12) physical and mental components of the KDQOL-36 instrument.

**ILLUMINATE-B — 37 weeks gestational age to <6 years of age**

* 1. A summary of the clinical results for ILLUMINATE-B for both the primary analysis period (6 months) and extension period (30 months) is provided in Table 6.

Table 6: Primary and secondary outcomes reported in ILLUMINATE-B to 6 months and 30 months

|  |  |
| --- | --- |
| **ILLUMINATE-B (primary analysis period to 6 months)** | **Lumasiran (n=18)** |
| Percent change in spot urinary oxalate:creatinine ratio from baseline to month 6, %, LSM (95% CI) | **-72.0 (-77.5, -66.4)\*\*** |
| Absolute change in spot urinary oxalate:creatinine ratio from baseline to month 6, mmol/mmol, LSM (95% CI) | -0.49 (-0.52, -0.46) |
| Proportion of patients with spot urinary oxalate excretion ≤ULN at month 6a | 0.06 |
| Proportion of patients with spot urinary oxalate excretion ≤1.5×ULN at month 6a | 0.50 |
| Absolute change in plasma oxalate from baseline to month 6, μmol/L, LSMb (95% CI) | -5.2 (-6.2, -4.2) |
| Percent change in plasma oxalate from baseline to month 6, %, LSMb (95% CI) | -31.7 (-39.5, -23.9) |
| Change from baseline in eGFR at 6 months, mL/min/1.73m2, mean (SD) | -0.3 (15) |
|  |
|  **ILLUMINATE-B – Extension period (to 30 months)** | **Lumasiran (n=18)** |
| Percent change in spot urinary oxalate: creatinine ratio from baseline to month 30, %b | -76.0 (NR) |
| Absolute change in spot urinary oxalate:creatinine ratio from baseline to Month 30, mmol/mmolb (95% CI) | -0.52 (NR) |
| Proportion of patients with spot urinary oxalate excretion ≤ULN at month 30a | 0.39 |
| Proportion of patients with spot urinary oxalate excretion ≤1.5×ULN at month 30a | 0.72 |
| Absolute change in plasma oxalate from baseline to month 30, μmol/Lb,c (SEM) | -6.94 (1.57) |
| Percent change in plasma oxalate from baseline to month 30, %b,c (SEM) | -42.48 (6.01) |
| Change from baseline in eGFR at 30 months, mL/min/1.73m2, mean (SD) | NR |

Abbreviations: CI, confidence interval; eGFR; estimated glomerular filtration rate; LLOQ, lower limit of quantification; LSM, least squares mean; NR, not reported; SD, standard deviation; SEM, standard error of the mean; ULN, upper limit of normal.

\*\* P value of <0.05 = statistically significant

a Proportion of patients at 6 months with normal or near normal spot (≤1.5xULN, ULN=0.514 mmol/24hr/1.73m2 for 24-hour urinary oxalate corrected for BSA) urinary oxalate excretion but is not a mean change

b Plasma oxalate outcomes were analysed in the Plasma Oxalate Analysis Set, defined as those patients who received any amount of study drug and had baseline plasma oxalate level ≥1.5×LLOQ. LLOQ is 5.55 μmol/L. This included 13 patients in the lumasiran arm.

c LSM was not used

Source:Section 2.5.2, pp77-86 of the submission, ILLUMINATE-B Clinical Study Report 2 (Alnylam Pharmaceuticals Inc. 2020c)

* 1. In ILLUMINATE-B, lumasiran treatment resulted in a statistically significant reduction in spot urinary O:C ratio from baseline to 6 months (LSM percent change: -72.0%; 95% CI: -77.5, -66.4; p<0.001). Patients continued to demonstrate a sustained reduction in urinary O:C ratio through 30 months of lumasiran treatment. The submission considered the percent change in spot urinary O:C ratio from baseline to 6 months and sustained reduction to 30 months to be clinically meaningful.
	2. Lumasiran was associated with a reduction in absolute spot urinary O:C ratio from baseline to 6 months in treated patients (LSM absolute change: -0.49 mmol/mmol [95% CI: -0.52, -0.46], p=NR).
	3. Nine of 18 patients (50%) achieved a urinary oxalate level of near-normal and one patient (5.6%) achieved normalisation of spot urinary O:C ratio levels at 6 months. These numbers increased throughout the extension period, and 13 of 18 patients (72.2%) achieved a urinary oxalate level of near-normal and 7 patients (38.9%) achieved normalisation of spot urinary O:C ratio levels at 30 months.
	4. Lumasiran-treated patients experienced a reduction in absolute change (-5.2; 95% CI: -6.2, -4.2 µmol/L, p=NR) and percent change (-31.7%; 95% CI: -39.5%, -23.9%, p=NR) of plasma oxalate from baseline to 6 months. These reductions were maintained through the extension period.
	5. No change in eGFR was reported from baseline to 6 months. For eGFR, the mean (SD) change from baseline to 6 months was -0.3 (15) mL/min/1.73 m2.

**ILLUMINATE-C — ≥37 weeks gestational age**

* 1. A summary of the results for ILLUMINATE-C for both the primary analysis period (6 months) and extension period (24 months) is provided in Table 7.

Table 7: Primary and secondary outcomes reported in ILLUMINATE-C to 6 months and 24 months

|  |  |  |
| --- | --- | --- |
|  | **Lumasiran Cohort A:** **No dialysis (n=6)** | **Lumasiran Cohort B: Dialysis (n=15)** |
| **ILLUMINATE-C (6-month primary analysis period)** |
| Percent change in plasma oxalate from baseline to Month 6, %, LSM (95% CI) | -33.3 (-81.8, 15.2) | **-42.4 (-50.7, -34.2)\*\*** |
| Absolute change in plasma oxalate from baseline to Month 6, μmol/L, LSM (95% CI) | **-35.3 (-56.3, -14.2)\*\*** | **-48.3 (-55.9, -40.8)\*\*** |
| Percent change in plasma oxalate AUC (0–24 h) between dialysis sessions from baseline to Month 6, %, LSM (95% CI) | NA | **-41.4 (-51.0, -31.8)\*\*** |
| Percent change in BSA-corrected 24-h urinary oxalate from baseline to Month 6, %, LSM (95% CI) | -10.6 (-32.0, 10.9) | NA |
| Absolute change in BSA-corrected 24-h urinary oxalate from baseline to Month 6, mmol/24hr/1.73m2, LSM (95% CI) | -0.53 (-0.89, -0.18) | NA |
| Percent change in spot urinary oxalate:creatinine ratio from baseline to Month 6, %, LSM (95% CI) | -39.5 (-64.1, -14.9) | NA |
| Absolute change in spot urinary oxalate:creatinine ratio from baseline to Month 6, mmol/mmol, LSM (95% CI) | **-0.188 (-0.229, -0.147)\*\*** | NA |
| **ILLUMINATE-C – Extension period (to 24 months)** |
|  | **Lumasiran Cohort A:** **No dialysis (n=6)** | **Lumasiran Cohort B: Dialysis (n=15)** |
| Percent change in plasma oxalate from baseline to Month 24a, %(95% CI) | -60.5 (NR) | -30.6 (NR) |
| Absolute change in plasma oxalate from baseline to Month 24a,μmol/L (95% CI) | -27.9 (NR) | -67.6 (NR) |

Abbreviations: AUC; area under the curve; BSA, body surface area; CI, confidence interval; LSM, least squares mean; NA, not applicable; NR, not reported.

Cohort A - patients not on dialysis; Cohort B: patients on dialysis

\*\* P value of <0.05 = statistically significant

a LSM has not been used

Source: Section 2.5.3, pp86-92 of the submission, ILLUMINATE-C Clinical Study Report 1.

* 1. In ILLUMINATE-C, a reduction in plasma oxalate was reported in both patients not on dialysis (Cohort A) (LSM −33.3%; 95% CI −81.8%, 15.2%, p=0.1299) and on dialysis (Cohort B) (LSM −42.4%; 95% CI −50.7%, −34.2%, p<0.001) from baseline to 6 months. The submission considered the percent change in plasma oxalate from baseline to 6 months to be clinically meaningful. Interim results for the ILLUMINATE-C extension period demonstrated sustained reduction in plasma oxalate in both Cohort A (60.5%) and Cohort B (30.6%) through to 24 months of lumasiran treatment.
	2. Reduction in absolute plasma oxalate levels were reported in both Cohort A (LSM −35.3; 95% CI −56.3, −14.2 μmol/L, p<0.01) and Cohort B (LSM −48.3; 95% CI −55.9, −40.8 μmol/L, p<0.01) from baseline to 6 months.
	3. The percent change in plasma oxalate area under the curve (AUC) (0–24 h) between dialysis sessions from baseline to 6 months was −41.4% (95% CI: −51.0%, −31.8%, p<0.01) in Cohort B.
	4. Lumasiran-treated patients in Cohort A demonstrated a reduction in percentage change (LSM −10.6%; 95% CI: −32.0%, 10.9%, p=NR) and absolute change (LSM −0.53; 95% CI: −0.89, −0.18 mmol/24 h/1.73 m2, p=NR) of urinary oxalate levels from baseline to 6 months.
	5. Lumasiran-treated patients in Cohort A demonstrated reductions in percentage change (LSM −39.5%; 95% CI −64.1%, −14.9%, p=NR) and absolute change (LSM −0.188; 95% CI −0.229, −0.147 mmol/mmol, p<0.01) of spot urinary O:C ratio from baseline to 6 months.

Comparative harms

* 1. A summary of the adverse events (AEs) reported in ILLUMINATE-A, -B and -C to 6 months and through each extension period is presented in Table 8.

**ILLUMINATE-A — ≥6 years of age**

* 1. During the 6-month double-blind period, 22 of 26 patients (85%) in the lumasiran group and 9 of 13 patients (69%) in the placebo group reported at least one AE. The most common AEs that occurred more frequently with lumasiran than with placebo were injection-site reactions (ISRs; 38% vs 0%). No serious or severe AEs were reported, and no deaths occurred.
	2. At 60 months 37 of 39 patients (94.9%) treated with lumasiran reported AEs. AEs related to lumasiran treatment occurred in 19 patients (48.7%). Six patients (15.4%) reported serious AEs, four patients (10.3%) had severe AEs and there were no deaths.

**ILLUMINATE-B — 37 weeks gestational age to <6 years of age**

* 1. All 18 patients (100%) reported at least one AE during the first 6 months of lumasiran treatment. Three patients (17%) experienced treatment-related AEs, including ISRs in two patients and headache in one patient. One patient (6%) had a serious AE, but it was deemed unrelated to the study drug. There were no deaths, severe AEs, or AEs leading to treatment discontinuation.
	2. At 30 months, all 18 treated patients experienced at least one AE, of which AEs in 5 patients (28%) were related to lumasiran. There were no serious AEs beyond the one event reported by one patient during the first 6 months and considered unrelated to lumasiran treatment. There were no severe AEs, AEs leading to treatment discontinuation, or death in patients receiving lumasiran for 30 months.

**ILLUMINATE-C — ≥37 weeks gestational age**

* 1. At 6 months 17 of 21 (81%) patients reported at least one AE, of which AEs in 6 patients (28.6%) were considered related to lumasiran. The most frequently reported treatment-related AEs were pyrexia (29%) and ISRs (24%). Six (29%) lumasiran-treated patients reported serious and 3 (14%) lumasiran-treated patients reported severe AEs, however they were deemed not lumasiran-related. No deaths were reported.
	2. At 24 months, all 21 treated patients (100%) experienced at least one AE. Serious AEs were reported in 15 (71%) patients, with 11 (52%) patients experiencing severe AEs. However, there were no lumasiran-related severe AEs, serious AEs, discontinuations, or withdrawals.

Table 8: Summary of key adverse events in ILLUMINATE-A, -B and -C to 6 months and through extension period

|  |
| --- |
| **ILLUMINATE-A (6 month)** |
| **AE, n (%)** | **Lumasiran (n=26)** | **Placebo (n=13)** | **RR (95% CI)a** |
| Any AE | 22 (85) | 9 (69) | 1.22 (0.82, 1.82) |
| **AE occurring in ≥10% of patients in either group** |
| ISRb | 10 (38) | 0 | NE |
| Headache | 3 (12) | 3 (23) | 0.50 (0.12 to 2.14) |
| Rhinitis | 2 (8) | 2 (15) | 0.50 (0.80 to 3.16) |
| Upper respiratory infection | 2 (8) | 2 (15) | 0.50 (0.80 to 3.16) |
| Any serious AE | 0 | 0 | NE |
| Any severe AE | 0 | 0 | NE |
| Death | 0 | 0 | NE |
| **ILLUMINATE-A extension (60 months)** |
| **AE, n (%)** | **Lumasiran/lumasiran (n=26)** | **Placebo/lumasiran (n=13)** | **All lumasiran (n=39)** |
| Any AE | 25 (96.2) | 12 (92.3) | 37 (94.9) |
| Any serious AE | 5 (19.2) | 1 (7.7) | 6 (15.4) |
| Any severe AE | 4 (15.4) | 0 | 4 (10.3) |
| Death | 0 | 0 | 0 |
| **ILLUMINATE-B (6 month)** |
| **AE, n (%)** | **Lumasiran (n=18)** | **RR (95% CI)** |
| Any AE | 18 (100) | NA |
| **AE occurring in ≥3 patients overall** |
| Pyrexia | 6 (33) | NA |
| Rhinitis | 4 (22) | NA |
| ISRc | 3 (17) | NA |
| URTI | 3 (17) | NA |
| Vomiting | 3 (17) | NA |
| Any serious AE | 1 (6) | NA |
| Any severe AE | 0 | NA |
| Death | 0 | NA |
| **ILLUMINATE-B extensions (30 months)** |
| **AE, n (%)** | **Lumasiran (n=18)** | **RR (95% CI)** |
| Any AE | 18 (100) | NA |
| Any serious AE | 1 (6) | NA |
| Any severe AE | 0 | NA |
| Death | 0 | NA |
| **ILLUMINATE-C (6 month)** |
| AE, n (%) | **Lumasiran Cohort A:** **No dialysis (n=6)** | **Lumasiran Cohort B:** **Dialysis (n=15)** | **Overall(n=21)** |
| Any AE | 5 (83) | 12 (80) | 17 (81) |
| **Any AE occurring in ≥10% of either cohort** |
| Pyrexia | 1 (17) | 5 (33) | 6 (29) |
| ISRd | 1 (17) | 4 (27) | 5 (24) |
| Device-related infection | 0 | 2 (13) | 2 (10) |
| Diarrhoea | 0 | 2 (13) | 2 (10) |
| Vomiting | 1 (17) | 1 (7) | 2 (10) |
| Any serious AE | 1 (17) | 5 (33) | 6 (29) |
| Any severe AE | 0 | 3 (20) | 3 (14) |
| Death | 0 | 0 | 0 |
| **ILLUMINATE-C extension (24 months)** |
| AE, n (%) | **Lumasiran Cohort A:** **No dialysis (n=6)** | **Lumasiran Cohort B:** **Dialysis (n=15)** | **Overall(n=21)** |
| Any AE | 6 (100) | 15 (100) | 21 (100) |
| Any serious AE | 3 (50) | 11 (73) | 15 (71) |
| Any severe AE | 3 (50) | 8 (53) | 11 (52) |
| Death | 0 | 0 | 0 |

Abbreviations: AE, adverse event; CI, confidence interval; HD, haemodialysis; ISR, injection-site reaction; NE, not estimable; NA, not applicable RR, relative risk; URTI, upper respiratory tract infection.

Notes:

a Calculated during evaluation

b Includes AEs of injection-site reaction, injection-site pain, injection-site erythema, injection-site discomfort

c Included symptoms of injection-site erythema, discoloration, and pain at the injection site.

dIncludes AEs of injection-site discoloration, erythema, hematoma

Source: Tables 2.22-2.27, pp95-99 of the submission, ILLUMINATE-C Clinical Study Report 1

Benefits/harms

* 1. A summary of the comparative benefits and harms for lumasiran versus placebo is presented in Table 9**.**

Table 9: **Summary of comparative benefits and harms for lumasiran and placebo**

|  |
| --- |
| Benefits |
| **ILLUMINATE-A: Continuous outcomes (baseline to 6 months)**  | Lumasiran | Placebo | Mean difference: lumasiran vs. placebo (95% CI) |
| N | Mean ∆ baseline  | 95% CI | N | Mean ∆ baseline | 95% CI |
| Percent change in 24-h urinary oxalate excretion from baseline to Month 6, %, LSM | 26 | -65.39 | -71.3, -59.5 | 13 | -11.84 | -19.5, -4.1 | -53.55 (-62.3, -44.8) |
| Proportion of patients with 24-h urinary oxalate ≤1.5×ULN at Month 6 | 26 | 0.84 | 0.64, 0.95 | 13 | 0 | 0.00, 0.25 | 0.84 (0.55, 0.94) |
| Proportion of patients with 24-h urinary oxalate ≤ULN at Month 6 | 26 | 0.52 | 0.31, 0.72 | 13 | 0 | 0.00, 0.25 | 0.52 (0.23, 0.70) |
| Harms |
| **ILLUMINATE-A: Adverse events** **(baseline to 6 months)** | Lumasiran**n/N** | Placebo**n/N** | RR**(95% CI)** | **Event rate/100 patients** | RD with lumasiran**(95% CI)** |
| **Lumasiran** | **Placebo** |
| Any AE | 22/26 | 9/13 | 1.22  | 84  | 69 | 0.15  |
| AE occurring in ≥10% of patients in either group |
| Injection site reaction | 10/26 | 0/13 | NE | 38 | 0 | 0.38 |
| Headache | 3/26 | 3/13 | 0.50  | 12 | 23 | -0.12 |
| Rhinitis | 2/26 | 2/13 | 0.50  | 8  | 15 | -0.08  |
| Upper respiratory infection | 2/26 | 2/13 | 0.50  | 8  | 15 | -0.08  |
| **AEs related to study drug** | 11/26 | 1/13 | 5.50  | 42  | 8 | 0.35  |

Abbreviations:AE, adverse event; CI, confidence interval; h, hour; NA, not applicable; NE, not estimable; RD, risk difference; RR, risk ratio; SD, standard deviation; ULN, upper limit of normal.

Source: constructed during the evaluation, based on data from the CSR and the submission.

* 1. On the basis of the direct evidence presented in the ILLUMINATE-A trial, patients (at least 6 years of age) with PH1 treated with lumasiran in comparison to placebo, over 6 months would on average experience:
* approximately a 54 percentage point greater reduction in 24-hour urinary oxalate excretion from baseline.
	1. On the basis of the direct evidence presented in the ILLUMINATE-A trial (patients at least 6 years of age), for every 100 patients with PH1 treated with lumasiran in comparison to placebo, over 6 months:
* approximately 84 more patients would achieve an improvement in 24-hour urinary oxalate level normalisation (≤ULN) or near-normalisation (≤1.5xULN) from baseline.
* approximately 38 more patients would experience an injection site reaction.

Clinical claim

* 1. The ESC considered that the clinical claim of superior effectiveness compared with BSC alone was adequately supported by the clinical data presented in the submission. However, the magnitude of benefit was uncertain due to the rarity of primary hyperoxaluria type 1 and the associated small number of patients included in the clinical trials.
	2. The ESC noted that while treatment is intended for lifelong use or until patients receives a liver transplant, the long-term effectiveness and safety of lumasiran versus BSC was unknown.
	3. The ESC noted that no comparative data was available for paediatric patients less than 6 years of age. The ESC considered that the superior effectiveness of lumasiran versus BSC observed for individuals ≥ 6 years (ILLUMINATE-A) was likely generalisable to younger children, based on the study results of ILLUMINATE-B (patients were enrolled between 37 weeks estimated gestational age and <6 years).
	4. The submission described lumasiran, when used in addition to BSC, as ’comparable’ in terms of safety compared to BSC alone. The ESC considered that this claim was not adequately supported. While lumasiran appeared to be generally well tolerated in the ILLUMINATE studies, injection site reactions were common for lumasiran-treated patients. For this reason, the ESC considered that lumasiran likely had inferior safety compared to BSC.
	5. The PBAC considered that the claim of superior comparative effectiveness was reasonable.
	6. The PBAC considered that the claim of ‘comparable’ comparative safety was not adequately supported by the data.

Economic analysis

* 1. The submission presented a modelled economic evaluation of lumasiran with BSC compared to BSC alone in patients with PH1. The economic evaluation was based on data from the three ILLUMINATE trials and included additional literature data. The economic analysis was presented as a cost-utility analysis (CUA) over a lifetime time horizon.
	2. Table 10 presents a summary of the model structure and key inputs and rationale of the economic evaluation.

Table 10: Key components of the economic evaluation

| Component | Description |
| --- | --- |
| Treatments | Lumasiran with BSC vs BSC alone |
| Type of analysis | Cost-utility analysis |
| Perspective | Australian healthcare system |
| Outcomes | LYsQALYsCosts |
| Patient cohort | The model assumed the initial cohort to have 70.6% paediatric patients at a mean initial age of 6.9 years and 29.4% adult patients at a mean initial age of 34.2 years (derived from the ILLUMINATE trials). The cohorts entered the model across different distributions of CKD stages. Paediatric: CKD1-2: 22%; CKD3a: 19%; CKD3b: 19%; CKD4: 19%; ESKD: 20%Adult: CKD1-2: 13%; CKD3a: 13%; CKD3b: 13%; CKD4: 19%; ESKD: 42% |
| Time horizon | Lifetime, allowing for up to 100 years (200 model cycles) regardless of patients’ initial age.Sensitivity analyses include time horizon of 20 years. |
| Methods used to generate results | Markov cohort model |
| Health states | The model incorporates 10 health states based on CKD stage (CKD 1-2, CKD 3a, CKD 3b), oxalate levels (for late-stage disease only: CKD 4-OxC, CKD 4-OxU, ESKD-OxC, and ESKD-OxU) and transplantation status (oxalate controlled or not), plus death. |
| Cycle length | 6 months |
| Transition probabilities | Changes in plasma oxalate levels were mapped to transition probabilities signifying progression of CKD disease stage, based on ILLUMINATE trial data and two published studies by Singh et al. (2022) and Shah et al. (2020). Transitions to cLKT were calculated based on data from Metry et al. (2022) and re-transplantations were modelled based on data from Compagnon et al. (2014).Mortality for patients in CKD 1-2 was assumed equal to age-and gender-specific general population mortality, derived from Australian life tables. For higher severity CKD health states, mortality multipliers were applied to general population rates, based on data from Go et al. (2004). Mortality post-cLKT was modelled separately for patients with controlled vs uncontrolled oxalate levels prior to transplantation based on Jamieson (2005). |
| Exploration method | The model assumed that lumasiran was 100% effective in stopping CKD progression, based on observations of plasma oxalate. The model assumed that patients receiving lumasiran who do start in, or progress to the CKD 4-5 stage (due to age-related decline in kidney function equivalent to the general population) would be treated with normal-intensity dialysis and would achieve oxalate control within 2 years. Treatment effectiveness of lumasiran was assumed to be maintained over time, with no loss of therapeutic effect. Treatment discontinuations were modelled for those in the CKD1-3b health states—a time-on-treatment curve was derived from ILLUMINATE A and B patient-level data obtained at the 12-month cut off. Beyond 12 months, time-on-treatment was extrapolated by fitting parametric models to the observed data. For patients receiving lumasiran in the CKD4-5 health states, a discontinuation rate of zero was applied, based on the observation of no discontinuations in ILLUMINATE-C within the first 6 months. |
| Utility values | Each health state (defined by CKD stage [including post cLKT states] and oxalate level) was assigned a utility value. Utility values differed depending on the type of dialysis, which was assigned based on treatment received (lumasiran or BSC). The health state utility values were obtained from a variety of sources, including pooled patient-level EQ-5D data from the ILLUMINATE A trial (CKD1-3b health states), a vignette study conducted by the sponsor (CKD 4-5 health states with uncontrolled oxalate on high-intensity dialysis, and the post-cLKT states), or via adjustments to the early-stage health state utility values (remaining states). The model applied different utilities for paediatric and adult patients. The health state utility values are listed below.Health state utility valuesPaediatric * CKD 1 to 3b: 0.851
* CKD 4-OxU/C + normal-intensity dialysis, CKD 4-OxC + high-intensity dialysis: 0.683
* CKD 4-OxU + high-intensity dialysis: 0.283
* CKD 5-OxU + normal-intensity dialysis: 0.433
* CKD 5-OxC + normal-intensity dialysis, CKD 5-OxC + high-intensity dialysis: 0.486
* CKD 5-OxU + high-intensity dialysis: 0.202
* Post-LKT: 0.855

Adult* CKD 1 to 3b: 0.963
* CKD 4-OxU + normal-intensity dialysis: 0.764
* CKD 4-OxC + normal-intensity dialysis, CKD 4-OxC + high-intensity dialysis: 0.783
* CKD 4-OxU + high-intensity dialysis: 0.586
* CKD 5-OxC + normal-intensity dialysis, CKD 5-OxC + high-intensity dialysis: 0.575
* CKD 5-OxU + normal-intensity dialysis: 0.532
* CKD 5-OxU + high-intensity dialysis: 0.246
* Post-LKT: 0.765

Disutility values were applied for renal stone events, systemic oxalosis manifestations not captured via the defined health state utility value, transplant, graft failure and treatment-related AEs. A caregiver disutility was also included in the model base case, applied to the CKD4 and CKD 5 health states. Inclusion of a caregiver disutility in the base case does not align with the PBAC Guidelines (Version 5.0).  |
| Discount rate | 5% costs and outcomes  |

Abbreviations: AE, adverse event;BSC**,** best supportive care; CKD, chronic kidney disease; ESKD, end-stage kidney disease; cLKT, combined kidney liver transplant; LY, life-years; NR: not reported; OxC, controlled oxalate levels; OxU, uncontrolled oxalate levels; QALY, quality-adjusted life-years; SD, standard deviation.

Source: Table 3.1 and Table 3.33, p99 of the submission.

* 1. The economic model applied a lifetime time horizon with a 6-month cycle length. The patients transitioned through health states defined by CKD stages (Figure 2). Plasma oxalate levels and transplant status were used to further stratify late CKD stages (4 and 5). All patients in the model could transition to death. These health states were able to capture key clinical events, costs and quality of life changes for patients’ disease progression. The model assumed that both paediatric and adult patients follow a similar pathway for disease progression. There were no structural variations for different age groups, which the evaluators considered to be a reasonable simplification in the modelling design. The ESC noted that the extrapolation of short-term clinical data over a lifetime introduced uncertainty. However, it was noted that the model was not sensitive to reducing the time horizon from a lifetime to 20 years. Overall, the ESC considered that the choice of the health states, the time horizon and the cycle length were likely reasonable.

Figure 2: Markov model structure



Source: Figure 3.2, p103 of the submission

Abbreviations: CKD, chronic kidney disease; cLKT combined liver–kidney transplantation; ESKD end-stage kidney disease; OxC, controlled oxalate levels; OxU, uncontrolled oxalate levels; PH1, primary hyperoxaluria type 1

Notes: A threshold of 50 μmol/L was used to distinguish controlled vs. uncontrolled oxalate based on the treatment target in PH1 identified from the literature

* 1. The cohorts entered the model across different distributions of CKD stages, with more early-stage disease in paediatric patients compared to adults (see Table 10).
	2. The starting CKD distributions were informed by Singh et al. (2022) and modified based on input from Australian PH1 experienced specialists. Compared with Singh et al. (2022) the specialists suggested that a larger proportion of patients with PH1 in Australia present in CKD 3 and CKD 4, while a smaller proportion present in CKD 1-2. Therefore, the distributions published by Singh et al. (2022) were modified by halving the proportion of the cohort in CKD 1-2 and redistributing this proportion equally across the CKD 3 and CKD 4 health stages. Patients entering the model in the late-stage health states were assumed to have uncontrolled oxalate levels, i.e., higher than the threshold of 50 μmol/L.
	3. Changes in plasma oxalate levels were mapped to transition probabilities for progression of CKD disease stage, based on ILLUMINATE trial data and two observational studies, Shah et al. (2020) and Singh et al. (2022). According to Shah et al., there is a mean absolute eGFR decrease of 1.27 mL/min/1.73 m2 per 1 μmol/L increase in plasma oxalate. Together, these values were used to estimate the transition rate per cycle across pre-ESKD health states (from CKD 1-2 to CKD 3a, from CKD 3a to CKD 3b, and from CKD 3b to CKD 4) in the BSC cohort. For example, the increase in plasma oxalate concentration (2.23 μmol/L) calculated for the placebo arm of the ILLUMINATE-A trial corresponded to a per-cycle decrease in eGFR of 2.83 units based on the relationship between oxalate and eGFR quantified by Shah et al (2021). The ESC noted that the 2.23 μmol/L applied to this calculation could not be verified. The pre-PBAC response clarified that the patients included in the analysis conducted for the economic model differed to that presented in the CSR and the submission (Table 4). The assumed increase in plasma oxalate of 2.23 μmol/L applied to the economic model was higher than the change from baseline to Month 6 presented in the CSR (1.25 μmol/L).
	4. Transition from CKD 4 to ESKD was based on the mean annual decline in eGFR reported by Singh et al. (2022) for patients with PH1 who were in CKD 4 (‑16.6 mL/min/1.73 m2). The per-cycle change in eGFR for CKD 4 was obtained by dividing the mean annual change by two (i.e., -8.3 mL/min/1.73 m2) to match the 6‑month model cycle length.
	5. The ESC noted that plasma oxalate results can vary substantially due to the use of different analytes, the lack of calibrators and the lack of appropriate quality assurance material (Stokes et al. 2020) and in clinical practice urinary oxalate excretion is generally a more widely accepted marker to predict kidney function decline.The ESC also noted that the evaluation considered that the quality of reporting for this outcome was poor, with many unverifiable values used in the model, and for this reason the plasma oxalate as a surrogate outcome used to build the model was unlikely to be appropriate, which made the economic model highly uncertain. The PSCR stated change in eGFR is gradual and therefore its assessment, in a realistic time frame for a clinical trial, is not feasible in PH1. The PSCR also stated that as there are no studies available that define the relationship between changes in urinary oxalate and eGFR, urinary oxalate data could not be used directly to model changes in eGFR over time in the economic model. The PSCR stated that the mapping of plasma oxalate is clinically valid and there is widely published association of plasma oxalate and eGFR. Overall, the ESC considered that while the transformation calculations were complex and associated with some uncertainty, the use of plasma oxalate in the economic model was likely reasonable. However, the ESC considered that the studies sourced for the mapping calculations had separate limitations and uncertainties and how these collectively compounded and impacted the economic model was unclear.
	6. The evaluation considered that the modelled kidney function decline in the BSC arm was associated with a number of issues. Firstly, patients in the CKD1-2 health states in the BSC arm were subject to a ~50% faster rate of disease progression than what was reported in Singh et al. 2022. Moreover, the submission applied a population background kidney function decline for patients >30 years in the BSC arm in addition to the disease progression modelled based on data from PH1 patient cohorts, exacerbating disease progression. The ESC considered that applying PH1 decline in addition to the background population decline was likely double counting and therefore overestimated the disease progression in the BSC arm.
	7. Patients in the lumasiran arm of the model had a complete halt of disease progression (100% effective), with patients not progressing until the age of 30, then the population background kidney function decline was assumed. The assumption of 100% efficacy was based on the effects in oxalate control from the ILLUMINATE A trial. However, the pivotal trials and the clinical evidence base were limited, which prevented any reliable extrapolation modelling of the drug effectiveness in the long-term. The short-term effectiveness of lumasiran was assumed to last for a lifetime. The submission justified this assumption based on the following: 1) data from extension studies showing sustained therapeutic effect over the duration of follow-up (to 60 months) in patients treated with lumasiran, including sustained kidney function as measured by eGFR; 2) the mechanism of action of lumasiran, which selectively and durably silences the mRNA for the enzyme glycolate oxidase in the liver; 3) lack of evidence from preclinical or clinical studies to suggest the potential for tachyphylaxis (rapidly diminishing response to successive doses) with lumasiran; 4) lack of recognised mechanisms by which the biological pathways responsible for PH1 could adapt, so that patients develop tolerance to chronic administration of hepatic glycolate oxidase enzyme RNAi-silencing therapeutics. In the absence of robust clinical data, these assumptions were subject to a number of uncertainties and the economic model was not programmed to allow the examination of a scenario of potential long-term treatment waning.
	8. Transition from CKD4 to CKD5/ESKD health states in the lumasiran arm were based on the observed effects of lumasiran on plasma oxalate in ILLUMINATE-C.
	9. For the CKD4 and ESKD health states, a threshold of 50 μmol/L was used to distinguish between controlled vs. uncontrolled oxalate based on the treatment target in PH1 identified from the literature. [[10]](#footnote-11),[[11]](#footnote-12),[[12]](#footnote-13) All patients in the BSC arm were assumed to have uncontrolled oxalate. For these late CKD stages, the economic model may not reflect current clinical practice in Australia. Patients in CKD5 could receive consistent intensive dialysis for prolonged periods, and up to 80% of their lifetime or 20 years until they die. This was likely not justified. An annual transplant probability of 0.8% (Metry et al 2022[[13]](#footnote-14)) was applied to all patients in any of the CKD4 or 5 health states, regardless of adequate oxalate control. Patients in early CKD stages were assumed to not be considered for transplant. The submission did not distinguish between a combined or sequential transplant, and CKD4 and 5 patients also shared the same transplant priority via the same probability. The ESC considered that these assumptions and the applicability of a transplant rate, based on European data from 1978−2018, to the Australian setting were all subject to uncertainty.
	10. Treatment discontinuations were modelled in the early CKD health states (CKD1–3b) using patient-level data from the ILLUMATE-A and -B trials, extrapolated through the fitting of parametric models to the observed data. Treatment discontinuations were not modelled in the late-stage heath states (CKD4–5), based on the observation of no discontinuations in ILLUMINATE-C within the first 6 months. The extrapolation of the patient-level data from the ILLUMINATE-A and -B trials to inform treatment discontinuation in the early-stage health states was appropriate; nevertheless, the extrapolations were based on 12-month trial data therefore their long-term applicability is unclear. There is a high degree of uncertainty in assuming patients with late-stage disease do not discontinue treatment. Nevertheless, this assumption appears to favour the comparator; adding treatment discontinuations for these late disease stages reduces the incremental cost-effectiveness ratio (ICER).
	11. Mortality multipliers were applied to the general population mortality according to CKD health state membership. The multipliers were based on a retrospective database analysis by Go et al. (2004)[[14]](#footnote-15) of longitudinal eGFR data (CKD1-2: 1.0; CKD3a: 1.2; CKD3b: 1.8; CKD4: 3.2; CKD5: 5.9). The ESC considered that the applicability of Go et al. (2004) to the CKD 3a and 3b health states was uncertain.
	12. Data published by Jamieson et al. (2005)[[15]](#footnote-16) were used to model overall survival following transplantation. Kaplan-Meier (KM) curves were digitised, and patient-level data were reconstructed via the Guyot method (based on the published number at risk). The submission assumed that patients in better clinical condition before transplant would have better post-transplant outcomes compared to those that were in a worse clinical condition. Mortality post-transplantation was therefore modelled separately for patients with controlled vs uncontrolled oxalate levels prior to transplantation. The ESC noted that the use of different survival outcomes depending on oxalate control assumes improved post-transplantation outcomes for patients in the lumasiran arm relative to the BSC arm, given the majority of patients in the lumasiran arm receive transplantation from a controlled oxalate state, while all patients in the BSC arm receive transplantation from an uncontrolled oxalate state. The ESC considered there was some uncertainty related to whether these projected outcomes reflect the true benefits of lumasiran post-transplantation, however considered the modelled mortality was likely reasonable.
	13. The likelihood of complications associated with systemic oxalosis in patients with late-stage CKD and uncontrolled oxalate was obtained from a survey of UK PH1 clinical experts (the sponsor consulted with Australian PH1 experts, who were stated to validate these assumptions as reasonably representative of Australian patients; this communication was not provided with the submission). The submission stated that given that systemic oxalosis is associated with incomplete renal clearance of oxalate, which is typically observed after CKD 3b in PH1, no systemic oxalosis complications were assumed to occur for CKD 1–3b health states. The probability of experiencing systemic oxalosis complications in the economic model is shown in Table 11. A 20% relative reduction was applied to the values observed in patients with late-stage CKD and uncontrolled oxalate levels to estimate the probability of complications for patients with controlled oxalate levels. Whether systemic oxalosis outcomes for patients treated with lumasiran differ is unknown, with no evidence provided to support the assumption.

Table 11: Probability of systemic oxalosis complications in CKD 4 and ESKD health states

|  |  |
| --- | --- |
| Systemic oxalosis complication | Probability per cycle |
| **CKD 4-OxU** | **ESKD-OxU** | **CKD 4-OxC** | **ESKD-OxC** |
| Bone | 30% | 80% | 24% | 64% |
| Cardiac | 15% | 40% | 12% | 32% |
| Cutaneous and vascular | 15% | 35% | 12% | 28% |
| Ophthalmic | 18% | 40% | 14% | 32% |
| Neurologic | 18% | 40% | 14% | 32% |

Abbreviations: CKD, chronic kidney disease; ESKD, end-stage kidney disease; OxC, controlled oxalate levels; OxU, uncontrolled oxalate levels
Source: Table 3.19, p 119 of the submission.

* 1. In the economic model, the intensity of dialysis (normal- vs high-intensity) was modelled according to the treatment received. Patients receiving lumasiran treatment were assumed to receive normal intensity dialysis (according to the submission, given the use of lumasiran to control oxalate levels). Patients receiving BSC were assumed to receive high-intensity dialysis (according to the submission, given regular dialysis regimens are unable to counteract the high rate of oxalate production in patients in uncontrolled oxalate health states). Overall, 50% of the adult population and 100% of the paediatric population in CKD4, and 100% of the CKD5 health states were assumed to receive dialysis. The evaluation considered that the assumption of high-intensity dialysis regimens for patients with PH1 appears consistent with clinical practice guidelines. The submission suggested the assumed dialysis regimens were confirmed as reasonable by Australian PH1 experts (communication not provided with the submission). However, the evaluation considered that it remained unclear to what extent lumasiran may reduce the need for intensified dialysis regimens in practice. The model cohorts spent a considerable proportion of time in the CKD4 and CKD5 health states (43.3 and 29.2 years for paediatric patients in the BSC and lumasiran arms, respectively; 25.2 and 21.9 years for adult patients in the BSC and lumasiran arms, respectively); indicating the assumed benefits of reduced dialysis intensity are accumulated over many years. The assumed reduction in dialysis intensity due to lumasiran treatment has a large impact on incremental costs. Overall, total cost (discounted) for dialysis were $385,354 and $1,491,832 for lumasiran and BSC arms, respectively (incremental discounted cost of -$1,106,478, reflecting ~-||| |||% of total incremental cost).
	2. Renal stone events were incorporated for patients in the CKD1-5 health states using data from the ILLUMINATE trials. Estimates of annualised renal stone event rates derived from the data were applied in each cycle of the model, with the rates used in Cycle 1 (or Cycle 2) applied consistently for all subsequent cycles. A large benefit in terms of a reduced number of renal stone events was attributed to lumasiran. This benefit was highly uncertain. Notably, imbalances in the baseline rates between the lumasiran and placebo groups were evident in the ILLUMINATE A trial, potentially introducing confounding to the result. For the CKD4-5 health states, baseline (‘pre-intervention’) data from the ILLUMINATE C trial were used to inform the renal stone event rate for the BSC arm, while 12 months data were used for the lumasiran arm. . A sensitivity analysis undertaken during the evaluation in which the impact of renal stone events was not considered (i.e. per event cost and disutility inputs were both set to zero) led to a small increase in the ICER of +||| |||% (ICER: $455,000 to < $555,000 per quality adjusted life year [QALY] relative to the base case ICER of $455,000 to < $555,000 per QALY).
	3. The incidence of treatment-related AEs were based on 6-month data from ILLUMINATE-A. Treatment-related AEs reported by at least 10% of patients in either arm of the trial were included in the model. The costs for treatment-related AEs were only captured in the initial cycle of the model (6 months), although utility decrements appear to have been captured beyond the first cycle. This was likely inappropriate. The Pre-PBAC Response noted that this discrepancy in the model had minimal impact on the ICER.
	4. The submission used a variety of sources to inform the health state utility values applied in the economic model, including the ILLUMINATE-A trial, primary research conducted by the Sponsor (i.e. a vignette study) and additional published peer-reviewed literature (Table 10). The use of patient-level ILLUMINATE-A trial EQ-5D data, adjusted using Australian weights to inform the health state utility for the CKD 1 to 3b states was appropriate and applicable to the Australian context.
	5. The health state utilities derived from ILLUMINATE-A were adjusted using decrements sourced from peer-reviewed literature to estimate the relative impact of CKD 4 and CKD 5 with controlled oxalate levels, compared to early CKD states. Adjusting ILLUMINATE-A provides internal consistency, as the data were carried over from CKD 1 to 3b health states. There were limited to no data available on PH1-related CKD 4 and CKD 5 for patients with controlled oxalate. Therefore, decrements where sourced from 5 published articles on populations that did not have PH1-related CKD. The use of non-PH1 related CKD decrements to value the health state utilities for CKD 4 and CKD 5 with controlled oxalate levels states relies on the assumption that the relative utility decrements from non-PH1 studies apply equally to PH1 patients. This may not accurately reflect the unique burden of PH1. The ESC noted that the same utility value was applied to the CKD-4 and -5 normal and high intensity dialysis health states (paediatric: 0.683; adult: 0.783) and considered that this was likely inappropriate.
	6. The ESC considered the application of the vignette study to obtain utilities for the CKD 4, CKD 5 and LKT with uncontrolled oxalate health states using a time-trade off (TTO) method was likely not appropriate. The submission provided only limited information on the study design, sample population, healthcare context and study aim. The study design was further complicated due to the study being designed to capture HRQoL utility values in patients with a rare disease, including children. The ESC further noted that the vignette study reported very low utility values (e.g. CKD uncontrolled – normal dialysis vs high-intensity: 0.663 vs 0.283), particularly in comparison to the CKD1-3b health states, where for adults a high 0.963 utility was assumed. The ESC considered the reduction in utilities assumed for more severe disease health states compared to early stages of disease was over-estimated and a key driver of the model. The ESC advised that utilities from ILLUMINATE-C should be used to inform the later states of disease in the model. The Pre-PBAC Response maintained that the low utility values applied to the economic model appropriately reflected the devasting impact severe PH1 has on the physical and mental health of patients. The response also stated that the quality of life data from ILLUMINATE-C were not applied to the economic model because it was considered to be unreliable due to small sample sizes and stated that individual EQ-5D index scores from adults in ILLUMINATE-C were higher than general population norms and therefore lacked credibility. The Response provided sensitivity analyses which applied EQ-5D derived utilities from the vignette study (stated to include negative values) and a subgroup of the ILLUMINATE-C study. Both analyses resulted in reductions to the ICER (the values applied to the model were not provided).
	7. The use of multiple sources to value health state utility values introduces several uncertainties into the economic evaluation. Different methods or populations may interpret or value health states differently. The vignette study relied on the general population to value health states of which they have no lived experience, while the late-stage health states were based on clinical trial data sourced from a PH1 cohort, adjusted for CKD stage based on relative adjustments sourced from non-PH1 cohorts. Overall, the lack of consistency across sources makes it challenging to gain a uniform understanding of how the impact of dialysis treatment and oxalate control on patient quality of life was modelled. The ESC considered that utilities assumed for the economic model were highly uncertain. The ESC further noted that a range of disutility values, from a variety of sources and conditions (e.g. general liver transplant [-0.095], graft failure [-0.055], system oxalosis [ranging between -0.041 to -0.234], renal stones [-0.064]), had been applied on top of the health state utilities, and considered there was a high likelihood of double counting, which would favour the lumasiran arm due to the substantial time the BSC arm was assumed to spent in the uncontrolled ESKD health state compared to the lumasiran arm (Figure 3).
	8. The ESC noted that the Markov traces of the economic model (Figure 3) illustrated that paediatric and adult patients in the BSC arm spend a considerable number of years over a lifetime in the uncontrolled ESKD health state compared to lumasiran patients. A considerable mortality benefit for lumasiran patients versus BSC was also modelled. The ESC considered the substantial life-long benefits modelled for lumasiran over BSC, based on relatively short clinical trial evidence, were highly uncertain.

Figure 3: Markov traces of the economic model



Source: Submission economic model, Oxlumo Section 3 CUA.xlsm

* 1. The economic model included a caregiver disutility in the base case analysis to capture how caregivers are impacted by the illness experienced by PH1 patients. The values focus on the impact of advanced kidney disease (CKD 4 and CKD 5) on caregiver QoL. No disutility values were calculated or applied to CKD 1–3b health states, as these states were assumed to have no activity limitation. The disutility values were informed by an observational study conducted by the sponsor, which compared the health burden on caregivers of children with and without abnormal renal function. The EQ-5D values were adjusted to Australian weightings. The inclusion of caregiver disutilities in the base case analysis is not aligned with the PBAC Guidelines (Version 5.0). The PSCR maintained that the inclusion of a caregiver disutility was appropriate. The ESC advised that the inclusion of a caregiver disutility in the base case analysis was not appropriate and does not align with the PBAC Guidelines (Version 5.0), although the guidelines allow for a broader societal perspective to be presented as a supplementary analysis. Exclusion of the caregiver disutility increased the ICER from $455,000 to < $555,000 per QALY to $455,000 to < $555,000 per QALY (+||| |||%).
	2. The drug costs were calculated from a patient’s weight given lumasiran had a weight-based regimen. The submission assumed a constant weight for both paediatric and adult patients. Weight growth for children before reaching adulthood was not considered, resulting in the drug consumption and cost to be underestimated.
	3. The submission assumed 99% treatment compliance, and 80% as a sensitivity analysis value. As the variations of treatment compliance was only on the cost of lumasiran (as an additional multiplier to the drug price), this was essentially a sensitivity analysis for the price of lumasiran and demonstrated the drug cost to be a key driver of the ICER.
	4. The key drivers of the model were presented in Table 12. Sensitivity and scenario analyses presented below were run on an alternative base case excluding the caregiver disutility.

Table 12: Key drivers of the model

| Description | Method/Value | ImpactAlternate base case: $|||| 1 per QALY gained |
| --- | --- | --- |
| CKD4 and CKD5 utilities | While occupying a late-stage CKD health state, patients treated with BSC remain in an uncontrolled oxalate state while those treated with lumasiran spend most of the time in a controlled oxalate state. Moreover, lumasiran was assumed to remove the need for intensified dialysis. Utilities were assigned differentially based on oxalate control and dialysis regimen.The true benefits of lumasiran in reducing the need for intensified dialysis or reducing the occurrence of systemic oxalosis manifestations is not yet established.  | High, favours lumasiran.A scenario analysis undertaken during the evaluation in which the health state utility values for the CKD4 and CKD5 states were set to be equal irrespective of the assumptions around improved oxalate control or reduced dialysis intensity (i.e. set to the utility for high-intensity dialysis and uncontrolled oxalate) increased the ICER by 40.1%.Setting systemic oxalosis disutility values to zero in addition further increased the ICER, by 66.5% (systemic oxalosis disutility decrements were also built into the post-cLKT states). |
| Lumasiran treatment benefit  | For the lumasiran arm, an assumption of a complete halt of disease progression (100% effective) was specified where patients would not progress until the age of 30, then the population background kidney function decline was assumed. The true effectiveness on lumasiran in halting progression of CKD is unknown. Assuming 100% effectiveness may be optimistic. | High, favours lumasiran.A scenario analysis of setting the probabilities of progression between CKD stages to be equal across arms (to the literature-based values without background population decline adjustments) increased the ICER by 18.4%. Additionally setting the probability of transition between controlled and uncontrolled states to zero further increased the ICER, by 32.2% (under this scenario, lumasiran was still associated with reduced dialysis intensity and associated utility benefits, as this was not assigned solely based on health state). |
| Disease progression in BSC arm | For the BSC arm, disease progression modelling was derived using the ILLUMINATE-A trial and literature data. The method led to rapid kidney function decline.  | Likely moderate, favours lumasiran. As worse CKD disease stages correspond to higher costs and lower utilities, a rapid decline in patients disease status would lead to higher costs (predominantly dialysis) and more significant disutilities, hence favouring lumasiran.Scenario analysis undertaken during the evaluation exploring alternate methods to model progression in the BSC arm and found the ICER could be underestimated by ~7.4%. |
| Dialysis costs | The intensity of dialysis (normal- vs high-intensity) was modelled according to treatment received (lumasiran vs BSC, respectively). It remains unclear to what extent lumasiran may reduce the need for intensified dialysis regimens.  | Moderate, favours lumasiranA sensitivity analysis undertaken during the evaluation in which the costs for dialysis were set to be equal across arms (i.e. set to the cost for high-intensity dialysis across both arms) reported an increase in the ICER of 9.5%. |
| Initial cohort distribution | The submission modified the initial CKD severity to have more patients in the CKD 4 and 5 in the initial cohort. Worse CKD stages were associated with higher costs and lower utility for patients in the BSC arm, predominately driven by dialysis and other comorbidities such as systemic oxalosis. Therefore, to have patients with more severe disease in the initial cohort would make BSC arm seem worse. | Moderate, favours lumasiran.A sensitivity analysis undertaken during the evaluation in which the original literature-based values prior to adjustment were used reported an increase in the ICER of 7.9%. |

Abbreviations: BSC, best supportive care; CKD, chronic kidney disease; ESKD, end-stage kidney disease; QALY, quality-adjusted life-years; ICER, incremental cost effectiveness ratio, TTO, time trade off.

The redacted values correspond to the following ranges:

1 $455,000 to < $555,000

* 1. The results of the modelled economic evaluation are presented in Table 13. Results under the alternative base case scenario are included in italics.

Table 13: Results of the modelled economic evaluation (discounted)

|  | Lumasiran | BSC | Increment |
| --- | --- | --- | --- |
| Costs | $|||| | $1,953,419 | $|||| |
| Life years gained | 18.71 | 17.46 | 1.26 |
| QALYs gained | 12.18*13.51* | 3.12*5.26* | 9.06*8.25* |
| Incremental cost per life year gained | **$|||| 1** |
| Incremental cost per QALY gained | **$|||| 2*****$||||*  2** |

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LY, life-year; QALY, quality-adjusted life-year

Source: Table 3.48 and 3.49, pp148-149 and The Excel workbook of the submission (Oxlumo Section 3 CUA HPP009243.xlsm, economic model of the submission).

Italics: alternative base case

The redacted values correspond to the following ranges:

1 > $1,055,000

2 $455,000 to < $555,000

* 1. The ESC considered that the ICER for the model base case was high and uncertain. The ESC noted that the QALYs accrued in the BSC arm, over a lifetime time horizon, were implausibly low (discounted: 3.12; undiscounted: 9.13 vs lumasiran discounted: 12.18; undiscounted: 37.87) when considering 70% of the cohort comprised of paediatric patients with a median survival time of 60 years. The ESC noted this was due to paediatric and adult patients in the BSC arm spending a considerable number of years over a lifetime in the uncontrolled ESKD health state compared to lumasiran patients (to which a very low utility value was applied) (Figure 3).
	2. The incremental costs for healthcare resource used in the economic evaluation are summarised in Table 14. It was observed that the key drivers of the costs were lumasiran, dialysis, and systemic oxalosis.
	3. The cost associated with the treatment of lumasiran for each patient in the model over a lifetime time horizon was $||| ||| million discounted ($||| ||| million undiscounted). For the lumasiran arm, costs were predominately accrued in the early CKD stages and in the controlled CKD 4 and ESKD states. For BSC, costs were accrued predominately in the ESKD uncontrolled health state. Both the dialysis and the management of systemic oxalosis were presented as cost savings to offset the lumasiran costs. As noted above, it may not be realistic to allow patients to remain on intensive dialysis for 60% to 70% of their life. Therefore, the dialysis cost offset may be significantly overestimated. Further, transplant costs were small in the model base case. This was possibly due to the assumed low probability of patients receiving transplant until very late CKD stages.

Table 14: Disaggregated summary of costs (discounted) in the economic evaluation

| **Item**  | **Lumasiran** | **BSC** | **Incremental** | **% of total incremental** |
| --- | --- | --- | --- | --- |
| **Entire cohort** |
| **Cost across type of resource item** |
| Drug | $|||| | $6,762 | $||||  | ||||% |
| Administration cost | $19,742 | $0 | $19,742  | ||||% |
| Monitoring | $18,532 | $32,316 | -$13,784 | -||||% |
| Dialysis | $385,354 | $1,491,832 | -$1,106,478 | -||||% |
| RSE | $22,794 | $57,084 | -$34,290 | -||||% |
| Systemic oxalosis | $135,413 | $340,339 | -$204,926 | -||||% |
| Post cLKT | $15,885 | $23,688 | -$7,803 | -||||% |
| AEs | $2,339 | $1,398 | $941  | ||||% |
| **Total** | **$||||** | **$1,953,419** | **$||||**  | **100.00%** |
| **Cost across health state** |
| CKD 1-2 | $|||| | $6,035 | $||||  | 23.48% |
| CKD 3a | $|||| | $4,662 | $||||  | 19.87% |
| CKD 3b | $|||| | $2,704 | $||||  | 21.96% |
| CKD 4-OxC | $|||| | $0 | $||||  | 30.64% |
| CKD 4-OxU | $|||| | $50,849 | -$|||| | -0.32% |
| ESKD-OxC | $|||| | $0 | $||||  | 44.27% |
| ESKD-OxU | $|||| | $1,865,482 | -$|||| | -39.72% |
| cLKT-OxC | $|||| | $0 | $||||  | 0.33% |
| cLKT-OxU | $|||| | $23,688 | -$|||| | -0.52% |
| **Total** | **$||||** | **$1,953,419** | **$||||**  | **100.00%** |

Abbreviations: CKD, chronic kidney disease; ESKD, end stage kidney disease; cLKT, combined liver kidney transplantation; BSC, best supportive care; RSE, renal stone event; AEs, adverse events; OxC, controlled oxalate levels; OxU, uncontrolled oxalate levels; Source: Table 3.50 and 3.51, pp149- and the Excel workbook of the submission (Oxlumo Section 3 CUA HPP009243.xlsm, economic model of the submission).

* 1. The majority of QALYs accrued with lumasiran were accumulated in early health states. Patients with adequate oxalate control in the CKD 4 health state also had significant QALY gains, whereas the QALYs accrued by CKD 5 (ESKD) patients was substantially reduced due to inadequate oxalate control where intensive dialysis and other treatment of morbidities were applied.

Table 15: Disaggregated health outcomes (discounted) for the overall population

|  |
| --- |
| QALYs by health state |
| **Item**  | **Lumasiran** | **BSC** | **Incremental** | **% of total incremental** |
| CKD 1-2 | 2.74 | 0.75 | 1.99  | 21.96% |
| CKD 3a | 2.31 | 0.58 | 1.73  | 19.09% |
| CKD 3b | 2.48 | 0.33 | 2.15  | 23.73% |
| CKD 4-OxC | 2.00 | 0.00 | 2.00  | 22.08% |
| CKD 4-OxU | 0.04 | 0.09 | -0.05 | -0.55% |
| ESKD-OxC | 1.76 | 0.00 | 1.76  | 19.43% |
| ESKD-OxU | 0.07 | 0.58 | -0.51 | -5.63% |
| cLKT-OxC | 0.73 | 0.00 | 0.73  | 8.06% |
| cLKT-OxU | 0.05 | 0.79 | -0.74 | -8.17% |
| **Total** | **12.18** | **3.12** | **9.06** | **100.00%** |

Abbreviations: cLKT, combined liver kidney transplantation; BSC, best supportive care; CKD, chronic kidney disease; ESKD, end stage kidney disease; QALY, quality-adjusted life-year; OxC, controlled oxalate levels; OxU, uncontrolled oxalate levels

Source: Table 3.50 and 3.51, p151 and the Excel workbook of the submission (Oxlumo Section 3 CUA HPP009243.xlsm, economic model of the submission).

* 1. The results of sensitivity analyses are presented in Table 16. To ensure the consistency of the modelling perspective with the PBAC guidelines (Version 5.0), the caregiver disutility was removed, and an alternate base case provided. The updated base case was $455,000 to < $555,000 per QALY gained. Sensitivity and scenario analyses presented in Table 16 are based on the alternative base case.

Table 16: Results of sensitivity and scenario analyses

| **Analyses** | **Incremental cost** | **Incremental QALY** | **ICER****$** | **Change from base case ICER** |
| --- | --- | --- | --- | --- |
| Base case | $|||| | 9.06 | $|||| 1 | - |
| Alternative base caseNo caregiver utility reduction | $|||| | 8.25 | $|||| 1 | - |
| **Discount rate (base case 5% costs and outcomes)** |
| 0% costs and outcomes | $|||| | 27.09 | $|||| 1 | -||||% |
| 3.5% costs and outcomes | $|||| | 10.87 | $|||| 1 | -||||% |
| **Time horizon (base case was for lifetime)**  |
| Time horizon of 10 years  | $|||| | 2.99 | $|||| 1 | ||||% |
| Time horizon of 20 years | $|||| | 5.33 | $|||| 1 | ||||% |
| **Utility** |  |  |  |  |
| EQ-5D derived utilities | $|||| | 13.30 | $|||| 2 | -||||% |
| Remove systemic oxalosis-related disutility values | $|||| | 7.53 | $|||| 3 | ||||% |
| Remove all disutility values | $|||| | 7.14 | $|||| 3 | ||||% |
| Set CKD4-5 health state utility values equivalent for lumasiran and BSC (by setting to high-intensity Oxu health state utility values)  | $|||| | 5.89 | $|||| 4 | ||||% |
| Set CKD4-5 health state utility values equivalent for both lumasiran and BSC (by setting to high-intensity Oxu health state utility values) and set SO disutility decrements to zero  | $|||| | 4.95 | $|||| 5 | ||||% |
| **Inclusion of renal stone events** |  |  |  |  |
| Remove renal stone events (by setting cost and utility inputs to zero) | $|||| | 7.84 | $|||| 1 | ||||% |
| **Treatment discontinuation in the CKD4-5 health states** |
| Set equal to rates in early disease stage | $|||| | 8.20 | $|||| 1 | -||||% |
| Set equal to 5% discontinuation rate per year | $|||| | 8.06 | $|||| 6 | -||||% |
| **Disease progression** |  |  |  |  |
| Slower disease progression in BSC by using Singh et al (2022) values for CKD1-3a health states | $|||| | 7.87 | $|||| 3 | ||||% |
| Remove additional background CKD progression for BSC | $|||| | 8.22 | $|||| 1 | ||||% |
| Use of Singh et al (2022) values and remove additional background progression  | $|||| | 7.82 | $|||| 3 | ||||% |
| Set progression in lumasiran arm equivalent to BSC arm (with use of Singh et al (2022) values and removal of background progression)  | $|||| | 7.00 | $|||| 3 | ||||% |
| Set progression in lumasiran arm equivalent to BSC arm (as above), and remove transitions between uncontrolled and controlled states  | $|||| | 6.23 | $|||| 4 | ||||% |
| **Dialysis costs** |  |  |  |  |
| Set dialysis costs equivalent to high-intensity regimen for both lumasiran and BSC | $|||| | 8.25 | $|||| 3 | ||||% |
| **Probability of transplant** |
| Double the transition probability | $|||| | 7.98 | $|||| 1 | -||||% |
| Increase by factor of 10 | $|||| | 6.85 | $|||| 1 | -||||% |

Abbreviations: BSC, best standard of care; ICER, incremental cost-effectiveness ratio; EQ-5D, EuroQol- 5 dimension**.**

Source: Table 3.57, p157 and the Excel workbook of the submission (Oxlumo Section 3 CUA HPP009243.xlsm, economic model of the submission).

The redacted values correspond to the following ranges:

1 $455,000 to < $555,000

2 $255,000 to < $355,000

3 $555,000 to < $655,000

4 $655,000 to < $755,000

5 $855,000 to < $955,000

6 $355,000 to < $455,000

* 1. The ESC considered the economic model was associated with a number of uncertainties and potentially optimistic assumptions, which if taken into account would lead to a higher ICER than presented. Due to the uncertainties related to the economic model, the ESC considered a supplementary method for assessing the cost-effectiveness of lumasiran versus BSC may be informative. The PBAC has made previous decisions using incremental cost per responder analyses (Table 10, osildrostat Public Summary Document (PSD), March 2024 PBAC meeting).
	2. Cost per responder analyses are provided in Table 17.

Table 17: Cost and clinical outcome ratio analyses at 6 months and over a lifetime a

| Step and component | Lumasiran+ BSC | BSC | Increment |
| --- | --- | --- | --- |
| Lumasiran costs per 6 months | $||||b | $0 | $|||| |
|  |
| Proportion of patients 24-h urinary oxalate ≤ULN (at 6 months) | 0.52 | 0.00 | 0.52 |
| **Incremental cost per patient with a 24-h urinary oxalate ≤ULN** | **$|||| 1** |
|  |
| Proportion of patients 24-h urinary oxalate 1.5 ≤ULN (at 6 months) | 0.84 | 0.00 | 0.84 |
| **Incremental cost per patient with a 24-h urinary oxalate 1.5≤ULN** | **$|||| 1** |
| Modelled lumasiran drug cost (lifetime time horizon/undiscounted) | $|||| | $0 | $|||| |
|  |
| Modelled years on dialysis (lifetime time horizon/undiscounted)c | 26.91 | 37.86 | 10.95 |
| **Cost per year of dialysis avoided (undiscounted)** | **$|||| 2** |

Abbreviations: BSC, best supportive care; ULN, upper limit of normal

a The cost of vitamin B6 (Pyridoxine) not considered

b Maintenance doses applied, weighted by child/adult ratio assumed in the economic model: $| | x 0.706 + $| | x 0.294

c Estimated by summing life years (undiscounted) accrued in the CKD4-Oxc, CKD4-Oxu, ESRD-Oxc, and ESRD-OXu health states over the model time horizon. It should be noted that dialysis in the lumasiran arm is assumed to be of normal intensity, whereas dialysis in the BSC is assumed to be of high intensity.

*The redacted values correspond to the following ranges:*

1 $155,000 to < $255,000

2 > $1,055,000

* 1. The pre-PBAC Response maintained that the submitted economic model provided a robust and plausible estimate of the cost-effectiveness of lumasiran, however acknowledged that using a cost-per-responder analysis may provide additional information relevant to PBAC’s decision-making.

Drug cost/patient/year

* 1. The recommended dose of lumasiran consists of loading doses given once a month for 3 doses, followed by maintenance doses beginning one month after the last loading dose. Dosing is based on body weight. Including loading doses, the drug cost per paediatric patient per year is $||| |||; in subsequent years on maintenance doses only, the drug cost per paediatric patient per year is $||| |||.
	2. Including loading doses, the drug cost per adult patient per year is $||| |||; in subsequent years on maintenance doses only, the drug cost per adult patient per year is $||| |||. The model assumes 71% are paediatric patients and 29% are adult patients. On average, the annual cost of lumasiran (including loading doses) for all patients is $||| |||. On average, the annual cost of lumasiran (maintenance doses only) for all patients is $||| |||.

Table 18: Lumasiran drug costs per cycle – from the economic model

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Lumasiran cycle | Admin. per cycle, mean | Vials per cycle, mean | RDI | Drug cost per cycle ($) |
| Paediatric |  |  |  |  |
| Cycle 1 | 4 | 6.18 | 0.99 | |||| |
| Cycle 2+ | 2 | 3.09 | 0.99 | |||| |
| Total per year – with loading dose | 6 |  |  | |||| |
| Total per year – with 2 maintenance doses | **4** |  |  | **||||** |
| Adult |  |  |  |  |
| Cycle 1 | 4 | 12.17 | 0.99 | |||| |
| Cycle 2+ | 2 | 6.09 | 0.99 | |||| |
| Total per year – with loading dose | 6 |  |  | |||| |
| Total per year – with 2 maintenance doses | **4** |  |  | **||||** |

Source: Table 3.36 of the submission. Cycle = 6 months

Abbreviations: Admin, administration; RDI, relative dose intensity.

Notes: Effective DPMQ $|| applied

* 1. The weight distribution modelled (based on pooled data on baseline weight in the ILLUMINATE-A,-B, and -C trials) is presented below.

Table 19: Distribution of adult and paediatric ILLUMINATE participants among weight categories

|  | **Distribution (%)** |
| --- | --- |
| **Weight categories, kg** | **Adult participants (n=23)** | **Paediatric participants (n=55)** |
| 0–10.00 | 0.0% | 16.4% |
| 10.00–15.75 | 0.0% | 16.4% |
| 15.75–20.00 | 0.0% | 16.4% |
| 20.00–31.50 | 0.0% | 23.6% |
| 31.50–63.00 | 13.0% | 18.2% |
| 63.00–94.50 | 69.6% | 7.3% |
| 94.50–126.00 | 17.4% | 1.8% |

Source: Table 3.35 of the submission

Estimated PBS usage & financial implications

* 1. This submission was considered by DUSC.
	2. The submission took an epidemiological approach. The prevalence was assumed to be 2 cases per million, based on Kopp and Leumann (1995)[[16]](#footnote-17). This value was the intermediate figure of three reported values (1.05, 2, 2.9 per million) from literature published between 1995 to 2003. The evaluation considered that the prevalence data appeared outdated. A study by Mandrile et al. (2014) reported an upward trend of diagnoses between 1990 to 2009 and considered this trend to be driven by improved diagnostic services and advancement of genetic testing. The DUSC considered the prevalence of PH1 was highly uncertain, however considered that 2 cases per million was likely a reasonable estimate in the absence of alternative prevalence data.
	3. The Australian population projection data was outdated. The DUSC considered the approach reasonable but required revision as the outdated source led to a small overestimation of the eligible population.
	4. The lumasiran uptake rates were estimated to be 60% in Year 1 and increased to 80% in Year 6. The submission argued that rapid and high uptake was likely due to lumasiran being an add-on regimen to BSC, and a high awareness in specialised settings. The evaluation considered that this was uncertain. The DUSC considered this assumption to be unreasonable and not supported by the evidence. The DUSC considered that as lumasiran is an add on treatment to BSC with high awareness in the specialist care setting, a higher uptake of 90−100% may be more likely.
	5. The evaluation noted that very few patients discontinued treatment with lumasiran in the ILLUMINATE trials. Therefore, the evaluation considered that a discontinuation rate of 5% per annum may be an overestimate, resulting in a moderate underestimation of drug utilisation. The DUSC agreed with the evaluation and noted that there had been little indication that patients discontinue treatment in the clinical trials. Given the side effects of lumasiran appear generally minor in nature, the DUSC considered that it was not expected that patients would have reason to discontinue.
	6. As lumasiran was a weight-based regimen, patients’ weight distribution was derived based on the pooled population from the ILLUMIANTE trials. However, it was observed that the submission assumed patients’ weight to stay constant, and the calculation did not consider the growth in paediatric patients. Assuming constant weights, particularly for paediatric patients likely substantially underestimated the drug dosage and consequently the cost. The DUSC advised that a sensitivity analysis should be conducted that incorporates age-specific growth rates for each group to better account for weight progression over time.
	7. The key inputs for the financial estimates were summarised in Table 20 below with comments.

Table 20: Key inputs for financial estimates

| **Parameter** | **Value applied and source** | **Comment** |
| --- | --- | --- |
| Prevalence | Prevalence of 2 cases per million based on Kopp and Leumann, 1995[[17]](#footnote-18). Three sources were provided, and the prevalence ranged between 1.05 and 2.9 cases per million[[18]](#footnote-19),[[19]](#footnote-20),[[20]](#footnote-21) | The DUSC considered the estimated prevalence was highly uncertain, however a reasonable estimate in the absence of alternative prevalence data. Overall, the DUSC considered the estimate may be overestimated. |
| Population | ABS population projection (2013) | Outdated data source. The DUSC considered the approach reasonable but required revision as the outdated source led to a small overestimation of the eligible population. |
| Uptake rate | 60% in Year 1 increased to 80% by Year 6.Uptake was assumed to be rapid and high due to lack of alternative treatment options and high awareness in specialist care setting. | The DUSC considered that a higher uptake of 90-100% may be more likely. |
| Number of newly initiated patients | Eligible patients minus continued patients from last year | The DUSC considered that this approach may be reasonable because in the case of rare diseases, incidence remains relatively stable, keeping prevalence low. |
| Discontinuation per annum | 5% patients discontinued stated to be based clinical trial data. | Not supported by clinical data, likely overestimated. The DUSC agreed with the evaluation and considered this assumption to be potentially unreasonable. |
| Dose/duration | Weight based dosages continue for a lifetime (all 6 years). | Consistent with the TGA approved drug regimen, and consistent with the economic section. |
| Weight distribution | Pooled ILLUMINATE trials baseline. | The evaluation considered that this approach likely led to an underestimate of drug costs due to the lack of consideration in weight growth, particularly in paediatric patients. The DUSC agreed with the evaluation and advised that it was inappropriate to apply the baseline average pooled estimate as children gain weight over time and as a result higher doses are required. |
| Proposed medicine effective DPMQ, per vial | $|||| (Paediatric)$|||| (Adult) | It is incorrect to use average number of vials for a DPMQ calculation. Pricing calculations should be performed using an integer number of vials. Consequently, the population should be split based on the integer number of vials required in each age group. The DUSC agreed with the evaluation. Revised calculations were provided by the Secretariat (see paragraph 6.104 and Table 19). |
| MBS Item  | MBS Item 13950 (Parenteral administration of one or more antineoplastic agents, $123.05). | Appropriate |

Abbreviations: ABS, Australian bureau of statistics; MBS, medicine benefits schedule; TGA, therapeutic goods administration.

Source: Table 31, 4.1-4.6, text in Section 4.1 (p159-p165), and Excel workbook of the submission.

* 1. The projected patient numbers and vial usage estimated by the submission are presented in in Table 21. The estimated number of patients was < 500 in Year 1, increasing to < 500 in Year 6. In the first year of listing, a vial usage of < 500 was estimated and this number increased to < 500 in Year 6.
	2. The net cost to the PBS was estimated by the submission to be $10 million to < $20 million in the first year of listing and increased to over $10 million to < $20 million in Year 6.
	3. Revised utilisation and financial estimates for lumasiran were provided by the DUSC Secretariat. The revised analysis included dosing assumptions for the paediatric and adult populations that were based on the treatment phase, dosing frequency and the number of vials for each administration (adults: 2 vials: 13.04%, 3 vials: 69.57%, 4 vials: 17.39%; paediatric: 1 vial: 56.36%; 2 vials: 34.55%, 3 vials: 7.27%, 4 vials: 1.82%). Additional corrections to the revised estimates were provided in the Pre-PBAC Response and are shown in Table 21.

Table 21: Estimated lumasiran use and its financial implications

|  | **Year 1** | **Year 2** | **Year 3** | **Year 4** | **Year 5** | **Year 6** |
| --- | --- | --- | --- | --- | --- | --- |
| Estimated extent of use |
| Number of patients estimated | |||| 1 | |||| 1 | |||| 1 | |||| 1 | |||| 1 | |||| 1 |
| Number of patients treated | |||| 1 | |||| 1 | |||| 1 | |||| 1 | |||| 1 | |||| 1 |
| Vial usage | |||| 1 | |||| 1 | |||| 1 | |||| 1 | |||| 1 | |||| 1 |
| **Estimated financial implications of lumasiran (effective price)** |
|  Cost to PBS | $|||| 2 | $|||| 2 | $|||| 2 | $|||| 2 | $|||| 2 | $|||| 2 |
|  Less co-payments | -$|||| 3 | -$|||| 3 | -$|||| 3 | -$|||| 3 | -$|||| 3 | -$|||| 3 |
| Net cost to PBS (submission) | $|||| 2 | $|||| 2 | $|||| 2 | $|||| 2 | $|||| 2 | $|||| 2 |
| Net cost to PBS (DUSC advice) | $|||| 2 | $|||| 2 | $|||| 2 | $|||| 2 | $|||| 2 | $|||| 2 |
| Net cost to PBS (pre-PBAC Response) | $|||| 2 | $|||| 2 | $|||| 2 | $|||| 2 | $|||| 2 | $|||| 2 |
| **Estimated financial implications for other medicines: None** |
| **Net financial implications** |
| Net cost to PBS | $|||| 2 | $|||| 2 | $|||| 2 | $|||| 2 | $|||| 2 | $|||| 2 |
| Net cost to MBS | $|||| 4 | $|||| 4 | $|||| 4 | $|||| 4 | $|||| 4 | $|||| 4 |
| Net cost to Services Australia | $|||| 4 | $|||| 4 | $|||| 4 | $|||| 4 | $|||| 4 | $|||| 4 |

Abbreviations: MBS, medicine benefits schedule; PBS, pharmaceutical benefits scheme

Source: Table 4.4, 4.7, 4.8, 4.10, 4.11 p163-166 of the submission; pre-PBAC response

The redacted values correspond to the following ranges:

1 < 500

2 $10 million to < $20 million

3 net cost saving

4 $0 to < $10 million

* 1. The DUSC considered that the estimates presented in the submission to be overestimated. This was primarily due to the data sources used to estimate the projected population and the prevalence of PH1.
	2. TheDUSC advised that minor changes to the methods used to derive the utilisation and financial estimates and structure of the estimates model should be considered as follows:
* A higher uptake rate of 90−100% may be more likely and should be tested in a sensitivity analysis.
* A discontinuation rate per annum of 0% and 1% should be tested in a sensitivity analysis.
* A sensitivity analysis be conducted that incorporates age-specific growth rates for each patient group to better account for weight progression and vial usage over time.

The pre-PBAC Response provided sensitivity analyses as per the DUSC advice. However, the analyses provided could not be verified prior to PBAC consideration.

Quality Use of Medicines

* 1. Quality use of medicine was not discussed in the submission. The DUSC considered that injection-site reactions could be minimised through proper injection technique, site rotation, and patient education. Post-injection care, such as cold compress application and avoiding site manipulation, helps reduce discomfort. Patients should be monitored for severe reactions, with documentation and timely consultation recommended. These strategies support the safe and effective use of lumasiran in clinical practice and should be considered.

Financial Management – Risk Sharing Arrangements

* 1. Risk sharing arrangement was not discussed in the submission.

*For more detail on PBAC’s view, see section 7 PBAC outcome.*

1. PBAC Outcome
	1. The PBAC recommended the listing of lumasiran for the treatment of primary hyperoxaluria type 1 (PH1). In making this recommendation, the PBAC accepted there is a high unmet clinical need for treatment options for patients with PH1, and that lumasiran is effective in reducing urinary oxalate and plasma oxalate and may also lead to a reduction in the utilisation of dialysis and liver-kidney transplantation. The PBAC considered that the incremental cost-effectiveness ratio (ICER) was high and that the economic model was not sufficiently reliable for decision making due to uncertainty related to the translation of trial evidence to final health outcomes and the use of optimistic assumptions, utilities, and structural relationships. The PBAC considered that in the context of this rare and life-limiting disease, lumasiran would be considered acceptably cost-effective with a price reduction that resulted in an acceptable cost per patient per year. The PBAC noted that the estimated utilisation of lumasiran had been corrected for errors in the pre-PBAC Response. The PBAC considered that the remaining uncertainties regarding the cost-effectiveness, cost per patient per year and utilisation could be managed by a risk sharing arrangement (RSA).
	2. The PBAC recognised the high unmet clinical need for treatment for PH1. The PBAC noted that PH1 is an ultra-rare disease with substantial impacts on the quality of life of patients and their families and caregivers. The PBAC noted the sponsor hearing and the consumer input descriptions of disease progression, which included painful and recurrent kidney stones, chronic kidney disease, and a range of severe and systemic complications of oxalate deposition in the bone, retina, heart, and skin. As such, lowering oxalate levels in patients and the potential to reduce the utilisation of dialysis and transplantation is highly valued by patients with PH1 and their caregivers. The PBAC noted comments stating that the current supportive treatments for PH1, which include intensive dialysis, regular medications, and strict fluid intake and diet modifications, impose a significant burden on patients, particularly for young children with PH1, and their caregivers. The PBAC also acknowledged that the effective management of PH1 often requires access to frequent and specialised multidisciplinary care which often requires significant travel and time, adding to the overall burden on patients and carers.
	3. The PBAC considered that the submission’s proposed clinical criteria for the initial treatment of lumasiran were appropriate, and reference to a specific level of eGFR to define renal impairment was not required. The PBAC considered that given the very high cost of treatment, it was important that discontinuation from treatment be considered where patients are no longer receiving clinical benefit. However, the PBAC also considered that it was appropriate for the assessment of ‘clinical benefit’ from treatment with lumasiran to be at the discretion of the treating physician, and that a quantifiable measure to describe ‘clinical benefit’ was not required. The PBAC considered that it was appropriate for the treatment criterion stating that patients must be treated by a nephrologist with experience in the management of hyperoxaluria or in consultation with a nephrologist with experience in the management of hyperoxaluria, to be expanded to include paediatricians. The PBAC also noted that different genotypes of PH1 respond differently to pyridoxine therapy (B6) and considered that patients carrying a pyridoxine responsive allele should trial pyridoxine therapy prior to treatment with lumasiran.
	4. The PBAC noted that an Authority Required (Streamlined) listing had been proposed by the submission. Given that lumasiran is a new chemical entity and a high-cost medicine, the PBAC advised that an Authority Required (Written/HPOS upload) listing for initial treatment and an Authority Required (Written/online PBS Authorities) listing for continuing treatment would be more appropriate. The PBAC also noted that the submission stated that the likely heaviest patient will require five vials per treatment (5 vials x 94.5mg = 283.5mg, at 3 mg/kg = up to 157.5 kg person). The PBAC therefore advised that the maximum number of vials per script should be 5 vials. The PBAC also noted that the proposed grandfather restriction did not include the same qualifying criteria proposed in the initial restriction. The PBAC considered the inclusion of the grandfather restriction, as suggested by the Secretariat, was appropriate.
	5. The submission nominated best supportive care (BSC) as the main comparator. The submission stated that BSC may include dietary management, hyper-hydration, citrate and pyridoxine (vitamin B6) administration, urological management of kidney stones, dialysis and combined liver-kidney transplantation (LKT). The PBAC considered that the nominated comparator was appropriate.
	6. The PBAC noted the submission included one head-to-head randomised control trial (RCT) comparing lumasiran plus BSC to placebo plus BSC (ILLUMINATE-A [N=39]) and 2 single-arm studies of lumasiran (ILLUMINATE-B [N=18], ILLUMINATE-C [N=21]). The PBAC noted that the small sample sizes of the trials, while increasing the uncertainty in the results, reflected the rarity of PH1. The PBAC noted that based on the ILLUMINATE-A trial, for patients aged >6 years of age (with an eGFR ≥30 mL/min/1.73 m2 and a mean 24-hour urinary oxalate excretion ≥0.70 mmol/24 h/1.73 m2), treatment with lumasiran led to a significantly greater reduction in 24-h urinary oxalate excretion compared to placebo (effect size -53.6%, 95% confidence interval [CI] -62.3%, -44.8%; p<0.001). The PBAC noted that the absolute change in 24-hour urinary oxalate and percent and absolute change in plasma oxalate were also significantly reduced for individuals in the lumasiran arm compared with the placebo arm. Furthermore, a significantly higher proportion of patients in the lumasiran group achieved oxalate level normalisation (≤ upper limit of normal [ULN]; effect size 0.52, 95% CI 0.23, 0.70; p = 0.001) or near-normalisation (≤1.5xULN; effect size 0.84, 95% CI 0.55, 0.94; p < 0.001) from baseline to 6 months, with no patients in the placebo group achieving either. The PBAC noted that reductions in urinary and plasma oxalate levels were maintained in the open-label extension period, through to 60 months.
	7. The PBAC noted that the ILLUMINATE-B trial included paediatric patients (37 weeks estimated gestational age to <6 years) with relatively preserved kidney function (eGFR ≥45 mL/min/1.73 m2 if aged ≥1 year or normal serum creatinine if aged <1 year, and urinary oxalate:creatinine ratio > ULN (0.514 mmol/24hr/1.73 m2). The PBAC noted that for individuals in the ILLUMINATE-B trial, treatment with lumasiran resulted in a statistically significant reduction in spot urinary O:C ratio from baseline to 6 months (LSM percent change: -72.0%; 95% CI: -77.5, -66.4; p<0.001) and patients continued to demonstrate a sustained reduction in urinary O:C ratio during the extension period (30 months). The PBAC noted that the ILLUMINATE-C trial included patients ≥37 weeks gestational age with more advanced chronic kidney disease (CKD) (eGFR ≤45 mL/min/1.73 m2, mean plasma oxalate level ≥20 μmol/L) and included both patients not on dialysis (Cohort A) and on dialysis (Cohort B). The PBAC noted that patients in Cohort B of the ILLUMINATE-C trial were receiving an average of 6 dialysis sessions per week at baseline. The PBAC noted that for individuals in the ILLUMINATE-C trial, treatment with lumasiran resulted in a reduction in percent and absolute plasma oxalate from baseline to 6 months. The PBAC noted that reductions in plasma oxalate levels were maintained during the extension period (up to 24 months). Overall, the PBAC considered that the claim of superior comparative effectiveness was reasonable based on the observed reduction in plasma and urinary oxalate across the three ILLUMINATE trials, however considered that the magnitude of benefit remained uncertain due to limitations related to the small sample sizes of the trials.
	8. The PBAC considered that lumasiran appeared to be generally well tolerated (see Table 8). The PBAC noted that there were few discontinuations due to adverse events from treatment across the three ILLUMINATE trials, however noted that injection-site reactions were common for lumasiran-treatment patients. For this reason, the PBAC considered that lumasiran had inferior safety to BSC.
	9. The submission presented a cost-utility analysis for the economic evaluation, based on the results from the three ILLUMINATE trials and additional literature data. The PBAC noted that the base case ICER for the economic model was high and associated with a high level of uncertainty ($455,000 to < $555,000/QALY gained, excluding caregiver utilities; $455,000 to < $555,000/QALY gained, including caregiver utilities). The PBAC noted that the economic model relied on complex conversion assumptions translating surrogate outcomes (plasma oxalate) to change in eGFR, chronic kidney disease and other health outcomes associated with systemic oxalosis and mortality over a lifetime time horizon.
	10. The PBAC noted that the economic model included several optimistic parametric and structural assumptions, which favoured lumasiran. In particular, the PBAC considered the assumption that lumasiran would be 100% effective at stopping disease progression related to PH1 over a lifetime time horizon was optimistic given the limited and relatively short clinical trial data. The PBAC also considered that the assumption that patients with CKD4 and CKD5 in the BSC arm would only have a small probability of transplant (0.8% per annum) and may remain on intensive dialysis for the majority of their lifetime was not well justified. The PBAC noted that a variety of sources had been used to inform health state utility values, which led to inconsistencies in how quality of life was quantified across model states. The PBAC noted that the reduction in utilities assumed for more severe disease health states compared to early stages of disease was likely over-estimated and that a range of disutility values had been applied on top of the health state utilities, which led to further uncertainty and high likelihood of double counting.
	11. Overall, the PBAC agreed with the ESC that the substantial life-long benefits modelled for lumasiran over BSC, based on relatively limited and short duration clinical trial evidence, were highly uncertain. The PBAC noted the advice from the ESC that it was not immediately clear how the clinical parameters could be made more certain within the context of limited clinical data for a rare disease and considered alternative analyses may be informative in this context.Overall, the PBAC considered that, given PH1 is a rare disease and the data to inform an economic model are limited, the uncertainty in the ICER was unlikely to be adequately resolved with further revision to the economic model. The PBAC acknowledged the high unmet clinical need, the clinically meaningful benefit of reduced oxalate levels, and the potential reduction in the utilisation of dialysis and transplantation, and overall improvement in the quality of life for individuals with PH1 and their carers. The PBAC considered that in order to accept the value proposition, in the context of a high degree of uncertainty in the economic model and ICER, and the potential lifetime use of lumasiran with limited long-term experience with the drug, a price reduction would be required to achieve an average cost/patient/year of approximately $||| ||| (currently $||| |||, see paragraph 6.93 and Table 18). The PBAC considered this would be consistent with that for previously recommended treatments for rare diseases funded on the PBS when accounting for the clinical need, available evidence, nature of the benefits, estimated ICER and size of the patient population.
	12. The PBAC noted the DUSC advice that the modelled utilisation was overestimated primarily due to the data sources used to estimate the projected population and the prevalence of PH1 (see Table 20). The PBAC noted that the DUSC suggested amendments to the assumed uptake rate, discontinuation rate per annum and the incorporation of age-specific growth rates for each patient group to better account for weight progression and vial usage over time. The PBAC also noted that corrections to the financial estimates were provided in the pre-PBAC Response (see Table 21). Overall, the PBAC considered that the revised estimates provided in the pre-PBAC Response were likely to be a reasonable estimate of the projected net cost to the PBS, however noted that there were some remaining uncertainties. The submission did not propose an RSA. However, the PBAC considered that an RSA with expenditure caps would be required to mitigate the risk of higher costs due to uncertainty related to the calculation of the financial estimates including the uptake rate, discontinuation, and patient age distributions. The PBAC considered that given the high level of uncertainty in the cost-effectiveness, the rebate level should be close to 100%.
	13. The PBAC advised that lumasiran should not be treated as interchangeable with any other drugs.
	14. The PBAC advised that lumasiran is suitable for prescribing by medical practitioners and nurse practitioners only, as treatment of PH1 would not ordinarily occur in the normal course of providing dental, optometry or midwifery treatment. Prescribing is to be by a nephrologist or paediatrician with experience in the management of hyperoxaluria in the first instance due to the complexity and seriousness of the condition, but in instances where this may not be practical, prescribing could be by a medical practitioner (who is not a nephrologist or paediatrician) or a nurse practitioner, who has consulted a nephrologist or paediatrician.
	15. The PBAC recommended that the Early Supply Rule should not apply.
	16. The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were met. Specifically the PBAC found that in the circumstances of its recommendation for lumasiran:
	17. The treatment is expected to provide a substantial and clinically relevant improvement in efficacy over BSC, by reducing oxalate levels and potentially the frequency of dialysis and kidney/liver transplantation for patients with PH1;
	18. The treatment is expected to address a high and urgent unmet clinical need as there are currently no effective alternative therapies other than liver transplantation;
	19. It would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A on the basis of the preceding findings.
	20. The PBAC advised that this submission would not meet the criteria for an Independent Review as received a positive PBAC recommendation.

**Outcome:**

Recommended

1. Recommended listing

Initial treatment

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **MEDICINAL PRODUCT****medicinal product pack** | **PBS item code** | **Max. qty packs** | **Max. qty units** | **№.of****Rpts** | **Available brands** |
| LUMASIRAN |
| lumasiran 94.5 mg/0.5 mL injection, 0.5 mL vial | NEW | 5 | 5 | 2 | Oxlumo |
|  |
| **Restriction Summary / Treatment of Concept:**  |
|  | **Category / Program:** [x]  GENERAL - General Schedule (Code GE) |
| **Prescriber type:** [x] Medical Practitioners [x]  Nurse practitioners  |
| **Restriction type:** [x] Authority Required - delayed assessment (in writing only via post/HPOS upload) |
| **Authority type:**[x]  Complex Authority Required (CAR) |
|  | **Episodicity:** [blank] |
| **Severity:** [blank] |
| **Condition:** Primary hyperoxaluria type 1  |
|  | **Indication:** Primary hyperoxaluria type 1 |
|  | **Treatment Phase:** Initial treatment – loading doses |
|  | **Clinical criteria:** |
|  | The condition must be primary hyperoxaluria type 1 confirmed by genetic testing |
|  | **AND** |
|  | **Clinical criteria:** |
|  | Patient must have undergone treatment with pyridoxine therapy OR |
|  | Patient must have a PH1 allele that is considered not responsive to pyridoxine therapy |
|  | **AND** |
|  | **Clinical criteria:** |
|  | Patient must have urinary oxalate greater than or equal to 0.70 mmol/24 h/1.73 m2 measured by mean 24-h urinary oxalate excretion from a valid 24-h urine collection; OR |
|  | Patient must have urinary oxalate:creatinine ratio greater than the upper limit of normal based on age on at least two of three single-void collections during screening; OR |
|  | Patient must have clinical symptoms indicative of hyperoxaluria, such as (i) nephrocalcinosis; (ii) renal stones; (iii) renal impairment; (iv) systemic oxalosis |
|  | **AND** |
|  | **Clinical criteria:** |
|  | Patient must not have previously undergone liver transplant for primary hyperoxaluria type 1  |
|  | **AND** |
|  | **Treatment criteria:** |
|  | Must be treated by a nephrologist with experience in the management of hyperoxaluria OR  |
|  | Must be treated by a paediatrician with experience in the management of hyperoxaluria OR |
|  | Must be treated by an authorised prescriber in consultation with one of the above specialty types |
|  | **Prescribing Instructions:** At the time of the authority application, prescribers should request the appropriate number of vials based on the patient's weight, as per the TGA approved Product Information. Up to 2 repeats may be requested for initial treatment. |
|  | **Prescribing Instructions:** The authority application must be made via the Online PBS Authorities System, or in writing via HPOS form upload or mail.  |
|  | **Prescribing Instructions:**If the application is submitted through HPOS form upload or mail, it must include:(1) details of the proposed prescription; and(2) a completed PBS Authority Application Form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice)  |
|  | **Administrative Advice:** Special Pricing Arrangements apply. |
|  | **Administrative Advice:** No increase in the maximum quantity or number of units may be authorised. |
|  | **Administrative Advice:** No increase in the maximum number of repeats may be authorised. |
|  | **Administrative Advice:**Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.auApplications for authorisation under this restriction should be made using the Online PBS Authorities system (see [www.servicesaustralia.gov.au/hpos](http://www.servicesaustralia.gov.au/hpos))Alternatively, applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hposOr mailed to:Services AustraliaComplex DrugsReply Paid 9826HOBART TAS 7001 |

Continuing treatment and Grandfather restriction

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **MEDICINAL PRODUCT****medicinal product pack** | **PBS item code** | **Max. qty packs** | **Max. qty units** | **№.of****Rpts** | **Available brands** |
| LUMASIRAN |
| lumasiran 94.5 mg/0.5 mL injection, 0.5 mL vial | NEW | 5 | 5 | 1 | Oxlumo |
|  |
| **Restriction Summary / Treatment of Concept:**  |
|  | **Category / Program:** [x]  GENERAL - General Schedule (Code GE) |
| **Prescriber type:** [x] Medical Practitioners [x]  Nurse practitioners  |
| **Restriction type:** [x] Authority Required- immediate assessment (Written/online PBS Authorities system)  |
| **Authority type:**[x]  Complex Authority Required (CAR) |
|  | **Episodicity:** [blank] |
| **Severity:** [blank] |
| **Condition:** Primary hyperoxaluria type 1  |
|  | **Indication:** Primary hyperoxaluria type 1 |
|  | **Treatment Phase:** Continuing treatment |
|  | **Clinical criteria:** |
|  | Patient must have previously received PBS-subsidised treatment with this drug for this condition |
|  | **AND** |
|  | **Clinical criteria:** |
|  | Patient must continue to demonstrate clinical benefit as assessed by the treating physician  |
|  | **AND** |
|  | **Clinical criteria:** |
|  | Patient must not have previously undergone liver transplant for primary hyperoxaluria type 1  |
|  | **AND** |
|  | **Treatment criteria:** |
|  | Must be treated by a nephrologist with experience in the management of hyperoxaluria OR |
|  | Must be treated by a paediatrician with experience in the management of hyperoxaluria OR |
|  | Must be treated by an authorised prescriber in consultation with a nephrologist with one of the above specialty types |
|  | **Prescribing Instructions:** At the time of the authority application, prescribers should request the appropriate number of vials based on the patient's weight, as per the TGA approved Product Information. Up to 1 repeat may be requested for continuing treatment. |
|  | **Prescribing Instructions:** The authority application must be made via the Online PBS Authorities System (real time assessment), or in writing via HPOS form upload or mail. |
|  |  |
|  | **Prescribing Instructions:** If the application is submitted through HPOS form upload or mail, it must include:(i) details of the proposed prescription; and(ii) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice). |
|  | **Administrative Advice:** Special Pricing Arrangements apply. |
|  | **Administrative Advice:** No increase in the maximum quantity or number of units may be authorised. |
|  | **Administrative Advice:** No increase in the maximum number of repeats may be authorised. |
|  | **Administrative Advice:** Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authorisation under this restriction should be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/hpos) Alternatively, applications for authority to prescribe can be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001 |
|  |  |
| **Restriction Summary / Treatment of Concept:**  |
|  | **Category / Program:** [x]  GENERAL - General Schedule (Code GE) |
| **Prescriber type:** [x] Medical Practitioners [x]  Nurse practitioners  |
| **Restriction type:** [x] Authority Required - delayed assessment (in writing only via post/HPOS upload) |
| **Authority type:**[x]  Complex Authority Required (CAR) |
|  | **Indication:** Primary hyperoxaluria type 1 |
|  | **Treatment Phase:** Transitioning from non-PBS to PBS-subsidised supply - Grandfather arrangements |
|  | **Clinical criteria:** |
|  | Patient must have received treatment with this drug for this condition prior to <PBS listing date> |
|  | **AND** |
|  | The condition must be primary hyperoxaluria type 1 confirmed by genetic testing |
|  | **AND** |
|  | **Clinical criteria:** |
|  | Patient must have undergone treatment with pyridoxine therapy prior to commencing non-PBS subsidised treatment with this drug for this condition OR |
|  | Patient must have a PH1 allele that is considered not responsive to pyridoxine therapy |
|  | **AND** |
|  | **Clinical criteria:** |
|  | Patient must have urinary oxalate ≥0.70 mmol/24 h/1.73 m2 measured by mean 24-h urinary oxalate excretion from a valid 24-h urine collection prior to commencing treatment with this drug for this condition; OR |
|  | Patient must have urinary oxalate:creatinine ratio greater than the upper limit of normal based on age on at least two of three single-void collections during screening prior to commencing treatment with this drug for this condition; OR |
|  | Patient must have, prior to commencing treatment with this drug for this condition, clinical symptoms indicative of hyperoxaluria, such as (i) nephrocalcinosis; (ii) renal stones; (iii) renal impairment; (iv) systemic oxalosis  |
|  | **AND** |
|  | **Clinical criteria:** |
|  | Patient must continue to demonstrate clinical benefit as assessed by the treating physician  |
|  | **AND** |
|  | **Clinical criteria:** |
|  | Patient must not have previously undergone liver transplant for primary hyperoxaluria type 1  |
|  | **AND** |
|  | **Treatment criteria:** |
|  | Must be treated by a nephrologist with experience in the management of hyperoxaluria OR |
|  | Must be treated by a paediatrician with experience in the management of hyperoxaluria OR |
|  | Must be treated by an authorised prescriber in consultation with a nephrologist with one of the above specialty types |
|  | **Prescribing Instructions:** At the time of the authority application, prescribers should request the appropriate number of vials based on the patient's weight, as per the TGA approved Product Information. Up to 2 repeats may be requested.  |
|  | **Prescribing Instructions:** The authority application must be made via the Online PBS Authorities System, or in writing via HPOS form upload or mail.  |
|  | **Prescribing Instructions:** If the application is submitted through HPOS form upload or mail, it must include:(1) details of the proposed prescription; and(2) a completed PBS Authority Application Form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice) |
|  | **Administrative Advice:** Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the 'Continuing treatment' criteria. |
|  | **Administrative Advice:** This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria. |
|  | **Administrative Advice:** Special Pricing Arrangements apply. |
|  | **Administrative Advice:** No increase in the maximum quantity or number of units may be authorised. |
|  | **Administrative Advice:** No increase in the maximum number of repeats may be authorised. |
|  | **Administrative Advice:**Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.auApplications for authorisation under this restriction should be made using the Online PBS Authorities system (see [www.servicesaustralia.gov.au/hpos](http://www.servicesaustralia.gov.au/hpos))Alternatively, applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hposOr mailed to:Services AustraliaComplex DrugsReply Paid 9826HOBART TAS 7001 |

***These restrictions may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.***

1. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

1. Sponsor’s Comment

The sponsor had no comment

1. Groothoff et al. Clinical practice recommendations for primary hyperoxaluria: an expert consensus statement from ERKNet and OxalEurope. Nature Reviews Nephrology, 2023,19:194-211. [↑](#footnote-ref-2)
2. Groothoff et al. Clinical practice recommendations for primary hyperoxaluria: an expert consensus statement from ERKNet and OxalEurope. Nature Reviews Nephrology, 2023,19:194-211. [↑](#footnote-ref-3)
3. Groothoff et al. Clinical practice recommendations for primary hyperoxaluria: an expert consensus statement from ERKNet and OxalEurope. Nature Reviews Nephrology, 2023,19:194-211. [↑](#footnote-ref-4)
4. Cochat P, Deloraine A, Rotily M, et al. Epidemiology of primary hyperoxaluria type 1. Societe de Nephrologie and the Societe de Nephrologie Pediatrique. *Nephrol Dial Transplant.* 1995;10 Suppl 8:3-7. [↑](#footnote-ref-5)
5. Kopp N, Leumann E. Changing pattern of primary hyperoxaluria in Switzerland. *Nephrol Dial Transplant.* 1995;10(12):2224-2227. [↑](#footnote-ref-6)
6. van Woerden CS, Groothoff JW, Wanders RJ, et al. Primary hyperoxaluria type 1 in The Netherlands: prevalence and outcome. *Nephrol Dial Transplant.* 2003;18(2):273-279. [↑](#footnote-ref-7)
7. Groothoff et al. Clinical practice recommendations for primary hyperoxaluria: an expert consensus statement from ERKNet and OxalEurope. Nature Reviews Nephrology, 2023,19:194-211. [↑](#footnote-ref-8)
8. Milliner DS et al. 2020. Clin J Am Soc Nephrol. 2020;15(7):1056-1065. [↑](#footnote-ref-9)
9. Zhao F, et al. 2016. Clin J Am Soc Nephrol. 11(1):119-126 [↑](#footnote-ref-10)
10. Marangella M, Cosseddu D, Petrarulo M, et al. Thresholds of serum calcium oxalate supersaturation in relation to renal function in patients with or without primary hyperoxaluria. Nephrol Dial Transplant. 1993;8(12):1333-1337 [↑](#footnote-ref-11)
11. Illies F, Bonzel KE, Wingen AM, et al. Clearance and removal of oxalate in children on intensified dialysis for primary hyperoxaluria type 1. Kidney Int. 2006;70(9):1642-1648. [↑](#footnote-ref-12)
12. Sas DJ, Enders FT, Gunderson TM, et al. Natural history of clinical, laboratory, and echocardiographic parameters of a primary hyperoxaluria cohort on long term hemodialysis. Front Med (Lausanne). 2021;8:592357. [↑](#footnote-ref-13)
13. Metry EL, Garrelfs SF, Peters-Sengers H, et al. Long-term transplantation outcomes in patients with primary hyperoxaluria type 1 included in the European Hyperoxaluria Consortium (OxalEurope) Registry. *Kidney Int Rep.* 2022;7(2):210-220. [↑](#footnote-ref-14)
14. Go AS, Chertow GM, Fan D, et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004;351(13):1296-1305. [↑](#footnote-ref-15)
15. Jamieson NV, European PHITSG. A 20-year experience of combined liver/kidney transplantation for primary hyperoxaluria (PH1): the European PH1 transplant registry experience 1984-2004. Am J Nephrol. 2005;25(3):282-289. [↑](#footnote-ref-16)
16. Kopp N, Leumann E. Changing pattern of primary hyperoxaluria in Switzerland. Nephrol Dial Transplant. 1995;10(12):2224-2227. [↑](#footnote-ref-17)
17. Kopp N, Leumann E. Changing pattern of primary hyperoxaluria in Switzerland. Nephrol Dial Transplant. 1995;10(12):2224-2227. [↑](#footnote-ref-18)
18. Kopp N, Leumann E. Changing pattern of primary hyperoxaluria in Switzerland. Nephrol Dial Transplant. 1995;10(12):2224-2227. [↑](#footnote-ref-19)
19. van Woerden CS, Groothoff JW, Wanders RJ, et al. Primary hyperoxaluria type 1 in The Netherlands: prevalence and outcome. Nephrol Dial Transplant. 2003;18(2):273-279. [↑](#footnote-ref-20)
20. Cochat P, Deloraine A, Rotily M, et al. Epidemiology of primary hyperoxaluria type 1. Societe de Nephrologie and the Societe de Nephrologie Pediatrique. Nephrol Dial Transplant. 1995;10 Suppl 8:3-7. [↑](#footnote-ref-21)