SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Oxlumo 94.5 mg/0.5 mL solution for injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Each vial contains 94.5 mg lumasiran in 0.5 mL.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless to yellow solution (pH of approximately 7; osmolality 240 to 360 mOsm/kg).

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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

Posology

Oxlumo is administered by subcutaneous injection. 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.

Special populations

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

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 to 1.5×ULN). Caution is required when treating patients with moderate or severe hepatic impairment (see sections 4.4 and 5.2).

Renal impairment
No dose adjustment is necessary in patients with renal impairment estimated glomerular filtration rate (eGFR) <90 mL/min/1.73 m^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 sections 4.4 and 5.2).

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).

Method of administration

For subcutaneous use only.

This medicinal product is provided as a ready-to-use solution in a single-use vial.

- The required volume of Oxlumo should be calculated based on the recommended weight-based dose as shown in Table 1.
- If the dose is more than 0.5 mL (94.5 mg), more than one vial will be needed.
- The maximum acceptable single injection volume is 1.5 mL Doses requiring more than 1.5 mL should be administered as multiple injections (the total dose divided equally between syringes with each injection containing approximately the same volume) to minimise potential injection site discomfort due to injection volume.
- Having the medicinal product on the needle tip before the needle is in the subcutaneous space should be avoided.
- This medicinal product should be injected subcutaneously into the abdomen, upper arms, or thighs.
- For subsequent injections or doses, rotating the injection site is recommended.
- This medicinal product should not be administered into scar tissue or areas that are reddened, inflamed, or swollen.

Oxlumo should be administered by a healthcare professional. For instructions on preparation of the medicinal product before administration see section 6.6. For instructions for use, see the information intended for healthcare professionals only, at the end of the package leaflet.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Severe or end-stage 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.

Moderate or severe 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).

Excipient with known effect

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per mL, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No clinical drug interaction studies have been performed (see section 5.2).

Concomitant use with pyridoxine

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

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of lumasiran in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). The use of Oxlumo may be considered during pregnancy taking into account the expected health benefit for the woman and potential risks to the foetus.

Breast-feeding

It is unknown whether lumasiran/ metabolites are 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.

Fertility

There are no data on the effects of lumasiran on human fertility. No impact on male or female fertility was detected in animal studies (see section 5.3).

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 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 and spontaneous reporting 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); not known (cannot be estimated from the available data).

Table 2: Adverse reactions

System organ class	Adverse reaction	Frequency
Immune system disorders	Hypersensitivity[a]	Not known
Gastrointestinal disorders	Abdominal pain[b]	Very common
General disorders and administration site conditions	Injection site reaction[c]	Very common

[a] Adverse reaction reported during post-marketing use.
[b] Includes abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, and abdominal tenderness.
[c] 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.

Long-term safety

The safety profile of lumasiran in the open-label extension periods of ILLUMINATE-A and ILLUMINATE-B (median treatment duration of 55.0 months and 55.5 months, respectively) was consistent with the known safety profile of lumasiran.

Paediatric population

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the Yellow Card Scheme at https://www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Various alimentary tract and metabolism products,
ATC code: A16AX18.

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.

Immunogenicity

In patients with PH1 and healthy volunteers dosed with Oxlumo in clinical studies anti-drug-antibodies (ADA) were detected (7 of 120 (5.8%) individuals tested positive for ADA). ADA titres were low and generally transient, and no evidence of ADA impact on pharmacokinetics, efficacy or safety was observed. However, data are still limited.

Clinical efficacy

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

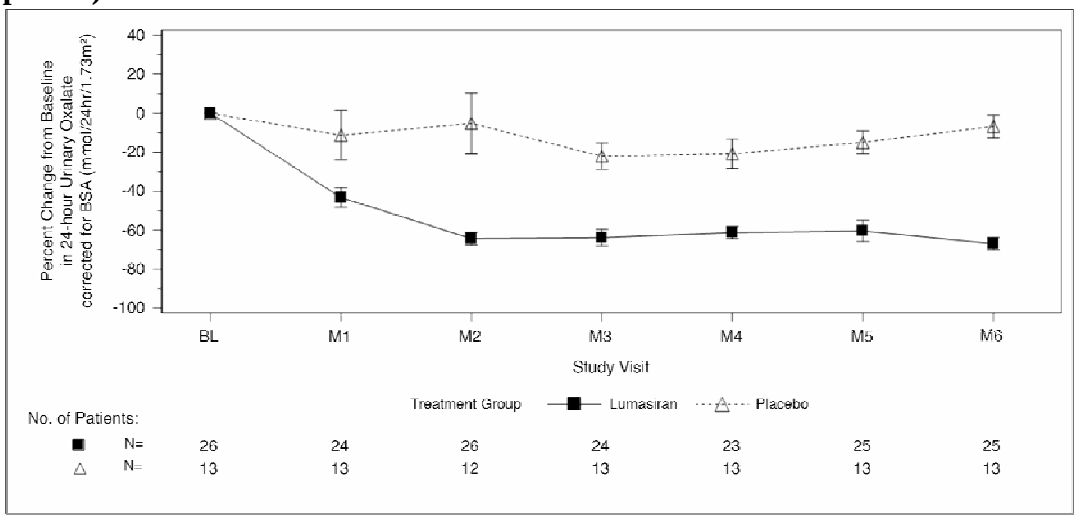
A total of 39 patients with PH1 were randomised 2:1 to receive subcutaneous doses of lumasiran or placebo during the 6-month double-blind, placebo-controlled period. Patients 6 years and older with an eGFR-≥30 mL/min/1.73 m^2 were enrolled, and received 3 loading doses of 3 mg/kg lumasiran or placebo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

of lumasiran for up to 54 months. The overall lumasiran exposure was 165.7 patient years.

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 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 (6-month double-blind, placebo-controlled period)



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 3.

Table 3: 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 24-hour urinary oxalate levels at or below 1.5×ULN[‡]	0.84 (0.64, 0.95)[§]	0 (0, 0.25)[§]	0.84 (0. 55, 0.94)[¶]	<0.0001[#]
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 m^2 for 24-hour urinary oxalate corrected for BSA.

[§]95% CI based on Clopper Pearson Exact confidence interval.

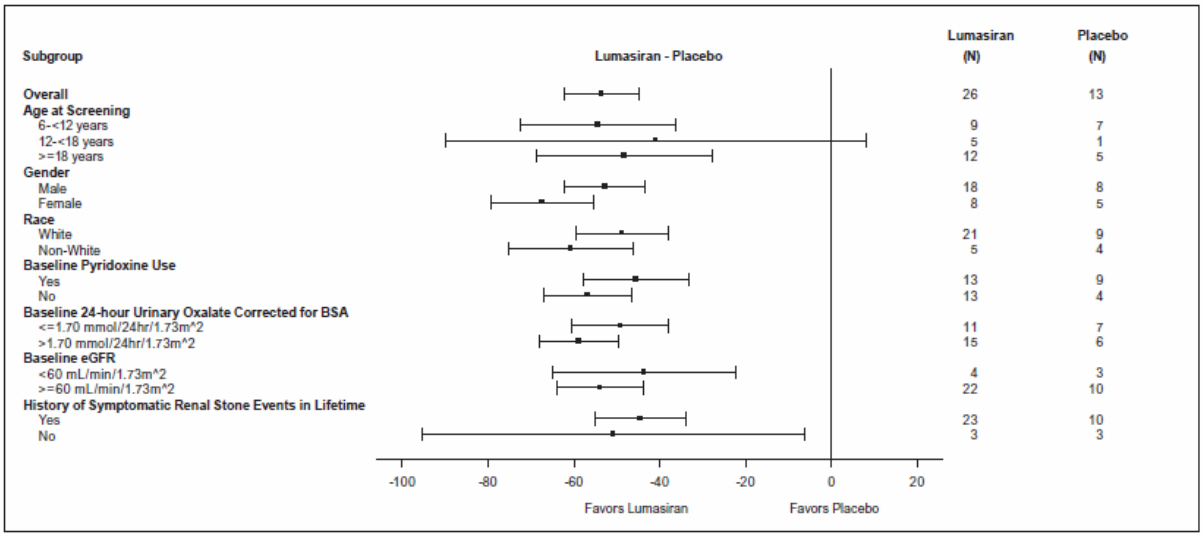
[¶]Calculated using the Newcombe Method based on the Wilson Score.

[#]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 m^2).

[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, gender, 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, subgroup analysis



Reduced oxalate levels observed in the double-blind period were maintained with continued lumasiran treatment up to 60 months during the extension period of the study. eGFR, renal stone events (reported by events per person-year) and medullary nephrocalcinosis were assessed through the 6-month double-blind and extension periods for a total of up to 60 months.

eGFR remained stable in patients administered lumasiran. The mean annual rate of change from baseline during treatment with lumasiran up to 60 months was -0.63 ml/min/1.73 m^2/year.

The rate of renal stone events per person-year reported in patients randomised to lumasiran and placebo in ILLUMINATE-A are presented in Table 4.

Table 4: ILLUMINATE-A: Rate of Renal Stone Events per Person-Year Reported in the Lumasiran and Placebo Group

Time Period	Lumasiran Rate (95% CI)	Placebo Rate (95% CI)
12 months prior to consent	3.19 (2.57, 3.96)	0.54 (0.26, 1.13)
6-month double-blind period	1.09 (0.63, 1.88)	0.66 (0.25, 1.76)

During extended open-label treatment with lumasiran up to 60 months, the rate of renal stone events was 0.49 per person-year, and 53.8% of the patients had no renal stone events.

Medullary nephrocalcinosis results, assessed by renal ultrasound, from month 6 relative to baseline are presented in Table 5.

Table 5: ILLUMINATE-A: Patients with Medullary Nephrocalcinosis at Month 6 Double-Blind, Placebo-Controlled Period Relative to Baseline*

Timepoint	Treatment (n)	Improvement	No Change	Worsening
Month 6	Lumasiran (N=22)	3	19	0
	Placebo (N=12)	0	11	1

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

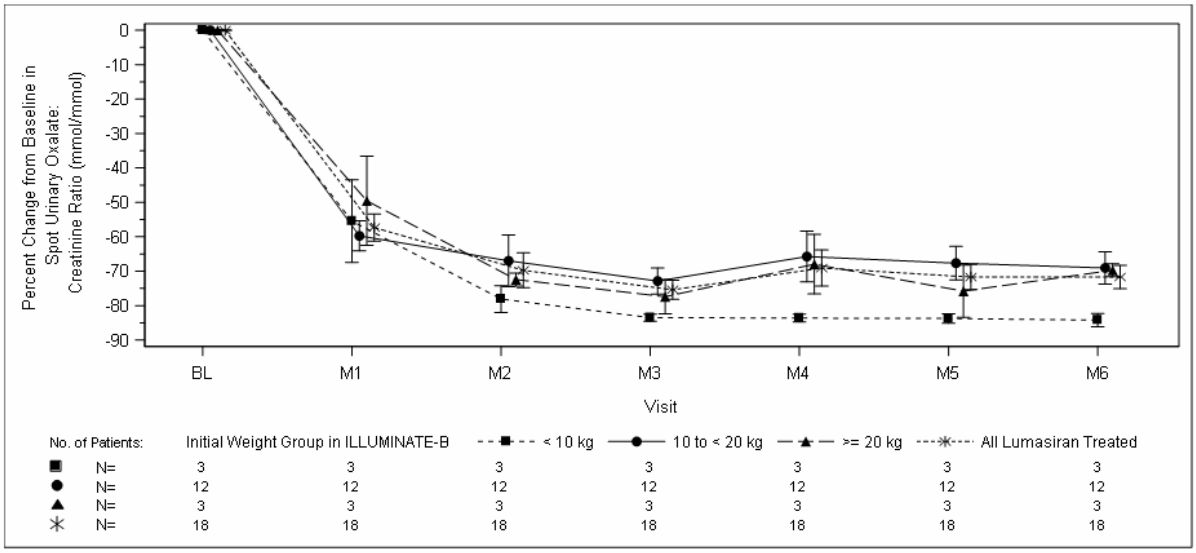
The evaluation of medullary nephrocalcinosis was performed only in a part of the study population (17/26 lumasiran/lumasiran patients and 6/13 placebo/lumasiran patients were evaluated at both baseline and at the end of the 54-month extension period). In this subpopulation a general trend for improvement over time was demonstrated.

ILLUMINATE-B

A total of 18 patients were enrolled and treated with lumasiran in an ongoing multi-center, 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 m^2 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 4to 74months), 55.6% were female, and 88.9% were white. The median spot urinary oxalate:creatinine ratio at baseline was 0.47 mmol/mmol. After the 6-month primary analysis period, patients entered an extension period with administration of lumasiran for up to 60 months. The overall lumasiran exposure was 83.2 patient years.

At month 6, patients treated with lumasiran achieved a reduction of 72% (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 60, with a 74.5% (4.25) mean (SEM) percent reduction from baseline in the spot urinary oxalate: creatinine ratio, and this treatment effect was consistent with data from ILLUMINATE-A.

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



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 through month 60, with a mean reduction of 24.8% (95% CI: 15.7, 59.5) at month 60.

eGFR remained stable in all patients with continued dosing. The annual rate of change in eGFR from baseline during treatment with lumasiran up to 60 months was 0.26 mL/min/1.73 m^2/year.

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 overall rate of renal stone events per person-year in the study at month 60 was 0.11 (95% CI: 0.06, 0.21), and 77.8% of the patients had no renal stone events during the study.

During the evaluation of medullary nephrocalcinosis, a trend toward improvement over a period of 60 months was demonstrated. Among the 18 patients treated for 60 months, 14 patients had presence of medullary nephrocalcinosis at baseline. Of the 14 patients, 12 showed improvement with 10 improving to the absence of nephrocalcinosis (defined as Grade 0 bilaterally), 1 had no change, and 1 was indeterminate (one kidney improved while the other worsened). Of the 4 patients who had absence of nephrocalcinosis at baseline, all 4 had no change at month 60.

ILLUMINATE-C

A total of 21 patients were enrolled and treated with lumasiran in an on-going multi-center, 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 enrollment and Cohort B consists of

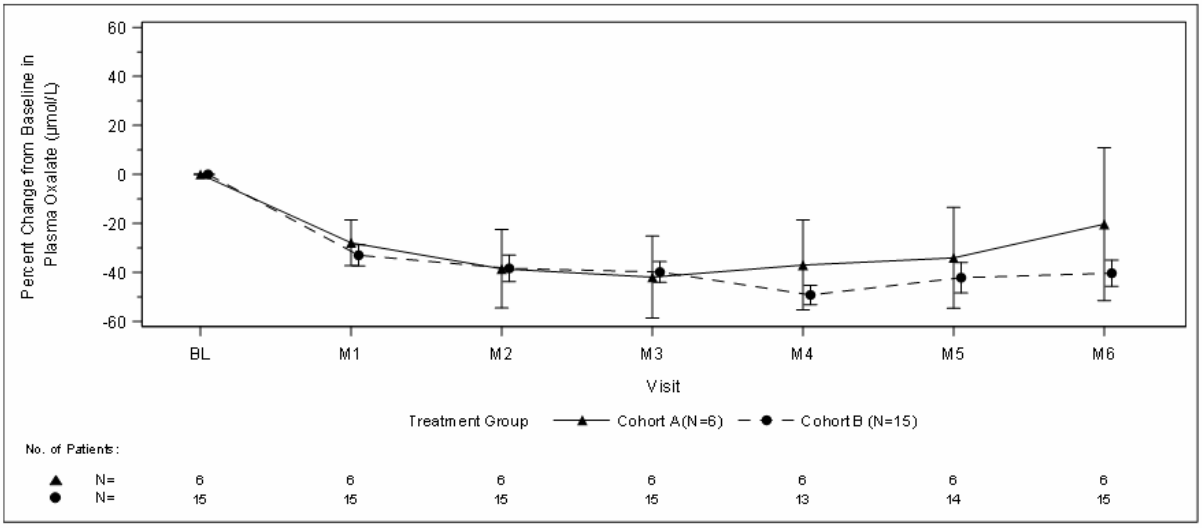
15 -patients who were on stable regimen of haemodialysis. Patients received the recommended dosing regimen of lumasiran based on body weight (see section 4.2).

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/1.73 m^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 (see section 4.2 for information on 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 (0.5 to 12) 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 1 130) ng/mL and 7 400 (2 890 to 10 700) 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 1 760) and 7 960 (5 920 to

13 300) respectively. 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.

Biotransformation

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.

Elimination

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%) 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 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.

Interactions

In vitro studies indicate that lumasiran is not a substrate or an inhibitor of cytochrome P450 (CYP) enzymes. Lumasiran is not expected to inhibit or induce CYP enzymes or modulate the activities of drug transporters.

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). Limited pharmacokinetic data in patients with mild and transient elevations in total bilirubin (total bilirubin >1 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), 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). 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).

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

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity and carcinogenic potential.

In rats, but not in monkeys, microscopic changes in the liver (e.g. hepatocellular vacuolation, mitosis and karyomegaly) were observed, accompanied by decrease in plasma fibrinogen levels and other laboratory changes. The reason for the apparent rodent-specificity is not understood and the relevance for humans is unclear.

Lumasiran did not show any adverse effects on male and female fertility and pre- and post-natal development in rats. In embryo-foetal development studies in rats and rabbits, skeletal abnormalities were observed, but at high exposure multiples relative to human therapeutic exposures. The no-observed-adverse-effect levels (NOAELs) were approximately 20- to 70-times higher (based on monthly exposures).

A dose-range finding toxicity study in neonate rats did not show increased sensitivity of the developing rat to either the toxicology or pharmacology of lumasiran at exposure multiples of 2 compared to human therapeutic exposures (based on monthly exposures).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide (pH adjustment) (E524)
Phosphoric acid (pH adjustment) (E338)
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

3 years.

After first opening

Once the vial is opened, the medicinal product should be used immediately.

6.4 Special precautions for storage

Do not store above 30°C.

Keep the vial in the outer carton in order to protect from light.

For storage conditions after first opening of the medicinal product, see section 6.3.

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

This medicinal product is ready-to-use and for single use only.

For subcutaneous use only

Preparation for administration

- Before administration, materials not included in the pack that are needed for administration should be collected, 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.
- The required volume of Oxlumo should be calculated based on the recommended weight-based dose (see section 4.2).
- An 18-G 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.
- For volumes less than 0.3 mL, a sterile 0.3 mL syringe is recommended.
- The medicinal product should be administered with a sterile 25 -G to 31-G needle with a 13 mm or 16 mm needle length for subcutaneous injection.

- Note: This medicinal product should not be pushed into the 25 G to 31 G needle.
- Syringes, transfer needles, and injection needles should only be used once.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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1083 HP Amsterdam

Netherlands

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