▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – OXLUMO (LUMASIRAN) INJECTION SOLUTION

1 NAME OF THE MEDICINE

Lumasiran

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of solution contains lumasiran sodium equivalent to 189 mg lumasiran.

Each vial contains 0.5 mL of lumasiran sodium solution equivalent to 94.5 mg lumasiran.

For the full list of excipients, see section 6.1 List of Excipients

3 PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless to yellow solution.

4 CLINCAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Oxlumo is indicated for the treatment of primary hyperoxaluria type 1 (PH1) in all age groups.

4.2 DOSE AND METHOD OF ADMINISTRATION

Therapy should be initiated and supervised by a physician experienced in the management of hyperoxaluria.

Dosage

The recommended dose of Oxlumo consists of loading doses given once a month for 3 doses, followed by maintenance doses beginning one month after the last loading dose, as shown in Table 1. Dosing is based on body weight.

The patient dose (in mg) and volume (in mL) should be calculated as follows:

Patient body weight (kg) × dose (mg/kg) = total amount (mg) of medicinal product to be administered.

Total amount (mg) divided by concentration (189 mg/mL) = total volume of medicinal product (mL) to be injected.

Table 1: Oxlumo weight-based dosing regimen

Body weight	Loading dose	Maintenance dose (beginning one month after the last loading dose)
less than 10 kg	6 mg/kg once monthly for 3 doses	3 mg/kg once monthly, beginning one month after the last loading dose
10 kg to less than 20 kg	6 mg/kg once monthly for 3 doses	6 mg/kg once every 3 months (quarterly), beginning one month after the last loading dose
20 kg and above	3 mg/kg once monthly for 3 doses	3 mg/kg once every 3 months (quarterly), beginning one month after the last loading dose

Patients on haemodialysis

Administer Oxlumo following haemodialysis if administered on dialysis days.

Missed dose

If a dose is delayed or missed, treatment should be administered as soon as possible. Prescribed monthly or quarterly dosing should be resumed from the most recently administered dose.

Method of administration

Oxlumo is for subcutaneous use only. This medicinal product is ready-to-use and for single use only. Oxlumo should be administered by a healthcare professional.

Administration instructions

- Collect materials not included in the pack that are needed for administration which will include a sterile syringe (0.3 mL, 1 mL, or 3 mL), an 18-gauge (G) needle, and a 25-G to 31-G needle.
- Calculate the required volume of Oxlumo based on the recommended weight-based dose. If the dose is more than 0.5 mL, you will need to use more than one vial. The maximum acceptable single injection volume to be administered is 1.5 mL. If more than 1.5 mL is needed, you may need to give more than one subcutaneous injection.
- An 18-gauge needle should be used to withdraw Oxlumo from the vial. The vial should be held upright or tilted at a slight angle, and the flat edge of the needle should be pointed downwards.
- Point the needle and syringe straight up and tap the syringe to move any bubbles to the top. Once the bubbles are at the top, gently push the plunger to force the bubbles out of the syringe. Check to ensure the correct amount of medicine is in the syringe.
- Administer the medicine with a sterile 25- to 31-G needle with a 13-mm or 16-mm needle length for subcutaneous injection. For volumes less than 0.3 mL, a sterile 0.3-mL syringe is recommended.

- Note: Do not push this medicine into the 25-G to 31-G needle before piercing the skin. When using 0.3 mL (insulin) syringes, do not force the bubble from syringe.
- Injection can be into the abdomen, upper arms, or thighs. Consider rotating injection sites. Do not administer into scar tissue or areas that are reddened, inflamed, or swollen.
- Note: When administering subcutaneous injections into the abdomen, avoid a 2.0-cm diameter circle around the navel.
- Clean the area of planned injection with an alcohol swab and wait for the area to dry completely.
- Ensure proper injection technique. Do not inject into a vein or muscle.
- Insert the needle at a right angle (90 degrees) to deliver the injection just below the skin. In patients with little subcutaneous tissue, the needle should be inserted at a 45-degree angle.
- Do not press down on the plunger while piercing the skin. Once the needle is inserted through the skin, release the pinched skin and administer the dose in a slow and steady manner. Once the medicine has been administered count for at least 5 seconds before withdrawing the needle from the skin. Lightly press gauze or cotton ball on the injection site as needed. Do not put the needle cap back on.
- Note: Do not aspirate after inserting the needle to prevent tissue damage, haematoma, and bruising.
- If more than one injection is needed for a single dose of Oxlumo, the injection sites should be at least 2 cm apart.
- Only use the vial once. After administering the dose, dispose of any unused medicine in the vial according to local regulations.
- Use the syringes, transfer needles, and injection needles only once. Dispose of any used syringes and needles in accordance with local regulations.

Dosage adjustment

Elderly

No dose adjustment is necessary in patients ≥65 years of age (see section 5.2 Pharmacokinetic Properties).

Hepatic impairment

Oxlumo has not been studied in patients with hepatic impairment. No dose adjustment is necessary in patients with transient elevation in total bilirubin (total bilirubin >1.0 to 1.5×ULN). Caution is required when treating patients with moderate or severe hepatic impairment (see section 4.4 Special Warnings and Precautions for Use and 5.2 Pharmacokinetic Properties).

Renal impairment

No dose adjustment is necessary in patients with renal impairment (eGFR <90 mL/min/1.73m^2) including end-stage renal disease (ESRD), or those on dialysis. Limited data are available in

patients with ESRD and on dialysis, and these patients should be treated with caution (see section 4.4 Special Warnings and Precautions for Use and 5.2 Pharmacokinetic Properties).

Paediatric population

In patients under 1 year of age, limited data are available. Caution should be used when treating these patients (see section 5.2 Pharmacokinetic Properties).

4.3 CONTRAINDICATIONS

Severe hypersensitivity to the active substance or any of the excipients listed in section 6.1 List of Excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Use in renal impairment

Treatment with lumasiran increases plasma glycolate levels, which may increase the risk of metabolic acidosis or worsening of pre-existing metabolic acidosis in patients with severe or end-stage renal disease. These patients should therefore be monitored for signs and symptoms of metabolic acidosis.

Use in hepatic impairment

In patients with moderate or severe hepatic impairment there is a potential for decreased efficacy. Therefore, efficacy should be monitored in these patients (see section 5.2 Pharmacokinetic Properties).

Use in the elderly

No special precautions are necessary in elderly patients.

Paediatric use

OXLUMO is approved for use in children. Dosing is based on patient weight (see section 4.2 Dose and Method of Administration).

Effects on laboratory tests

No data are available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No clinical drug interaction studies have been performed. *In vitro* studies indicate that lumasiran is not a substrate or an inhibitor of cytochrome P450 (CYP) enzymes or an inhibitor of CYP1A2, CYP2C8, CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5 at clinically relevant concentrations. Lumasiran is not expected to inhibit or induce CYP enzymes or modulate the activities of drug transporters.

Concomitant use with pyridoxine

Concomitant use of pyridoxine did not meaningfully influence the pharmacodynamics or pharmacokinetics of lumasiran.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There are no data on the effects of lumasiran on human fertility. Administration of lumasiran by weekly subcutaneous doses up to 50 mg/kg in male and female rats (up to 20 times the plasma AUC at the maximum recommended maintenance dose of 6 mg/kg/month) prior to and during mating, and continuing in females once on Day 6 of presumed gestation resulted in no adverse effects upon the male or female fertility endpoints evaluated.

Use in pregnancy

Pregnancy Category B1

There are no data from the use of lumasiran in pregnant women. In embryofetal development studies in rats and rabbits, skeletal abnormalities were observed when lumasiran was administered subcutaneously at 30 mg/kg/day during organogenesis. The plasma AUC at the no observed adverse effect level (10 mg/kg/day) was 12 and 33 times the plasma AUC at the maximum recommended maintenance dose of 6 mg/kg/month. The use of this medicinal product could be considered during pregnancy taking into account the expected health benefit for the woman and potential risks to the fetus.

Use in lactation

It is unknown whether lumasiran is excreted in human milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Oxlumo therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Oxlumo has no or negligible influence on the ability to drive and use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile

The most common adverse reaction reported was injection site reaction (35%).

Tabulated list of adverse reactions

Adverse reactions associated with lumasiran obtained from clinical studies are tabulated below. The adverse reactions are coded to preferred terms (PTs) under the MedDRA system organ class (SOC) and are presented by frequency. The frequency of the adverse reactions is expressed according to the following categories: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 2: Adverse reactions

System organ class	Adverse reaction	Frequency
Gastrointestinal disorders	Abdominal pain [a]	Very common
General disorders and administration site conditions	Injection site reaction [b]	Very common

a Includes abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, and abdominal tenderness.

b Includes injection site reaction, injection site erythema, injection site pain, injection site pruritus, injection site swelling, injection site discomfort, injection site discolouration, injection site mass, injection site induration, injection site rash, injection site bruising, injection site haematoma and injection site exfoliation.

Description of selected adverse reactions

Injection site reactions

In placebo-controlled and open-label clinical studies, injection site reactions were reported in 34 out of 98 patients (34.7%). The most commonly reported symptoms were erythema, swelling, pain, haematoma, pruritus, and discolouration. The majority of injection site reactions started on the day of administration, with <2% of injection site reactions occurring 5 or more days after administration. Injection site reactions were generally mild, resolved within two days, and did not result in interruption or discontinuation of treatment.

Abdominal pain

In the placebo-controlled study, abdominal pain was reported in 1 of 13 (7.7%) placebo-treated patients and 4 of 26 (15.4%) lumasiran-treated patients. In the placebo-controlled and open-label clinical studies, 16 of 98 patients (16.3%) reported abdominal pain, including upper or lower abdominal pain, abdominal discomfort, or abdominal tenderness. Most of the events have been mild, transient, and resolved without treatment. None have resulted in discontinuation of treatment.

Immunogenicity

In patients with PH1 and healthy volunteers dosed with Oxlumo in clinical studies, 7 of 120 (5.8%) individuals tested positive for anti-drug-antibodies (ADA). ADA titres were low and generally transient, with no impact on the efficacy, safety, pharmacokinetic, or pharmacodynamic profiles of the medicinal product.

Paediatric population

The safety profile of lumasiran was similar in paediatric (aged 4 months to 17 years) and adult patients with PH1.

Post marketing experience

Table 3: Adverse reactions reported during post marketing use of Oxlumo.

System organ class	Adverse reaction	Frequency
Immune system disorders	Hypersensitivity	Not known[a]

a Events are reported from a population of uncertain size, it is not possible to reliably estimate frequency from the available data

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

In case of overdose, it is recommended that the patient be monitored as medically indicated for any signs or symptoms of adverse reactions and appropriate symptomatic treatment be instituted.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Other Alimentary Tract and Metabolism Products.
ATC code: A16AX18.

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Lumasiran is a double-stranded small interfering ribonucleic acid (siRNA) that reduces levels of glycolate oxidase (GO) enzyme by targeting the hydroxyacid oxidase 1 (HAO1) gene messenger ribonucleic acid (mRNA) in hepatocytes through RNA interference. Decreased GO enzyme levels reduce the amount of available glyoxylate, a substrate for oxalate production. This results in reduction of urinary and plasma oxalate levels, the underlying cause of disease manifestations in patients with PH1. As the GO enzyme is upstream of the deficient alanine: glyoxylate aminotransferase (AGT) enzyme that causes PH1, the mechanism of action of lumasiran is independent of the underlying AGXT gene mutation.

Clinical Trials

The efficacy of lumasiran was studied in a randomised, double-blind, placebo-controlled clinical study in patients 6 years and older with PH1 (ILLUMINATE-A), in a single-arm clinical study in patients less than 6 years of age with PH1 (ILLUMINATE-B), and in a single-arm clinical study in paediatric and adult patients with PH1 who have advanced renal disease, including patients on haemodialysis (ILLUMINATE-C).

ILLUMINATE-A

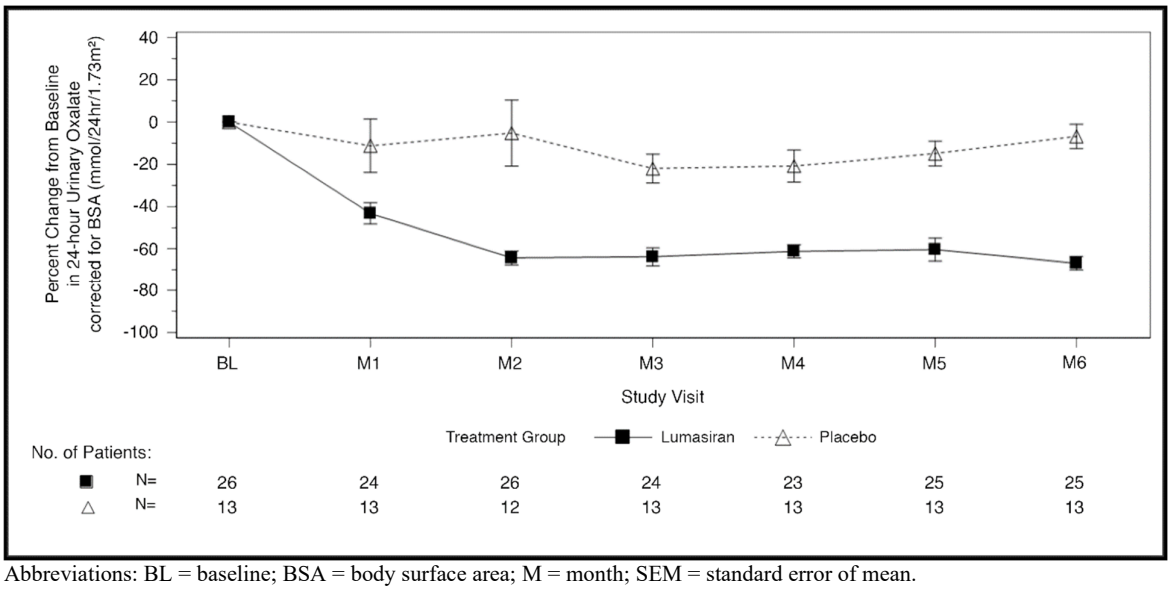
A total of 39 patients with PH1 were randomised 2:1 to receive subcutaneous doses of lumasiran or placebo during the 6-month double-blind, placebo-controlled period. Patients 6 years and older with an estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m^2 were enrolled and received 3 loading doses of 3 mg/kg lumasiran or placebo administered once monthly, followed by quarterly maintenance doses of 3 mg/kg lumasiran or placebo (see section 4.2 Dose and Method of Administration). After the 6-month double-blind treatment period, patients, including those originally assigned to placebo, entered an extension period with administration of lumasiran.

During the 6-month double-blind, placebo-controlled period, 26 patients received lumasiran, and 13 received placebo. The median age of patients at first dose was 14.9 years (range 6.1 to 61.0 years), 66.7% were male, and 76.9% were white. The median 24-hour urinary oxalate excretion corrected for body surface area (BSA) at baseline was 1.72 mmol/24 h/1.73 m^2, the median spot urinary oxalate: creatinine ratio at baseline was 0.21 mmol/mmol, and the median

plasma oxalate level at baseline was 13.1 µmol/L. Overall, 33.3% of patients had normal renal function (eGFR ≥90 mL/min/1.73 m^2), 48.7% had mild renal impairment (eGFR of 60 to <90 mL/min/1.73 m^2), and 18% had moderate renal impairment (eGFR of 30 to <60 mL/min/1.73 m^2). Of the patients enrolled in the study, 84.6% reported a history of symptomatic renal stone events and 53.8% reported a history of nephrocalcinosis at baseline. The treatment arms were balanced at baseline with respect to age, urinary oxalate level, and eGFR.

The primary endpoint was the percent reduction from baseline in 24-hour urinary oxalate excretion corrected for BSA averaged over months 3 through 6. Lumasiran was associated with a statistically significant reduction of 65.4% in 24-hour urinary oxalate corrected for BSA, as compared to 11.8% in the placebo group, representing a difference of 53.5% (95% CI: 44.8, 62.3; p<0.0001). Consistent with the primary endpoint, a reduction of 60.5% was observed at month 6 in spot urinary oxalate: creatinine ratio in the lumasiran arm compared to an 8.5% increase in the placebo arm. Furthermore, patients treated with lumasiran had a rapid and sustained decrease in 24-hour urinary oxalate corrected for BSA, as shown in Figure 1.

Figure 1: ILLUMINATE-A: Percent change from baseline in 24-hour urinary oxalate corrected for BSA by month



Abbreviations: BL = baseline; BSA = body surface area; M = month; SEM = standard error of mean.
Results are plotted as mean (±SEM) of percent change from baseline.

At month 6, a higher proportion of lumasiran-treated patients achieved normal or near-normal levels of 24-hour urinary oxalate corrected for BSA (≤1.5×ULN) compared to placebo-treated patients, as shown in Table 4.

Table 4: ILLUMINATE-A: Secondary endpoint results over the 6-month double-blind, placebo-controlled period

Endpoints	Lumasiran (N=26)	Placebo (N=13)	Treatment difference (95% CI)	p-value
Proportion of patients with 24-hour urinary oxalate levels at or below ULN‡	0.52 (0.31, 0.72)§	0 (0, 0.25)§	0.52 (0.23, 0.70)¶	0.001#
Proportion of patients with	0.84 (0.64,	0 (0, 0.25)§	0.84 (0.55,	<0.0001#

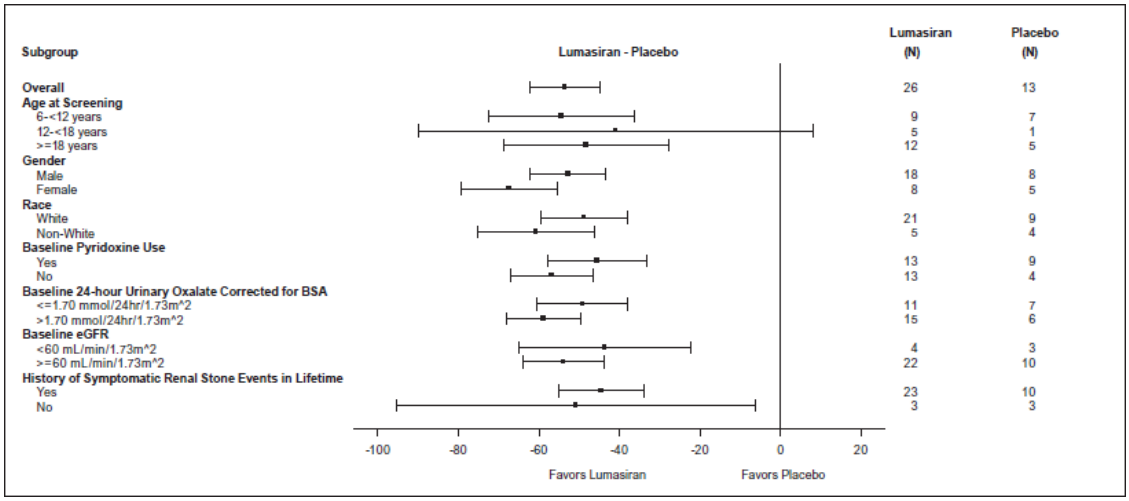
Endpoints	Lumasiran (N=26)	Placebo (N=13)	Treatment difference (95% CI)	p-value
24-hour urinary oxalate levels at or below 1.5×ULN‡	0.95)§		0.94)¶	
Percent reduction in plasma oxalate from baseline*Þ	39.8 (2.9)†	0.3 (4.3)†	39.5 (28.9, 50.1)	<0.0001

Abbreviations: ULN = upper limit of normal; SEM = standard error of mean

Results are based on liquid chromatography tandem mass spectrometry (LC-MS/MS) assay.
* The estimate based on the average of the least square mean of percent reduction at Months 3, 4, 5, and 6 using a mixed model for repeated measures.
† LS Mean (SEM).
‡ ULN=0.514 mmol/24 hr/1.73 m2 for 24-hour urinary oxalate corrected for BSA.
§ 95% CI based on Clopper Pearson Exact confidence interval.
¶ Calculated using the Newcombe Method based on the Wilson Score.
# p-value is based on Cochran–Mantel–Haenszel test stratified by baseline 24-hour urinary oxalate corrected for BSA (≤1.70 vs >1.70 mmol/24 hr/1.73 m2).
Þ Analysed in 23 lumasiran and 10 placebo patients who had baseline levels that allowed for reduction to occur.

Reduction in 24-hour urinary oxalate corrected for BSA from baseline in patients with PH1 receiving lumasiran compared to placebo was similar across all pre-specified subgroups, including age, sex, race, renal impairment, baseline pyridoxine (vitamin B6) use, and history of symptomatic renal stone events (Figure 2).

Figure 2: ILLUMINATE-A: Percent change from baseline in 24-hour urinary oxalate corrected for BSA by month



Reduced oxalate levels observed in the double-blind period were maintained with continued lumasiran treatment through 24 months during the extension period of study. eGFR and renal stone events (reported by events per person-year) were assessed through the 6-month double-blind and extension periods for a total of 24 months. eGFR remained stable in patients administered lumasiran.

The rate of renal stone events per person-year reported in patients treated with lumasiran in ILLUMINATE-A are presented in Table 5.

Table 5: Rate of Renal Stone Events per Person-Year Reported in the Lumasiran Group

Treatment	Time Period	Rate (95% CI)
No treatment	12 months prior to consent	3.19 (2.57, 3.96)
Lumasiran	6-month double-blind period	1.09 (0.63, 1.88)
	Month 6 to month 12	0.87 (0.47, 1.62)
	Month 12 to month 18	0.56 (0.25, 1.24)
	Month 18 to month 24	0.63 (0.30, 1.33)

The rate of renal stone events per person-year reported in patients treated with placebo in ILLUMINATE-A are presented in Table 6. The patients in the placebo group were initially randomised to placebo for the 6-month double-blind period and subsequently treated with lumasiran in the extension periods: month 6 to month 12, month 12 to month 18, and month 18 to month 24.

Table 6: Rate of Renal Stone Events per Person-Year Reported in the Placebo Group

Treatment	Time Period	Rate (95% CI)
No treatment	12 months prior to consent	0.54 (0.26, 1.13)
Lumasiran	6-month double-blind period	0.66 (0.25, 1.76)
	Month 6 to month 12	0.16 (0.02, 1.17)
	Month 12 to month 18	0.67 (0.25, 1.78)
	Month 18 to month 24	0.00 (0.00, 0.62)

Medullary nephrocalcinosis results, assessed by renal ultrasound, at month 6 and month 12 relative to baseline are presented in Table 7.

Table 7: ILLUMINATE-A: Patients with Medullary Nephrocalcinosis at Month 6 and Month 12 Relative to Baseline*

Timepoint	Treatment (n)	Improvement	No Change	Worsening
Month 6	Lumasiran (n=23)	3	20	0
	Placebo (n=12)	0	11	1
Month 12	Lumasiran (n=18)	11	4	3
	Placebo/Lumasiran** (n=11)	1	9	1

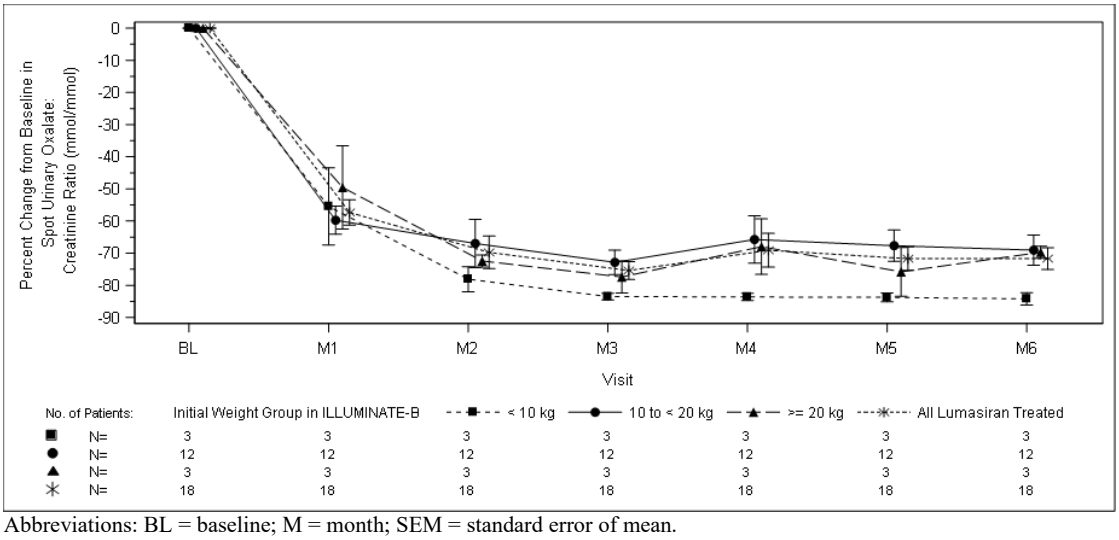
* Patients with renal ultrasounds at baseline and the relevant timepoint were assessed.
** Patients received placebo for 6 months followed by lumasiran treatment for 6 months.

ILLUMINATE-B

A total of 18 patients were enrolled and treated with lumasiran in an ongoing multi-centre, single-arm study in patients with PH1 (ILLUMINATE-B). The study enrolled patients less than 6 years of age with an eGFR >45 mL/min/1.73 m2 in patients 12 months of age and older, and normal serum creatinine in patients less than 12 months of age. In the 6-month primary analysis, at first dose, 3 patients were less than 10 kg, 12 were 10 kg to less than 20 kg, and 3 were 20 kg and above. The median age of patients at first dose was 51.4 months (range 4.0 to 74.0 months), 55.6% were female, and 88.9% were white. The median spot urinary oxalate: creatinine ratio at baseline was 0.47 mmol/mmol.

At month 6, patients treated with lumasiran achieved a reduction of 72.0% (95% CI: 66.4, 77.5) in spot urinary oxalate: creatinine ratio from baseline (averaged over months 3 through month 6), the primary endpoint. Lumasiran was associated with rapid, and sustained reductions in spot urinary oxalate: creatinine ratio (Figure 3), which were similar across all weight strata. The percent reduction in urinary oxalate excretion was maintained with continued lumasiran treatment through month 12 and consistent with data from ILLUMINATE-A.

Figure 3: ILLUMINATE-B: Percent change in spot urinary oxalate: creatinine ratio from baseline by month



Abbreviations: BL = baseline; M = month; SEM = standard error of mean.
Results are plotted as mean (±SEM) of percent change from baseline.

At month 6, nine of 18 patients achieved near normalisation (≤1.5×ULN), including 1 patient who achieved normalisation (≤ULN), in spot urinary oxalate: creatinine ratio. At month 12, ten of 18 patients achieved near normalization (≤1.5×ULN), including 2 patients who achieved normalization (≤ULN), in spot urinary oxalate: creatinine ratio.

Furthermore, from baseline to month 6 (average of month 3 to month 6), a mean plasma oxalate reduction of 31.7% (95% CI: 23.9, 39.5) was observed. Reduced plasma oxalate levels observed in the primary analysis period were maintained with continued lumasiran treatment. The eGFR remained stable in all patients with continued dosing.

The rate of renal stone events per person-year reported in the 12-month period prior to consent and during the 6-month primary analysis period was 0.24 (95% CI: 0.09, 0.63) and 0.24 (95% CI: 0.06, 0.96), respectively. The rate of events from month 6 to month 12 was 0.12 (95% CI: 0.02, 0.84).

Medullary nephrocalcinosis results, assessed by renal ultrasound, at month 6 and month 12 relative to baseline are presented in Table 8.

Table 8: ILLUMINATE-B: Patients with Medullary Nephrocalcinosis at Month 6 and Month 12 Relative to Baseline*

Timepoint	Improvement (n)	No Change	Worsening
Month 6 (n=18)	8	10	0
Month 12 (n=17)	11	6	0

*Patients with renal ultrasounds at baseline and the relevant timepoint were assessed.

ILLUMINATE-C

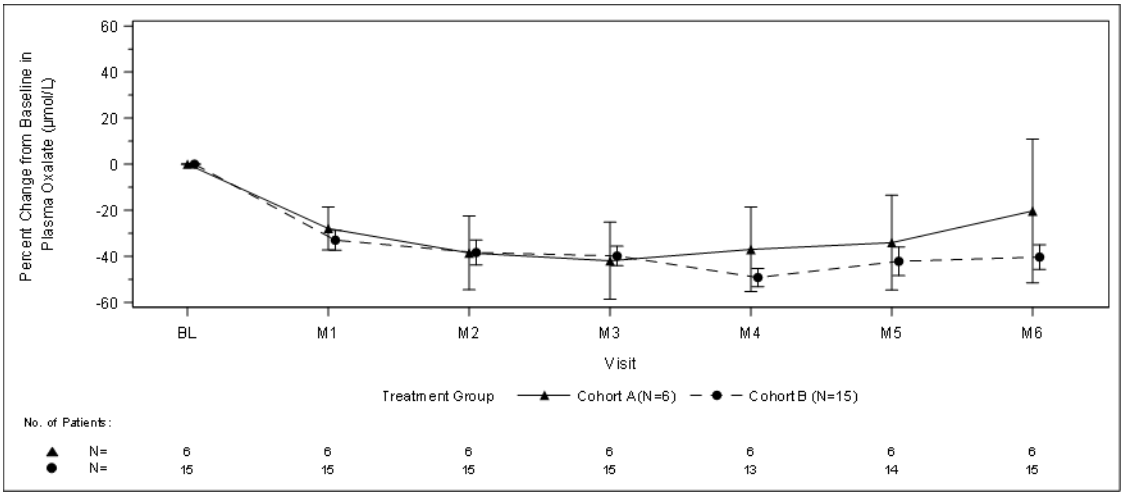
A total of 21 patients were enrolled and treated with lumasiran in an on-going multi-centre, single-arm study in patients with PH1 and advanced renal disease (eGFR ≤45 mL/min/1.73 m^2 in patients 12 months of age and older and elevated serum creatinine in patients less than 12 months of age), including patients on haemodialysis. ILLUMINATE-C includes 2 cohorts: Cohort A consists of 6 patients who did not require dialysis at the time of study enrolment and Cohort B consists of 15 patients who were on stable regimen of haemodialysis. Patients received the recommended dosing regimen of lumasiran based on body weight (see section 4.2 Dose and Method of Administration).

The median age of patients at first dose was 8.9 years (range 0 to 59 years), 57.1% were male, and 76.2% were white. For Cohort A patients, the median plasma oxalate level was 57.94 µmol/L. For Cohort B patients, the median plasma oxalate level was 103.65 µmol/L.

The primary endpoint of the study was the percent change in plasma oxalate from baseline to month 6 (average from month 3 to month 6) for Cohort A (N=6) and the percent change in pre-dialysis plasma oxalate from baseline to month 6 (average from month 3 to month 6) for Cohort B (N=15).

During the 6-month primary analysis period, patients in both cohorts had a reduction in plasma oxalate as early as month 1. The percent change from baseline to month 6 (average from month 3 to month 6) in plasma oxalate levels for Cohort A was an LS mean difference of -33.3% (95% CI: -81.82, 15.16) and for Cohort B the LS mean difference was -42.4% (95% CI: -50.71, -34.15).

Figure 4 ILLUMINATE-C: Percent Change from Baseline in Plasma Oxalate (µmol/L) at Each Visit during the Primary Analysis Period



Results are plotted as mean (±SEM) of percent change from baseline. Abbreviations: BL = baseline; M = month; SEM = standard error of mean.

For Cohort A, the baseline is defined as the mean of all plasma oxalate samples collected prior to the first dose of lumasiran; for Cohort B, the baseline is defined as the last four pre-dialysis plasma oxalate samples collected prior to the first dose of lumasiran. In Cohort B, only pre-dialysis samples are utilized.

In Cohort A the mean (SD) eGFR was 19.85 (9.6) mL/min/1.73 m^2 at baseline and 16.43 (9.8) mL/min/1.73m^2 at month 6.

The rate of renal stone events per person-year reported 12 months prior to consent for Cohort A and during the 6-month primary analysis period was 3.20 (95% CI: 1.96, 5.22) and 1.48 (95% CI: 0.55, 3.92), respectively.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Oxlumo in one or more subsets of the paediatric population in hyperoxaluria. Oxlumo is approved for use in children (see section 4.4 Paediatric use).

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Following subcutaneous administration, lumasiran is rapidly absorbed with a median (range) time to reach maximum plasma concentration (t_{max}) of 4.0 (0.5 to 12.0) hours. In children and adults with PH1 ≥20 kg, the peak plasma concentration of lumasiran (C_{max}) and area under the concentration curve from time zero to the last measurable concentration after dosing ($AUC_{0\text{-last}}$) following the recommended lumasiran dose of 3 mg/kg were 529 (205 to 1130) ng/mL and 7400 (2890 to 10700) ng·h/mL, respectively. In children less than 20 kg, C_{max} and $AUC_{0\text{-last}}$ of lumasiran following the recommended lumasiran dose of 6 mg/kg were 912 (523 to 1760) and 7960 (5920 to 13300). Lumasiran concentrations were measurable, up to 24 to 48 hours post-dose.

Distribution

In healthy adult plasma samples, the protein binding of lumasiran is moderate to high (77 to 85%) at clinically relevant concentrations. For an adult patient with PH1, the population

estimate for the apparent central volume of distribution ($V_{d/F}$) for lumasiran is 4.9 L. Lumasiran primarily distributes to the liver after subcutaneous dosing.

Metabolism

Lumasiran is metabolised by endo- and exonucleases to oligonucleotides of shorter lengths. *In vitro* studies indicate that lumasiran does not undergo metabolism by CYP450 enzymes.

Excretion

Lumasiran is primarily eliminated from plasma by hepatic uptake, with only 7 to 26% of the administered dose recovered in urine as lumasiran in the pooled data from healthy adult subjects and patients with PH1 >6 years of age. The mean (%CV) terminal plasma half-life of lumasiran is 5.2 (47.0%) hours. The population estimate for apparent plasma clearance was 26.5 L/h for a typical 70-kg adult. The mean renal clearance of lumasiran was minor and ranged from 2.0 to 3.4 L/h in paediatric and adult patients with PH1.

Linearity/non-linearity

Lumasiran exhibited linear to slightly nonlinear, time-independent pharmacokinetics in plasma following single subcutaneous doses ranging from 0.3 to 6 mg/kg and multiple doses of 1 and 3 mg/kg once monthly or 3 mg/kg quarterly. There was no accumulation of lumasiran in plasma after repeated once monthly or quarterly dosing.

Pharmacokinetic/pharmacodynamic relationship(s)

Plasma concentrations of lumasiran do not reflect the extent or duration of the pharmacodynamic activity of lumasiran. Rapid and targeted uptake of lumasiran by the liver results in rapid decline in plasma concentrations. In the liver, lumasiran exhibits a long half-life leading to maintenance of pharmacodynamic effect over the monthly or quarterly dosing interval.

Special populations

Elderly

No studies have been conducted in patients ≥65 years of age. Age was not a significant covariate in the pharmacokinetics of lumasiran.

Gender and race

In clinical studies, there was no difference in the plasma exposure or pharmacodynamics of lumasiran based on gender or race.

Hepatic impairment

No studies have been conducted in patients with hepatic impairment (see section 4.2 Dose and Method of Administration). Limited pharmacokinetic data in patients with mild and transient elevations in total bilirubin (total bilirubin >1.0 to 1.5×ULN) showed comparable plasma exposure of lumasiran and similar pharmacodynamics as patients with normal hepatic function. Published literature show lower expression of the asialoglycoprotein receptors in the liver, i.e. the receptors responsible for lumasiran uptake, in patients with hepatic impairment. Nonclinical data suggest that this may not influence liver uptake or pharmacodynamics at therapeutic doses. The clinical relevance of these data is unknown.

Renal impairment

Patients with mild renal impairment (eGFR 60 to <90 mL/min/1.73 m^2) had comparable plasma exposure of lumasiran as patients with normal renal function (eGFR ≥90 mL/min/1.73 m^2). In patients with moderate renal impairment (eGFR 30 to <60 mL/min/1.73 m^2) C_{max} was similar to that in patients with normal renal function; AUC was 25% higher based on limited data. In patients with severe renal impairment (eGFR 15 to <30 mL/min/1.73 m^2), ESRD (eGFR <15 mL/min/1.73 m^2), or who are on dialysis (see section 4.2 Dose and Method of Administration), within the same body weight category, a transient 1.8 to 3.6 fold higher C_{max} and 1.6 to 3.1 fold higher $AUC_{0\text{-last}}$ was observed (see section 5.2 Pharmacokinetic Properties). These increases were transient as plasma concentrations decline below the level of detection within 24 to 48 hours, similar to patients without renal impairment (see section 5.2 Pharmacokinetic/pharmacodynamic relationship(s)). The pharmacodynamics in patients with renal impairment (eGFR <90 mL/min/1.73 m^2), including ESRD (eGFR<15 mL/min/1.73 m^2) or those on dialysis were similar to patients with normal renal function (eGFR ≥90 mL/min/1.73 m^2) (see section 4.2 Dose and Method of Administration).

Paediatric population

Data in children younger than 1 year of age are limited. In children <20 kg, lumasiran C_{max} was 2-fold higher due to the nominally higher 6-mg/kg dose and faster absorption rate. The pharmacodynamics of lumasiran were comparable in paediatric patients (aged 4 months to 17 years) and in adults, despite the transiently higher plasma concentrations in children <20 kg, due to the rapid and predominant distribution of lumasiran to the liver.

Body weight

The recommended dosing regimens yielded up to 2-fold higher C_{max} in children <20 kg while AUC was similar across the body weights studied (6.2 to 110 kg).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Lumasiran was not genotoxic in an *in vitro* bacterial reverse mutation (Ames) assay, in the *in vitro* chromosomal aberration assay in cultured human peripheral blood lymphocytes, or in the *in vivo* micronucleus assay in rats.

Carcinogenicity

There was no evidence of an increased incidence of neoplasia in the transgenic Tg-rasH2 mouse following repeated monthly subcutaneous administration of lumasiran for 26 weeks at doses of 150, 500 or 1500 mg/kg (up to 212 times the plasma AUC at the maximum recommended maintenance dose of 6 mg/kg/month).

In a 2-year carcinogenicity study in rats, lumasiran was not carcinogenic up to the highest dose tested. Sprague Dawley rats were administered subcutaneous doses of 20, 55 or 110 mg/kg lumasiran once every 4 weeks (up to 26 times the plasma AUC at the maximum recommended maintenance dose of 6 mg/kg/month).

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sodium hydroxide (pH adjustment)

Phosphoric acid (pH adjustment)

Water for injections

6.2 INCOMPATIBILITIES

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 30°C.

Keep vial in the outer carton to protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

Glass vial with a fluoropolymer-coated rubber stopper and an aluminium overseal with a flip-off button. Each vial contains 0.5 mL solution for injection.

Pack size of one vial.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

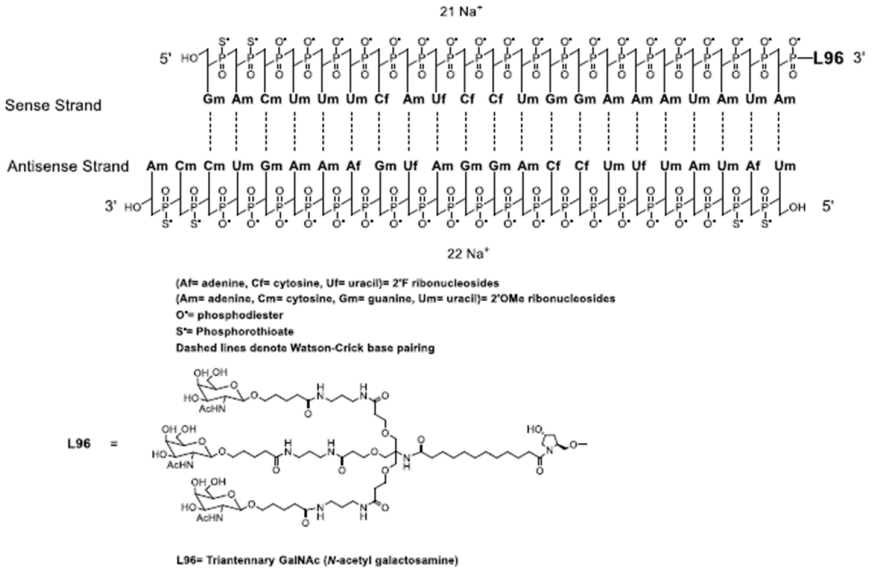
Each vial is for a single use in a single patient only. Discard any unused portion left in a vial, as the product contains no preservatives.

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

OXLUMO is a clear, colourless to yellow solution, with pH of approximately 7 and osmolality 240 to 360 mOsm/kg.

Chemical structure



CAS number

1834610-13-7 (lumasiran)

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine.

8 SPONSOR

Medison Pharma Australia Pty Ltd
1 Bligh Street
Sydney NSW 2000
Australia

Phone: 1800 566 020
Email: MedInfo.Australia@Medisonpharma.com
www.medisonpharma.com.au

9 DATE OF FIRST APPROVAL

24 June 2024

10 DATE OF REVISION

25 November 2024

Summary table of changes

Section Changed	Summary of new information
4.8	New adverse reaction (Hypersensitivity)