Medicines & Healthcare products Regulatory Agency

MHRA

Early Access to Medicines Scheme – Treatment protocol – Information for healthcare professionals

Introduction

The aim of the Early Access to Medicines Scheme (EAMS) is to provide earlier availability of promising new unlicensed medicines and medicines used outside their licence, to UK patients that have a high unmet clinical need. The medicinal products included in the scheme are those that are intended to treat, diagnose or prevent seriously debilitating or life-threatening conditions where there are no adequate treatment options. More information about the scheme can be found here: http://www.mhra.gov.uk/Howweregulate/Innovation/EarlyaccesstomedicinesschemeEAMS/index.htm

This information is intended for healthcare professionals and is provided by the pharmaceutical company that manufactures the EAMS medicine. This medicine does not yet have a licence (marketing authorisation) and the information is provided to assist physicians in prescribing this unlicensed medicine. Guidance on prescribing unlicensed medicines can be found on the GMC webpage:
https://www.gmc-uk.org/guidance/ethical_guidance/14327.asp

The scientific opinion is based on assessment of the information supplied to the MHRA on the benefits and risks of this promising new medicine. As such, this is a scientific opinion and should not be regarded as a medicine licensed by the MHRA or a future commitment by the MHRA to license such a medicine, nor should it be regarded as an authorisation to sell or supply such a medicine. A positive scientific opinion is not a recommendation for use of the medicine and should not be interpreted as such. Under EAMS the risk and legal responsibility for prescribing a 'special' remains with the physician, and the opinion and EAMs documentation published by the MHRA are intended only to inform physicians' decision making and not to recommend use. An EAMS scientific opinion does not affect the civil liability of the manufacturer or any physician in relation to the product.

Healthcare professionals should also refer to the summary information on the pharmacovigilance system which is provided in the document 'Early Access to Medicines Scheme – Treatment protocol – Information on the pharmacovigilance system'.

Scientific opinion period: The MHRA will withdraw the EAMS positive scientific opinion when a marketing authorisation (drug licence) is issued for the EAMS product covering the EAMS indication, or if following scientific assessment, the EAMS criteria are considered to be no longer met.

Treatment protocol update(s): In case of substantial new efficacy or safety data, the treatment protocol may need to be updated.

Contact information regarding queries on using this EAMS medicine can be found at the end of this document.

Information for the healthcare professionals:

1. NAME OF THE MEDICINAL PRODUCT

Lumasiran 189 mg/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.

Excipient with known effect

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 210 to 390 mOsm/kg).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Lumasiran 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 under the supervision of a healthcare professional experienced in the management of hyperoxaluria.

Posology

Lumasiran is administered by subcutaneous injection. The recommended dose of lumasiran consists of loading doses 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 vial concentration (189 mg/mL) = total volume of medicinal product (mL) to be injected.

Table 1: Lumasiran Weight-Based Dosing Regimen

Body Weight	Loading Dose	Maintenance Dose (begin 1 month after the last loading dose)
less than 10 kg	6 mg/kg once monthly for 3 doses	3 mg/kg once monthly
10 kg to less than 20 kg	6 mg/kg once monthly for 3 doses	6 mg/kg once every 3 months (quarterly)
20 kg and above	3 mg/kg once monthly for 3 doses	3 mg/kg once every 3 months (quarterly)

Missed dose
If a dose is delayed or missed, treatment should be administered as soon as possible. Resume prescribed monthly or quarterly dosing, 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
No dose adjustment is necessary in patients with mild hepatic impairment (total bilirubin ≤ upper limit of normal (ULN) and aspartate aminotransferase (AST) > ULN; or total bilirubin >1.0 to 1.5×ULN) (see section 5.2). Lumasiran has not been studied in patients with moderate or severe hepatic impairment.

Renal impairment
No dose adjustment is necessary in patients with mild (estimated glomerular filtration rate (eGFR) 60 to <90 mL/min/1.73 m2) or moderate (eGFR 30 to <60 mL/min/1.73 m2) renal impairment (see section 5.2). Lumasiran has not been studied in patients with severe renal impairment, end-stage renal disease, or those on dialysis, and this should be taken into consideration when assessing the individual benefit-risk in these patients.

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 lumasiran should be calculated based on the recommended weight-based dose as shown in Table 1.
- If the dose is more than 0.5 mL, more than one vial will be needed.
- Avoid having the medicinal product on the needle tip before the needle is in the subcutaneous space.
- 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.
- 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.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Excipient related considerations (sodium content)

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

Concomitant use with pyridoxine
Concomitant use of pyridoxine did not 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 this medicinal product could 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 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 lumasiran 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

Lumasiran 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 (≥20%) adverse reaction reported was injection site reaction. All adverse reactions were non-serious, and none resulted in discontinuation of treatment.

Tabulated list of adverse reactions
Adverse reactions associated with lumasiran obtained from clinical studies are tabulated below.

The adverse reaction is coded to preferred term (PT) under the MedDRA system organ class (SOC). The frequency of the adverse reaction is expressed according to the following categories:

- Very common (≥1/10)

Table 2: Adverse reactions

System organ class	Adverse reaction	Frequency
General disorders and administration site conditions	Injection site reaction	Very common

Description of selected adverse reactions

Injection site reactions
In placebo-controlled and open-label clinical studies, injection site reactions were reported in 19 of 75 patients (25%), occurring in 10% of injections. The most commonly reported symptoms were erythema, pain, pruritus, and swelling. Injection site reactions have been mild, transient, and have not resulted in discontinuation of treatment.

Immunogenicity

In patients with PH1 and healthy volunteers dosed with lumasiran, 5 of 89 (5.6%) 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 and adult patients with PH1.

4.9 Overdose
No case of overdose has been reported. 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: not yet assigned, ATC code: not yet assigned.

Mechanism of action

Lumasiran is a double-stranded small interfering ribonucleic acid (siRNA) that reduces levels of glycolate oxidase (GO) enzyme by targeting the *HAO1* 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.

Pharmacodynamic effects

The pharmacodynamic effects of lumasiran have been evaluated in adult and paediatric patients with PH1 across a range of doses and dosing frequency. Dose-dependent reductions in urinary and plasma oxalate levels were observed, resulting in the selection of the recommended body weight-based loading and maintenance dosing regimens. With the recommended dosing regimens, rapid onset of effect was observed within two weeks after the first dose and maximal reductions in urinary and plasma oxalate were observed by the end of the loading dose phase. The maximal reductions in urinary and plasma oxalate were sustained with the maintenance dosing regimen thereafter.

Clinical efficacy

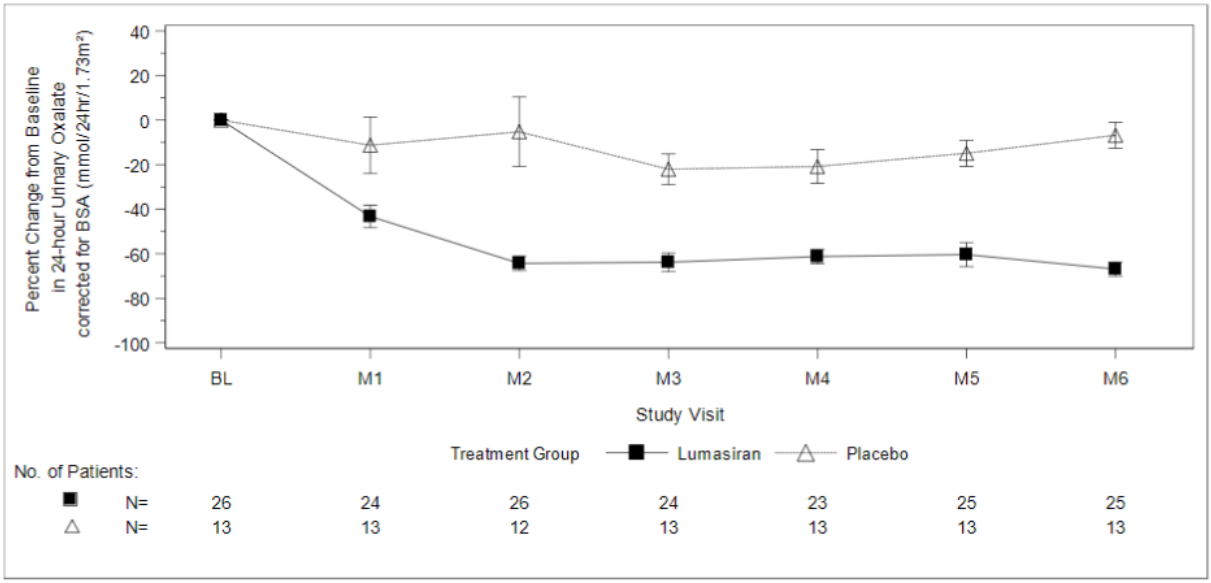
The efficacy of lumasiran was demonstrated in a randomized, double-blind, placebo-controlled clinical study in patients 6 years and older with PH1 (ILLUMINATE-A) and in a single-arm clinical study in patients less than 6 years of age with PH1 (ILLUMINATE-B).

ILLUMINATE-A
A total of 39 patients with PH1 were randomized 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.

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 1.7 mmol/24 h/1.73 m^2, and the median plasma oxalate level at baseline was 13.1 µmol/L. 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 clinically meaningful and statistically significant reduction of 53.5% (95% CI: 44.8, 62.3) in 24-hour urinary oxalate corrected for BSA compared to placebo ($p<0.0001$). Consistent with the primary endpoint, clinically meaningful reductions from baseline were observed in spot urinary oxalate:creatinine ratio. 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.

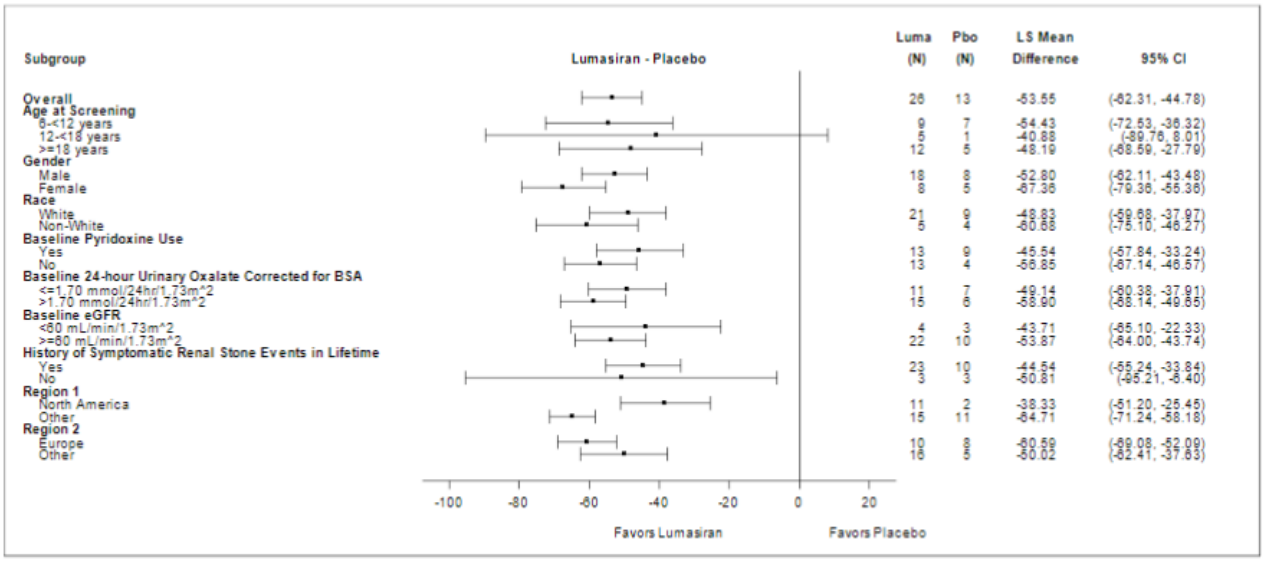
Table 3: ILLUMINATE-A: Secondary Endpoint Results Over the 6-Month Double-Blind, Placebo-Controlled Period

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, 0.3)§	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, 0.3)§	0.8 (0.6, 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).
ÞAnalyzed 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, region, 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



During the 6-month placebo-controlled period, the estimated glomerular filtration rate (eGFR) remained stable, and renal stone event frequency was comparable between treatment groups. 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 or placebo-treated 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. The median duration of treatment was 6.9 months (range: 1.9 to 9.7 months).

A primary interim analysis was conducted when the first 16 patients received 6 months of treatment with lumasiran. The percent reduction in urinary oxalate excretion was similar across ages and weight strata, and consistent with data from ILLUMINATE-A.

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with lumasiran 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 (0.5 to 12.0) hours. At the 3-mg/kg dose level, the peak plasma concentration of lumasiran (C_{max}) and area under the concentration curve from time zero to the last measurable concentration after dosing ($AUC_{0\text{-last}}$) were 462 (38.5 to 1500) ng/mL and 6810 (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

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 metabolized 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. 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 renal clearance of lumasiran was minor and ranged from 2.0 to 3.4 L/h.

Linearity/non-linearity

Lumasiran exhibited linear, 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.

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
Patients with mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN; or total bilirubin >1.0 to 1.5×ULN) had comparable plasma exposure of lumasiran and similar pharmacodynamics as patients with normal hepatic function. No studies have been conducted in patients with moderate or severe hepatic impairment (see section 4.2).

Renal impairment
Patients with mild (eGFR 60 to <90 mL/min/1.73 m^2) or moderate (eGFR 30 to <60 mL/min/1.73 m^2) renal impairment had comparable plasma exposure of lumasiran and similar pharmacodynamics as patients with normal renal function (eGFR ≥90 mL/min/1.73 m^2). No studies have been conducted in patients with severe renal impairment, end-stage renal disease, or those on dialysis (see section 4.2).

Paediatric population
The pharmacokinetics and pharmacodynamics of lumasiran were similar in adult and paediatric patients.

Body weight
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 recommended dosing regimens yielded similar AUC across the body weight groups 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, repeated dose toxicity, genotoxicity, toxicity to reproduction and development. In repeat-dose toxicity studies conducted in rats and monkeys, no target organs of toxicity were identified at the highest dose tested (plasma AUC exposure multiples 76- and 260-fold, respectively, when compared to the exposures achieved at the maximum recommended human dose of 6 mg/kg dose administered every 3 months (when normalized to 2 mg/kg/month). Based on an absence of findings in nonclinical studies, lumasiran is not considered to have an immunostimulatory or immunotoxicity potential. A juvenile animal toxicity study has not revealed any relevant findings.

Genotoxicity/carcinogenicity

Lumasiran did not exhibit a genotoxic potential in vitro and in vivo.

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

Reproductive toxicity

In an embryo-foetal development study in pregnant rats, lumasiran was administered subcutaneously at doses of 3, 10, and 30 mg/kg/day during organogenesis (gestational days 6-17). Administration of lumasiran resulted in no effects on embryo-foetal survival or foetal body weights. The lumasiran-related foetal skeletal variations (bipartite ossification of sternabrae and misshapen cervical arches) were not considered adverse and no lumasiran related foetal malformations were observed. The 30-mg/kg/day dose in rats is 45 times the maximum recommended human dose for women of 3 mg/kg/month normalized to 0.1 mg/kg/day, based on body surface area. In an embryo-foetal development study in female rabbits, lumasiran was administered subcutaneously at doses of 3, 10, and 30 mg/kg/day during organogenesis (gestational days 7-19). There were minimal decreases in maternal food consumption and maternal absolute body weights at ≥3 mg/kg/day. There were no lumasiran-related foetal findings identified at doses up to 30 mg/kg/day (90 times the normalised maximum recommended human dose based on body surface area).

In a postnatal development study, lumasiran administered subcutaneously to pregnant female rats on gestational days 7, 13, 19 and on lactation days 6, 12, and 18 through weaning at doses up to 50 mg/kg did not produce maternal toxicity or developmental effects in the offspring.

No adverse effects were observed in the fertility of male and female rats when administered with lumasiran.

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

Unopened vials
4.5 years.

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

6.4 Special precautions for storage

Store at 2-8 °C (Refrigerate, do not freeze).

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 and other handling

This medicinal product is for single use only.

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

7. SCIENTIFIC OPINON HOLDER

Alnylam UK Limited
Braywick Gate
Braywick Road
Maidenhead
SL6 1DA
United Kingdom

8. EAMS NUMBER(S)

43942/0002

9. DATE OF SCIENTIFIC OPINION

10th July 2020

Additional information:

Prior to requesting access to lumasiran, you will have the scheme explained to you using this leaflet. You will be requested to sign an Informed Consent Form and will be given a copy to keep.

In addition to pharmacovigilance reporting, data may be collected on clinical efficacy on a voluntary basis. These tests can include: results of blood and urinary tests, renal stone event form and physical assessments. This data may be shared with the EAMS Scientific Opinion Holder, and regulatory authorities.

Contact details:

EAMS queries:
To request access to EAMS or EAMS related enquiries: EAP@alnylam.com

Pharmacovigilance Reporting:
All reporting forms should be submitted to Clinigen at: drugsafety@clinigengroup.com

Alnylam Medical Information Hotline:
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Toll-free: 08001412569
medinfo@alnylam.com