Medicines & Healthcare products Regulatory Agency

MHRA

Early Access to Medicines Scientific Opinion - Public Assessment Report	
Product	**Triheptanoin**
EAMS indication	**Triheptanoin is indicated for the treatment of adult and paediatric patients with long-chain fatty acid oxidation disorders (LC-FAOD).**
Company	**Ultragenyx Netherlands B.V**
EAMS number	**41104/0001**
EAMS Scientific Opinion date	**07/04/2025**

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 medicines 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

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

What is triheptanoin?

Triheptanoin is the active substance of a medicine, which is available as a liquid that is mixed with food or other liquids and is taken by mouth or feeding tube (oral liquid).

What is triheptanoin used to treat?

Triheptanoin is used to treat long-chain fatty acid oxidation disorders (LC-FAOD), a group of rare inherited disorders, in adults and children of all ages.

How is triheptanoin used?

Treatment with triheptanoin must be started and supervised by a doctor. Triheptanoin should be taken at least 4 times a day, at a dose as instructed by a doctor, nurse or dietician. The treatment should start on a low dose of triheptanoin which is slowly increased over time, to help avoid gastrointestinal upset side effects.

Each dose should always be mixed well in soft food, a drink, medical food, or formula before taking orally. Alternatively, triheptanoin can be administered by feeding tube with medical food or formula.

How does triheptanoin work?

Triheptanoin enters the body's cells where it is broken down for energy. This helps prevent energy crises that can cause muscle breakdown (rhabdomyolysis), heart muscle damage (cardiomyopathy), and low blood sugar (hypoglycaemia).

Triheptanoin must be taken daily as part of a carefully controlled diet and is meant to be taken long-term.

How has triheptanoin been studied?

Two main studies supported the clinical safety and efficacy of triheptanoin.

In the first study (Study 1), 29 children and adult patients with serious symptoms of LC-FAOD were treated with triheptanoin for 78 weeks after receiving standard treatment (including medium chain triglycerides and a controlled diet). A total of 24 patients continued treatment in a second study (Study 2) to provide information on long-term treatment with triheptanoin. Study 2 also included 33 additional children and adult patients with LC-FAOD who had not been treated with triheptanoin.

In both studies, patients received triheptanoin at a dose targeted to achieve 25%–35% of the daily energy requirement (calories) or a maximum tolerated dose. The dose could be reduced if there were side effects.

The efficacy of triheptanoin (how well the medicine works) was assessed by looking at the reduction in frequency and duration of major clinical events (MCEs) such as muscle breakdown (rhabdomyolysis), heart muscle damage (cardiomyopathy), and low blood sugar (hypoglycaemia).

What are the benefits and risks of triheptanoin?

Benefits

Patients receiving triheptanoin in both studies showed meaningful improvements in the rate and duration of muscle breakdown (rhabdomyolysis), heart muscle damage (cardiomyopathy), and low blood sugar (hypoglycaemia). These studies compared the rate and duration of these events, before and after treatment with triheptanoin.

In Study 1, during the 78 week pre-triheptanoin period, the group of 29 patients experienced a total of 70 events between them (of which 57 events led to hospitalisation). This was reduced to a total of 39 events (of which 29 events led to hospitalisation) 78 weeks after treatment with triheptanoin was initiated. The annualised hospitalisation rate was reduced from 1.39 to 0.65 events/year. The number of annualised hospitalisation days was reduced from 5.66 to 2.74 days/year.

In Study 2, one group of 33 patients began triheptanoin treatment for the first time. Among this group, the median number of events per year was reduced from 2.0 to 0.3 events/year during treatment with triheptanoin. The median annualised hospitalisation rate decreased from 1.3 to 0.2 events/year. The

median number of annualised hospitalisation days decreased from 8.0 to 0.8 days/year.

Risks

The most common side effects with triheptanoin (which may affect more than 1 in 10 people) are stomach pain, diarrhoea (loose stools) and vomiting. Most of these side effects have been mild or moderate in clinical studies (bothersome, but do not cause severe illness), and were manageable with dose reductions.

Why has triheptanoin been given a positive Early Access to Medicine Scientific opinion?

LC-FAOD is a rare, life-threatening and seriously debilitating condition with a high unmet need and no approved treatment in the UK. Current management options include avoidance of fasting and a reduced long chain fat diet with even-chain medium-chain triglyceride (MCT) supplementation.
Patients with LC-FAOD may have difficulty producing enough energy because of their body's inability to use long-chain fats as an energy source. This can put patients at risk for medical emergencies, especially during times of illness, fasting, or prolonged exercise. Treatment with triheptanoin helps to prevent energy crises that can cause muscle breakdown (rhabdomyolysis), heart muscle damage (cardiomyopathy), and low blood sugar (hypoglycaemia). Patients treated with triheptanoin experienced these events less frequently and for a shorter time. Triheptanoin side effects were manageable, where necessary with dose reductions.

What are the uncertainties?

The main clinical studies that support triheptanoin as a treatment for LC-FAOD are open label, single arm studies, which means that they did not compare triheptanoin side-by-side with other treatments. The studies compared the rate and duration of muscle breakdown (rhabdomyolysis), heart muscle damage (cardiomyopathy), and low blood sugar (hypoglycaemia) for 78 weeks before and 78 weeks after starting treatment with triheptanoin. Because LC-FAOD is rare, triheptanoin has only been studied in a small number of patients. At this time, the company has limited information for triheptanoin use in pregnant and breastfeeding women and infants.

Are there on-going clinical studies?

A randomised, double-blind, multicentre study is currently ongoing to evaluate the effect of triheptanoin compared with even-chain MCTs on MCEs in paediatric patients with LC-FAOD.

What measures are in place to monitor and manage risks?

A risk management plan has been developed to ensure that triheptanoin is used as safely as possible. Based on this plan, the company that makes triheptanoin must ensure that all healthcare professionals expected to use the medicine, as well as patients, are provided with information on the medicine including the side effects and recommendations for preventing or minimising the impact of side effects.

Information will be collected about patients before they enter the scheme. Healthcare professionals will be asked by the company to report adverse effects experienced by patients receiving triheptanoin through the scheme. These safety data will be reviewed and reported to the MHRA on a regular basis by the company.

Healthcare professionals involved in the management of the scheme will receive specific training from the company prior to commencement of patient treatment.

Other information about triheptanoin – see EAMS Treatment Protocol