Early Access to Medicines Scientific Opinion - Public Assessment Report

<table>
<thead>
<tr>
<th>Product</th>
<th>Lumasiran</th>
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<tr>
<td>EAMS indication</td>
<td>Lumasiran is indicated for the treatment of primary hyperoxaluria type 1 (PH1) In adults and children of all ages.</td>
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<tr>
<td>Company</td>
<td>Alnylam UK Limited</td>
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<td>EAMS number</td>
<td>43942/0002</td>
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<td>EAMS Scientific Opinion date</td>
<td>10 July 2020</td>
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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 MHRA scientific opinion provides benefit and risk information to physicians who may wish to prescribe the EAMS medicine under their own responsibility. More information about the scheme can be found here: [http://www.mhra.gov.uk/Howweregulate/Innovation/EarlyaccesstomedicinesschemeEAMS/index.htm](http://www.mhra.gov.uk/Howweregulate/Innovation/EarlyaccesstomedicinesschemeEAMS/index.htm)

The scientific opinion is based on assessment of the information supplied to the MHRA on the benefits and risks of the 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.

The General Medical Council’s guidance on prescribing unlicensed medicines can be found here: [https://www.gmc-uk.org/guidance/ethical_guidance/14327.asp](https://www.gmc-uk.org/guidance/ethical_guidance/14327.asp)

What is lumasiran?
Lumasiran is the active substance of a medicine, which is available as a vial of solution for injection under the skin (‘subcutaneously’).

What is lumasiran used to treat?
Lumasiran is used to treat primary hyperoxaluria type 1 (PH1). PH1 is a rare illness that causes the liver to produce too much of something called ‘oxalate’. Oxalate is removed by the kidneys and through the urine. In people with PH1, the extra oxalate can cause kidney stones and kidney failure. The extra oxalate can also build up, and damage other parts of the body, including eyes, heart, skin, and bone. This is called ‘oxalosis’.
How is lumasiran used?
Treatment with lumasiran should be started and supervised by a specialist doctor experienced in treating PH1. The medicine may be given by a doctor or nurse. The doctor will carry out blood tests to check the patient’s functions before and during the treatment.

Lumasiran will be given as injections under the skin ("sub-cutaneous") into the stomach area (abdomen), or in some cases, the upper arm or thigh. The site of injection will be rotated.

Depending on the dose, more than one sub-cutaneous injection may be needed. The amount will be calculated according to the body weight and will be adjusted as the weight changes. The first doses, called "loading doses", will be given as once a month for three months. After the last loading dose, maintenance doses will start.

Body weight less than 10 kg
- Loading doses: 6 mg for every kg of body weight, given once a month for 3 months.
- Maintenance dosing: 3 mg for every kg of body weight, given once every month.

Body weight from 10 kg to less than 20 kg
- Loading doses: 6 mg for every kg of body weight, given once a month for 3 months.
- Maintenance dosing: 6 mg for every kg of body weight, given once every 3 months.

Body weight 20 kg or more
- Loading doses: 3 mg for every kg of body weight, given once a month for 3 months.
- Maintenance dosing: 3 mg for every kg of body weight, given once every 3 months.

How does Lumasiran work?
Lumasiran works by lowering the amount of ‘glycolate oxidase’ (GO) produced by the liver. GO is one of the proteins in the liver that produce oxalate. By lowering the amount of GO in the liver, less oxalate is produced. This leads to lower levels of oxalate in the urine and blood and can help reduce the damage caused by the extra oxalate.

How has lumasiran been studied?
The main study of the effects of lumasiran was demonstrated in a randomized, double-blind, placebo-controlled clinical study in patients 6 years or older with PH1 (ILLUMINATE-A) and a single-arm clinical study in patients less than 6 years of age with PH1 (ILLUMINATE-B). In ILLUMINATE-A, 39 patients with PH1 were randomised 2:1 to receive subcutaneous doses of lumasiran or placebo for 6 months. In ILLUMINATE-B, a total of 18 patients were treated with lumasiran. The median duration of treatment was around 7 months.

When should lumasiran not be given?
Lumasiran should not be given to patients who have hypersensitivity to the drug and excipients.

What are the benefits and risks of lumasiran?
Benefits
In ILLUMINATE A, treatment with lumasiran was associated with a significant reduction of oxalate in the urine of 24 hours by 54%, compared to placebo. After 6 months of treatment, a higher proportion of patients treated lumasiran had normal or near-normal oxalate levels in their urine of 24 hours, compared to those treated with placebo. The reduction in oxalate by lumasiran was similar in all patients, irrespective of their age, gender, race, geography of residence, kidney function, use of vitamin B6 or history of kidney stones.
In ILLUMINATE-B, children treated with lumasiran had reductions in oxalate of their urine consistent with the results of ILLUMINATE A.
**Risks**
One in 10 injections may cause redness, pain, itching, or swelling at the site of the injection (injection site reaction).

**Why has lumasiran been given a positive Early Access to Medicine Scientific opinion?**
There is no approved medicine for slowing down the liver in producing oxalate and the available treatments are aiming to reduce symptoms from kidney stones or to slow down the speed of developing kidney failure. For most patients, the only option of cure is liver or dual liver-kidney transplantation.

**What are the uncertainties?**
The number of patients being studied was very small, which makes it difficult to evaluate precisely the importance of the benefits and side effects. Furthermore, data on the reduction of oxalate in the urine are still preliminary. The company that makes lumasiran will provide additional information when it becomes available.

**Are there on-going clinical studies?**
The main studies mentioned above are still on-going.

**What measures are in place to monitor and manage risks?**
A risk management plan has been developed to ensure that lumasiran is used as safely as possible. Based on this plan, the company that makes lumasiran must ensure that doctors and other healthcare professionals expected to use the medicine, as well as patients, are provided with information on the medicine including the side effects related liver damage and recommendations for minimising these side effects.

Information will be collected about patients before they enter the scheme. Healthcare professionals will be asked by the company to report side effects experienced by patients receiving lumasiran through the scheme, as well as medication errors, overdose, and pregnancies. They will receive a physician pack and comprehensive training on adverse events prior to commencement of patient treatment. These safety data will be reviewed and reported to the MHRA on a regular basis by the company.

**Other information about lumasiran – see EAMS Treatment Protocol**