swissmedic

Date: 7 August 2024
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

OXLUMO®

International non-proprietary name: lumasiran
Pharmaceutical form: solution for injection
Dosage strength(s): each vial contains 94.5 mg lumasiran in 0.5 mL
Route(s) of administration: subcutaneous
Marketing authorisation holder: Alnylam Switzerland GmbH
Marketing authorisation no.: 68239
Decision and decision date: approved on 01.12.2021

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

Table of contents

1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for lumasiran in the above-mentioned medicinal product.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 a^{decies} no. 2 of the TPA.
Orphan drug status was granted on 14 January 2021.

Authorisation as human medicinal product in accordance with Article 13 TPA
The applicant requested a reduced assessment procedure in accordance with Article 13 TPA.

2.2 Indication and dosage

2.2.1 Requested indication

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

2.2.2 Approved indication

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

2.2.3 Requested dosage

Summary of the requested standard dosage:
The recommended dose of Oxlumo consists of loading doses given once a month for 3 months, followed by maintenance doses. 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.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	26 February 2021
Formal control completed	9 March 2021
Preliminary decision	7 July 2021
Response to preliminary decision	5 September 2021
Final decision	1 December 2021
Decision	approval

Swissmedic has not assessed the primary data (e.g. study reports) submitted with this application and relies for its decision on the assessment of the foreign reference authority, the EMA. This SwissPAR relates to the publicly available assessment report Oxlumo (EMA/568312/2020, Procedure No. EMEA/H/C/005040/0000, first published: 25.11.2020), issued by the EMA.

3 Quality aspects

Swissmedic has not assessed the primary data relating to quality aspects submitted with this application and relies on the assessment of the foreign reference authority, the EMA. The SwissPAR relating to quality aspects refers to the publicly available assessment report Oxlumo (EMA/568312/2020, Procedure No. EMEA/H/C/005040/0000, first published: 25.11.2020), issued by the EMA.

4 Nonclinical aspects

Swissmedic has not assessed the primary data relating to nonclinical aspects submitted with this application and relies on the assessment of the foreign reference authority, the EMA. The nonclinical aspects in this SwissPAR refer to the publicly available assessment report Oxlumo (EMA/568312/2020, Procedure No. EMEA/H/C/005040/0000, first published: 25.11.2020), issued by the EMA.

5 Clinical aspects

Swissmedic has not assessed the primary data relating to clinical aspects submitted with this application and relies on the assessment of the foreign reference authority, the EMA. The clinical aspects in this SwissPAR refer to the publicly available assessment report Oxlumo (EMA/568312/2020, Procedure No. EMEA/H/C/005040/0000, first published: 25.11.2020), issued by the EMA.

6 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

7 Appendix

Approved information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for Oxlumo was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the information for healthcare professionals approved in one of the official Swiss languages.

Placeholder for text approval stamp

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

OXLUMO®

Composition

Active substances

Lumasiran (as lumasiran-sodium).

Excipients

Sodium hydroxide, phosphoric acid, water for injections. Contains 5.5 mg sodium per 0.5 mL.

Pharmaceutical form and active substance quantity per unit

Solution for injection, subcutaneous
Clear, colourless to yellow solution (pH of approximately 7; osmolality 210 to 390 mOsm/kg).
Each mL of solution contains lumasiran sodium equivalent to 189 mg lumasiran.
Each vial contains 94.5 mg lumasiran in 0.5 mL.

Indications/Uses

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

Dosage/Administration

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

Posology

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Oxlumo is administered by subcutaneous injection. The recommended dose of Oxlumo consists of loading doses given once a month for 3 months, followed by maintenance doses, 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 (the maintenance dose should begin one month after the last loading dose)
less than 10 kg	6 mg/kg once monthly for 3 months	3 mg/kg once monthly
10 kg to less than 20 kg	6 mg/kg once monthly for 3 months	6 mg/kg once every 3 months (quarterly)
20 kg and above	3 mg/kg once monthly for 3 months	3 mg/kg once every 3 months (quarterly)

Patients with hepatic disorders

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 «Warnings and Precautions» and «Pharmacokinetics»).

Patients with renal disorders

No dose adjustment is necessary in patients with mild (estimated glomerular filtration rate (eGFR) 60 to <90 mL/min/1.73 m^2) or moderate (eGFR 30 to <60 mL/min/1.73 m^2) renal impairment (see section 5.2). Limited clinical data are available in patients with severe renal impairment (eGFR 15 to <30 mL/min/1.73 m^2), end-stage renal disease (eGFR <15 mL/min/1.73 m^2), or who are on dialysis. Safety monitoring is warranted when treating patients with severe or end-stage renal impairment (see «Warnings and Precautions» and «Pharmacokinetics»).

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Elderly patients

No dose adjustment is necessary in patients ≥65 years of age (see «Pharmacokinetics»).

Children and adolescents

In patients under 1 year of age, limited data are available. Caution should be used when treating these patients (see «Pharmacokinetics»).

Delayed administration

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.

Mode 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 the medicinal product before administration, see «Instructions for handling».

Contraindications

Severe hypersensitivity to the active substance or any of the excipients listed in «Composition».

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Warnings and precautions

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 «Pharmacokinetics»).

Other ingredients

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

Interactions

No clinical drug interaction studies have been performed (see «Pharmacokinetics»).

In vitro studies indicate that lumasiran is neither a substrate nor an inhibitor of cytochrome P450 (CYP) enzymes. 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.

Pregnancy, 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 «Preclinical data»). 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 foetus.

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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.

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 «Preclinical data»).

Effects on ability to drive and use machines

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

Undesirable effects

Summary of the safety profile

The most common adverse reaction reported was injection site reaction (32%).

List of adverse reactions

Adverse reactions associated with lumasiran obtained from clinical studies are tabulated below. The adverse reactions are arranged according to MedDRA system organ classes and the conventional frequencies as follows: "very common" (≥1/10); "common" (≥1/100, <1/10); "uncommon" (≥1/1,000, <1/100); "rare" (≥1/10,000, <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 (21.0%)
General disorders and administration site conditions	Injection site reaction[b]	Very common (32.1%)

[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.

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Description of specific adverse reactions and additional information

Injection site reactions

In placebo-controlled and open-label clinical studies, injection site reactions were reported in 26 of 81 patients (32.1%), occurring in 10% of injections. The most commonly reported symptoms were erythema, pain, pruritus, and swelling. The majority of injection site reactions started on the day of administration, with 7 of the patients having injection site reactions that started 5 or more days after administration (occurred in 1.6% of injections). 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, 17 of 81 patients (21.0%) 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, 6 of 100 (6.0%) 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.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk ratio of the medicinal product. Healthcare professionals are requested to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

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.

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Properties/Effects

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.

Pharmacodynamics

Not applicable.

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) and in a single-arm clinical study in patients less than 6 years of age with PH1 (ILLUMINATE-B).

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 «Dosage/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

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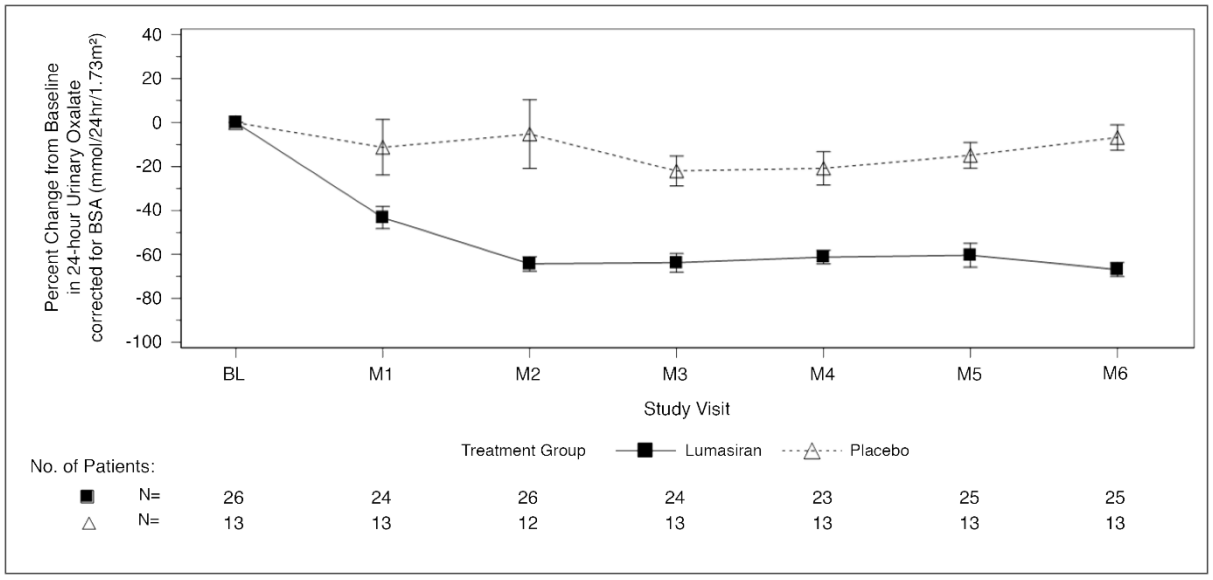
urinary oxalate: creatinine ratio at baseline was 0.21 mmol/mmol, and the median plasma oxalate level at baseline was 13.1 µmol/L. Overall, 33.3% of patients had normal renal function (eGFR ≥90 mL/min/1.73 m^2), 48.7% had mild renal impairment (eGFR of 60 to <90 mL/min/1.73 m^2), and 18% had moderate 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 3.

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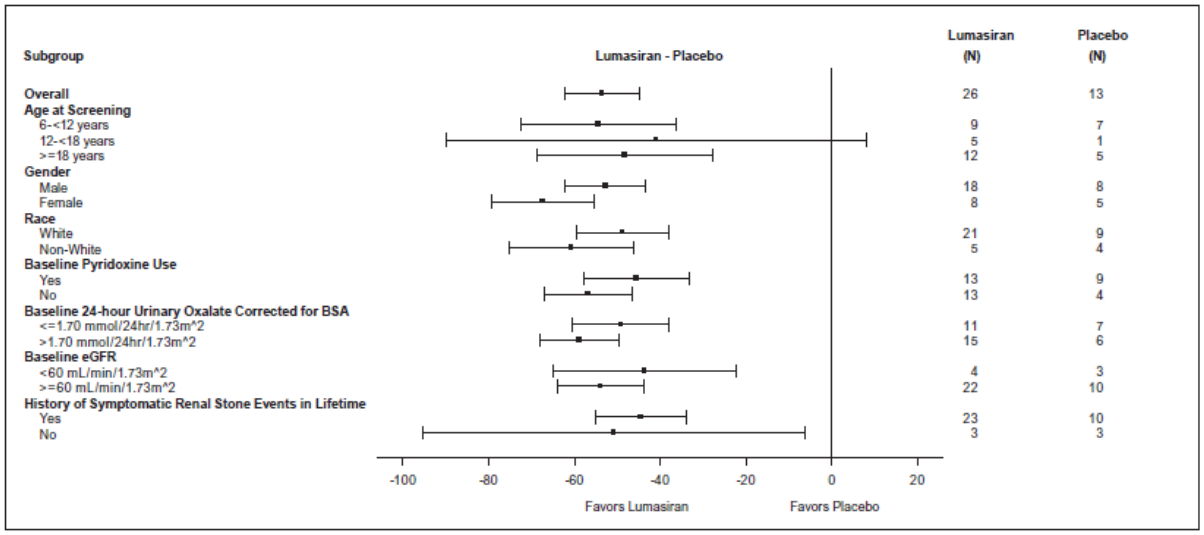
Table 3: ILLUMINATE-A: Secondary endpoint results over the 6-month double-blind, placebo-controlled period

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‡	0.5 (0.3, 0.7)§	0 (0, 0.2)§	0.5 (0.2, 0.7)¶	0.001#
Proportion of patients with 24-hour urinary oxalate levels at or below 1.5×ULN‡	0.8 (0.6, 1.0)§	0 (0, 0.2)§	0.8 (0.5, 0.9)¶	<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).
ÞAnalysed 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, subgroup analysis



Reduced oxalate levels observed in the double-blind period were maintained through 12 months during the extension period of study.

eGFR and renal stone events (reported by events per 100 person-days) were assessed through the double-blind and extension periods for a total of 12 months. eGFR remained stable in patients administered lumasiran. In the lumasiran arm, the rate of renal stone events reported 12 months prior to consent was 0.87 (95% CI: 0.70, 1.08). The observed events during the double-blind period and the first 6 months of the extension period were 0.30 (95% CI: 0.17, 0.51) and 0.23 (95% CI: 0.13, 0.43), respectively. In the placebo arm, the rate of renal stone events reported 12 months prior to consent was 0.15 (95% CI: 0.07, 0.31) and the observed events during the double-blind period were 0.18 (95% CI: 0.07, 0.48). During the first 6 months of lumasiran treatment in the extension period a rate of 0.05 (95% CI: 0.01, 0.32) events were observed in patients previously receiving placebo. For nephrocalcinosis, data through the 6-month double-blind period are available. Of the 34 patients with baseline and month 6 renal ultrasounds, 3 of 22 in the lumasiran group showed improvement in nephrocalcinosis, and 1 of 12 in the placebo group showed worsening in nephrocalcinosis. None of the other lumasiran (n=19) or placebo-treated (n=11) patients exhibited a change in nephrocalcinosis.

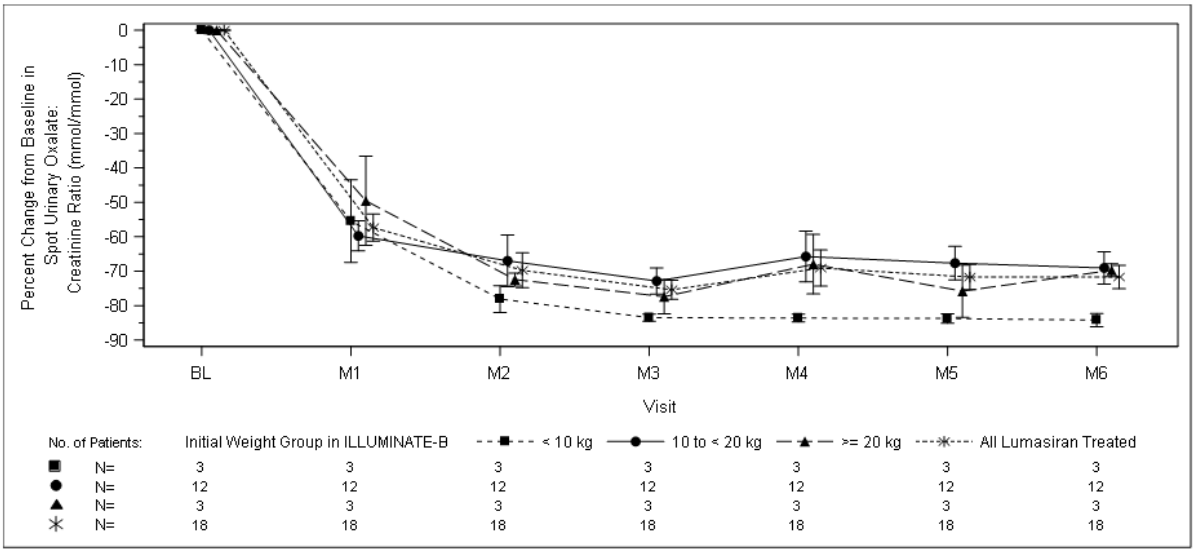
ILLUMINATE-B

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 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 consistent with data from ILLUMINATE-A.

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



Nine patients achieved near normalisation (≤1.5×ULN), including 1 patient who achieved normalisation (≤ULN), at month 6 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. During the 6-month period, the eGFR remained stable, and 2 post-baseline renal stone events in 2 patients were reported, compared to 4 renal stone events in 3 patients in the 12-month period prior to consent. Fourteen of 18 patients had baseline nephrocalcinosis. Renal ultrasound data at month 6 indicated improvement in 8 patients, including 3 with bilateral improvement. None of the 18 patients had new onset or worsening nephrocalcinosis.

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Paediatrics

For this medicinal product, Swissmedic has recognized an exemption from the obligation to submit results of studies in all pediatric age groups in the treatment of AHP

Pharmacokinetics

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.

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 (47.0%) 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.

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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.

Kinetics in specific patient groups

Hepatic impairment

No studies have been conducted in patients with hepatic impairment (see «Dosage/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 and similar pharmacodynamics 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. Limited clinical data are available in patients with severe renal impairment (eGFR 15 to <30 mL/min/1.73 m^2), end-stage renal disease (eGFR <15 mL/min/1.73 m^2), or who are on dialysis (see section 4.2). For ESRD patients on dialysis, within the same body weight category, a transient 3- to 7-fold higher C_{max} and 2- to 3.5-fold $AUC_{0\text{-last}}$ increase was observed (see «Pharmacokinetics», Pharmacokinetic/pharmacodynamic relationship(s)). However, plasma concentrations decline below the level of detection within 24 to 48 hours, similar to patients without renal impairment.

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Elderly patients

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

Children and adolescents

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).

Gender and race

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

Preclinical data

Safety pharmacology

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

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.

Carcinogenicity

Animal studies have not been conducted to evaluate the carcinogenic potential of lumasiran.

Reproductive toxicity

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

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were observed, but at high exposure multiples relative to human therapeutic exposures. The NOAELs were approximately 20- to 70-times higher (based on monthly exposures).

Toxicity tests with juvenile animals

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).

Other information

Incompatibilities

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

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.

Shelf life after opening

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

Special precautions for storage

Do not store above 30°C.
Keep vial in the outer carton to protect from light.

Keep out of the reach of children.

Instructions for handling

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

For subcutaneous use only.

- 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.

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- The required volume of Oxlumo should be calculated based on the recommended weight-based dose (see «Dosage/administration»).
- 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.
- 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- 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.

Authorisation number

68239 (Swissmedic).

Packs

Each pack contains one 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. [B]

Marketing authorisation holder

Alnylam Switzerland GmbH, Zug.

Date of revision of the text

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