Medicines & Healthcare products Regulatory Agency

MHRA

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Information for NHS Medical Directors

Regarding EAMS scientific opinion for
Lumasiran is indicated for the treatment of primary hyperoxaluria type 1 (PH1) in all age groups.

The aim of the Early Access to Medicines Scheme (EAMS) is to provide earlier availability of promising unlicensed medicines to UK patients that have a high unmet clinical need. A positive scientific opinion is only issued by the MHRA if the criteria for the EAMS are fulfilled, which includes demonstrating a positive benefit risk balance (quality, safety and efficacy assessment) and the ability of the pharmaceutical company to supply a medicine according to a consistent quality standard.

EAMS medicines are unlicensed medicines. The term 'unlicensed medicine' is used to describe medicines that are used outside the terms of their UK licence or which have no licence for use in the UK. GMC guidance on prescribing unlicensed medicines can be found below:

https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/prescribing-and-managing-medicines-and-devices/prescribing-unlicensed-medicines

The 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 licensed indication or a future commitment by the MHRA to licence 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.

EAMS procedural assessment at the MHRA

A full assessment of the quality, safety and efficacy of [product INN or code number] has been conducted by the MHRA's assessment teams, including pharmacists, toxicologists, statisticians, pharmacokinetic and medical assessors. This assessment process also includes consideration of the quality, safety and efficacy aspects by the UK independent expert committees including Expert Advisory Groups (EAGs) and the Commission on Human Medicines (CHM):

- The Commission on Human Medicines (CHM) advises ministers on the quality, safety and efficacy of medicinal products. The Chair and Commissioners are appointed in accordance with the Code of Practice for Ministerial Appointments to Public Bodies. The Chair and Commissioners follow a code of practice, in which they are precluded from holding personal interests. The Commission is supported in its work by Expert Advisory Groups (EAGs), covering various areas of medicine.

  https://www.gov.uk/government/organisations/commission-on-human-medicines/about

- Chemistry, Pharmacy and Standards EAG, which advises the CHM on the quality in relation to safety and efficacy of medicinal products

  https://www.gov.uk/government/organisations/commission-on-human-medicines/about/membership#chemistry-pharmacy-and-standards-eag

Pharmacovigilance system

A pharmacovigilance system for the fulfilment of pharmacovigilance tasks has been put in place for this EAMS medicine, including a risk management plan. As the safety profile of the EAMS medicine is not fully established it is particularly important that any harmful or unintended responses to EAMS medicines are reported. Healthcare professionals should be aware of their obligations to report adverse event information upon enrolment of any patients receiving EAMS medicines in the scheme. They will be required to follow the process which the pharmaceutical company which manufactures the EAMS medicine has in place to enable systematic collection of information on adverse events.

For more detailed information on this EAMS medicine, please refer to the Public Assessment Report, EAMS treatment protocol for healthcare professionals, EAMS treatment protocol for patients and EAMS treatment protocol for pharmacovigilance.

https://www.gov.uk/government/collections/early-access-to-medicines-scheme-eams-scientific-opinions

Justification for the fulfilment of the EAMS criteria

There are four EAMS criteria that need to be fulfilled before a medicine can enter the scheme and a positive scientific opinion is issued by the MHRA. The fulfilment of the criteria for this particular medicine is described below.

1	**(a) Life threatening and seriously debilitating condition** Primary hyperoxaluria type 1 (PH1), an ultra-rare, progressive, autosomal recessive disease, is caused by a deficiency in hepatic peroxisomal enzyme alanine glyoxylate aminotransferase (AGT), encoded by the AGXT gene. According to the National Registry of Rare Kidney Diseases (RaDaR), there were 34 PH1 patients aged under 16 years and 39 adults in the UK in 2017. In healthy individuals, glycolate, a product of intermediary metabolism, is oxidized in the liver to form glyoxylate by the enzyme glycolate oxidase (GO), which is encoded by the hydroxyacid oxidase-1 (HAO1) gene. Glyoxylate is predominantly converted into glycine by AGT. Patients with PH1 have reduced or absent AGT activity due to mutations in the AGXT gene and thus are unable to convert glyoxylate into glycine, causing accumulation of glyoxylate, and subsequent overproduction of oxalate by the liver. Oxalate is excreted through the kidneys, causing nephrocalcinosis and kidney stones. Following progression to end stage renal disease (ESRD), oxalate deposition occurs in skeletons, vasculatures, skin, heart, and eyes, causing a life-threatening and seriously debilitating condition called systemic oxalosis. According to the OxalEurope Consortium, among 526 registered PH1 patients, the median age of diagnosis was 8 years (interquartile range 2.6-22.2 years) and the most frequent symptom at diagnosis was urolithiasis; 29% of patients were infants, and of whom 39.9% had end stage renal disease (ESRD); 28% of patients were adults, and of whom 70% had ESRD at diagnosis. Hence, PH1 is a life threatening and seriously debilitating condition. **(b) High unmet need: there is no approved medicinal product** There are no approved medicinal products specific for the treatment of PH1 and the current standard of care is to alleviate nephrolithiasis and to delay the progression towards ESRD. In patients with preserved renal function, hyperhydration and crystallization inhibitors (potassium citrate or sodium citrate) are prescribed to reduce the incidence of nephrolithiasis. Pyridoxine is a cofactor of AGT, providing a potential means of correcting mistargeting. In patients homozygous for G170R mutation generally respond to high-dose pyridoxine therapy; others may show variably responsiveness. Despite only 5% PH1 patients respond to pyridoxine in normalising urinary oxalate

	excretion, high doses of pyridoxine are widely adopted as the standard of care. Nevertheless, most patients progress to ESRD and/or systemic oxalosis and the only option of metabolic cure is liver or dual liver-kidney transplantation. Therefore, there is an unmet medical need for PH1 worldwide, including UK.
2	**The medicinal product offers major advantage over existing methods in the UK** Lumasiran is a chemically synthesized, double-stranded, small interfering ribonucleic acid (siRNA) covalently linked to a triantennary N-acetylgalactosamine (GalNAc) specifically targeting hydroxy acid oxidase 1 (HAO1) messenger RNA (mRNA), which encodes glycolate oxidase (GO). As lumasiran targets the hepatic GO enzyme upstream of the deficient AGT enzyme in PH1, efficacy is seen regardless of AGXT mutations or residual AGT activities. In the pivotal ILLUMINATE A trial, 39 patients aged 6 years or above were randomised into lumasiran or placebo. Lumasiran has been shown to reduce urinary oxalate excretion by 65.38% from the baseline at six months, which is translated to 21 of 25 patients (84.0%) in the lumasiran group achieving normalization or near normalisation of urinary oxalate excretion versus none in the placebo group. In ILLUMINATE B trial, a single-arm study a total of 18 patients were treated for a median duration of around 7 months, the reductions of oxalate in the urine were consistent with the results of ILLUMINATE A. Based on these results, lumasiran would provide major advantages over the treatment options currently prescribed in the UK.
3	**The potential adverse effects of the medicinal product are outweighed by the benefits, allowing for a conclusion of a positive benefit/risk balance** In above 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. Other potential adverse reactions, e.g., hepatic or renal events, or malignancies, were not observed in the clinical trials. Hence, the benefit is considered outweighing the risk.
4	**The company is able to supply the product and to manufacture it to a consistent quality standard, including the presence of appropriate GMP certification.** The company has provided all documentation necessary to prove that the EAMS medicine is manufactured/packaged according to GMP.