Medicines & Healthcare products Regulatory Agency

MHRA

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Information for NHS Medical Directors

Regarding EAMS scientific opinion for Dojolvi (Triheptanoin) in the treatment of paediatric and adult patients with long-chain fatty acid oxidation disorders (LC-FAOD)
EAMS number 41104/0001

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 or seriously debilitating condition** *Long-chain fatty acid oxidation disorders (LC-FAOD) are ultra-rare, serious, and life-threatening inborn errors (autosomal recessive disorders) of metabolism caused by defects in 1 of 6 nuclear genes that encode mitochondrial enzymes critically involved in the conversion of long-chain fatty acids into energy. Patients experience severe episodes of metabolic decompensation due to metabolic stress in the setting of defects in the oxidation of fatty acids; mortality is high (approximately 50% in symptomatically diagnosed patients), and most deaths in these patients occur within the first 2 years of life.* *LC-FAOD include inherited defects in carnitine palmitoyl transferase 1 (CPT-I), carnitine palmitoyl transferase 2 (CPT II), carnitine/acylcarnitine translocase (CACT), very long-chain acyl-CoA dehydrogenases (VLCAD), long chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD), and mitochondrial trifunctional protein (TFP). The deficiencies of CPT-II, VLCAD, and LCHAD are the most common subtypes of LC FAOD.* *These enzyme defects result in incomplete oxidation of fatty acids, which leads to accumulation of potentially toxic fatty acid intermediates, reduced substrates for the tricarboxylic acid (TCA) cycle, and impaired gluconeogenesis. The FAOD enzyme defects consequently result in severe episodic deficiencies in energy metabolism, which are often associated with intercurrent infections that lead to hospitalisations and early death in many patients despite current best available care using medium even-number carbon chain (C8, C10) oil, i.e., medium-chain triglyceride (MCT).*

	The acute, often lethal, metabolic crises in patients with LC-FAOD are a result of depleted energy resources during times of increased energy demand, such as common infections, moderate exercise, or exposure to cold weather. LC-FAOD substantially limits the physical, mental, emotional, and social aspects of patients and caregivers. **(b) High unmet need: there is no method available/approved medicinal product or existing methods/licensed medicines have serious limitations** *Current disease management includes careful nutritional therapy, avoidance of fasting, and restriction of long-chain fatty acid intake, often with MCT supplementation. Despite MCT supplementation, patients continue to experience recurrent metabolic crises. Many patients experience impaired exercise tolerance and reduced quality of life to avoid activities that might induce metabolic crises. None of these management strategies, including the use of MCT, have been formally studied in controlled, randomized clinical studies.*
2	**The medicinal product offers major advantage over existing methods in the UK** *Based on the data provided, the benefit of triheptanoin include:* *-provides an alternative energy source that bypasses the enzyme defects and provides metabolites for anaplerosis and gluconeogenesis* *-reduced frequency and duration of hospitalisations* *-reduced the incidence and duration of major clinical events in 2 independent populations of patients with LC FAOD in prospective clinical studies* *-showed sustained reduction in frequency and duration of MCEs* *-improved physical function and exercise tolerance* *-improved cardiac function in patients experiencing severe episodes of metabolic decompensation despite standard therapy*
3	**The potential adverse effects of the medicinal product are outweighed by the benefits, allowing for a conclusion of a positive benefit/risk balance** *Based on the available data, the main ADRs are GI-related and consist of mild-to-moderate abdominal pain/cramps, diarrhoea/loose stools, vomiting, and nausea, which are largely associated with treatment initiation. No serious, life threatening, or fatal ADRs have been identified. Discontinuation of treatment due to ADRs is infrequent (2 of 89 subjects in the pooled LC-FAOD cumulative clinical trial data, with an average duration of treatment of 3 years).* *GI adverse reactions led to dose reductions in 35% and 18% of subjects in Studies CL201 and CL202, respectively. The median duration of GI ADRs was 3.0 days overall and most GI ADRs resolved within 7 days of onset. A small group of subjects continued to have intermittent or recurrent mild abdominal pain and/or diarrhoea/loose stools throughout treatment.* *Therefore, the ADRs are largely manageable with dose modification, dose titration, or change in the frequency of dosing and by ensuring adequate mixing with food.* *Other adverse events reported, included musculoskeletal pain/cramping/elevated CPK, and fatigue/lethargy, which are likely attributable to underlying LC FAOD disease.*

	These risks are outweighed by the benefits of reduction in life-threatening episodes of metabolic decompensation; improvements in cardiac performance, liver function, and energy production, thereby leading to less hospitalisations.
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.*