Medicines & Healthcare products Regulatory Agency

MHRA

Early Access to Medicines Scheme – Treatment protocol – Information on the pharmacovigilance system and requirements for reporting safety data

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 who 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 for which there are no adequate treatment options.

The scientific opinion is based on an 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 licenced 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 the medicine remains with the healthcare provider, and the opinion and EAMS documentation published by the MHRA are intended only to inform healthcare providers' decision making and not to recommend use. An EAMS scientific opinion does not affect the civil liability of the manufacturer or any healthcare provider in relation to the product.

As the safety profile of the EAMS medicine may not yet be fully established, it is particularly important that any harmful or unintended responses to EAMS medicines are reported. More information about the scheme can be found here:
http://www.mhra.gov.uk/Howweregulate/Innovation/EarlyaccesstomedicinesschemeEAMS/index.htm

Healthcare providers should enroll any patient receiving EAMS medicines in the drug registry put in place by the pharmaceutical company to enable systematic collection of information on adverse events. Suspected adverse drug reactions for any patient can also be reported directly to the MHRA via the Yellow card scheme at www.mhra.gov.uk/yellowcard. When reporting, please provide as much information as possible, including information about medical history, any concomitant medication(s), onset, treatment dates, outcome, and results of any tests or investigations.

The information below is intended for healthcare professionals and is provided by the pharmaceutical company that manufactures the EAMS medicine. It summarises the requirements for clinical monitoring and reporting of adverse events with medicines used under the scheme.

Healthcare professionals should also consult the relevant detailed information provided by the company.

EAMS Drug Indication

Triheptanoin is intended for the treatment of paediatric and adult patients with long-chain fatty acid oxidation disorders (LC-FAOD).

Information on the Pharmacovigilance System

Initial Request Process

Healthcare professionals (HCPs), including nurse prescribers, may request enrolment for patients with LC-FAOD in the Triheptanoin EAMS Programme (Programme) by emailing UX007_EarlyAccess@ultragenyx.com. After receiving the request, Ultragenyx will email an acknowledgment of the request, including information about the programme, programme application, and informed consent template as attachments:

1. Treatment Protocol – Information on PV System and Requirements for Reporting Safety Data (information)
2. Triheptanoin EAMS Programme Request Form (application)
3. Informed Consent Form (template)

Ultragenyx will inform the HCP within the body of the acknowledgment email that information shared between Ultragenyx and the HCP will be treated as confidential and proprietary information.

Ultragenyx will instruct the HCP to complete and return the following documentation to UX007_EarlyAccess@ultragenyx.com for programme consideration:

1. Triheptanoin EAMS Programme Request Form (application)
2. Curriculum Vitae (CV)
3. HCP licence (as appropriate)

After receiving all required information from the HCP, Ultragenyx will complete a medical review of the submission to evaluate patient eligibility and enrolment in the programme. If additional information is needed to complete the review, the HCP will receive an email from Ultragenyx detailing the requested information.

Following the Ultragenyx review of complete information, the HCP will receive either an email confirming approval for the programme or an explanation of why the request did not meet inclusion criteria.

Approved HCP requests will receive an email that includes a unique patient ID and the following forms, PDF information, and Agreement:

1. Safety Reporting Responsibilities Acknowledgement Form (as described in the Treatment Protocol – Information on PV System and Requirements for Reporting Safety Data)
2. Adverse Event Report Form (PDF)
3. Drug Registry Protocol (PDF)
4. Treatment Protocol – Information for HCPs (PDF)
5. Treatment Protocol – Information for Patients (PDF)
6. Drug Supply Request Form
7. Agreement (Contract)
8. Treatment Start Date Form

Ultragenyx will follow up with the HCP to collect all completed forms and a fully executed Agreement. Once HCP safety and start-up information has been received, Ultragenyx will proceed with the documentation review and ensure completeness.

The Ultragenyx drug release process will follow a documentation review, and drug will be shipped to the HCP's pharmacy. Ultragenyx will email the HCP confirmation of activation and approval to start treatment with triheptanoin.

Supply and Re-supply Process

The HCP will determine the dose, frequency, and route of administration and capture these data in the Triheptanoin EAMS Programme Drug Supply Request Form, as part of the start-up documentation.

The Treatment Start Date Form will be collected from the HCP following the initial patient dosing with triheptanoin. Ultragenyx will request the Drug Supply Request Form at three-month intervals (with a four-week lead time). To receive a re-supply of triheptanoin, the HCP will be required to complete all information on the form, including the patient's current total estimated energy intake (kcal per day), total daily dose of triheptanoin (mL per day), percentage of daily caloric intake, route of administration, and number of doses per day.

Two syringes will be provided with every Dojolvi (triheptanoin) pack. The oral syringe has been selected to allow measurement of an appropriate unit dose range from 4 mL to 44 mL for paediatric and adult patients (calculated per patient), for repeated use and with durable printing. Each syringe should be used for up to 60 doses.

Discontinuation Process

When a patient discontinues treatment, the HCP is required to inform Ultragenyx via UX007_EarlyAccess@ultragenyx.com. Ultragenyx will email a request to the HCP to complete the Triheptanoin EAMS Programme Treatment Discontinuation Form. Ultragenyx will review the form, ensure it is complete, and email the HCP a closure confirmation of the patient's discontinuation in the programme. The Treatment Discontinuation Form captures the date on which the patient ended treatment with triheptanoin; the reason for discontinuation; confirmation of adverse event (AE) reporting, if applicable; and drug accountability confirmation.

Safety Reporting

HCPs (physicians, pharmacists, and nurses) involved with the EAMS programme are required to report all AEs (serious or nonserious) occurring in patients receiving triheptanoin via this EAMS programme. Serious adverse events (SAEs) irrespective of causality should be reported within 24 hours of awareness, and non-serious AEs should be reported within 3 business days of awareness, using the Triheptanoin EAMS Programme Adverse Event Report Form that will have been sent to the HCP. Detailed AE definitions are provided in the Drug Registry Protocol, Section 3 (Safety Data Collection and Reporting).

For the purposes of this EAMS programme, an AE/human safety information (HSI) is defined as any untoward medical occurrence in an EAMS participant who is administered triheptanoin and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (either onset of new illness or exacerbation of pre-existing medical condition) temporally associated with the use of triheptanoin, whether or not considered related to the medicinal product. AEs and safety information may also include failure to produce expected benefits (ie, lack of efficacy); off-label use; medication errors or misuse, including drug overdose whether accidental or intentional; drug abuse or effects of drug withdrawal; occupational exposure; patient taking triheptanoin while pregnant (see below) or breastfeeding; safety information received as part of a product quality complaint; drug interaction; unexpected therapeutic benefit (ie, an unexpected improvement in a concurrent condition other than the one being treated).

Any pregnancy that occurs in a patient during the EAMS programme should be reported to Ultragenyx within 24 hours of learning of the pregnancy. The Triheptanoin EAMS Programme Pregnancy Notification Form should be used for this purpose. All pregnancies must be followed and reported through to pregnancy outcome.

AEs may be reported spontaneously by patients or identified and reported by an EAMS HCP. Patients should be instructed to contact their EAMS HCP if they experience any changes in their health.

The Triheptanoin EAMS Programme AE Report Form requires the EAMS HCP to categorise events by seriousness (serious or nonserious) and include an assessment of causality where possible. The definition of seriousness, severity, and causality are provided in Section 2 of the EAMS Drug Registry Protocol for triheptanoin.

Where AEs/HSI are considered related to any other medicinal product that the patient may be receiving whilst in the EAMS programme, HCPs should report these events to the MHRA via the Yellow Card scheme: https://yellowcard.mhra.gov.uk. Reporters should include the manufacturer of the treatment if known, the EAMS number, and the unique patient ID when reporting to the MHRA. HCPs involved in the EAMS programme are instructed to collect and report all AEs/HSI whilst a patient continues to receive treatment with triheptanoin under this EAMS programme.

If a patient permanently discontinues treatment with triheptanoin, the HCP is required to inform Ultragenyx. If the reason(s) for discontinuing triheptanoin is due to an AE(s), this should be reported in line with the instructions provided above.

Any AEs/HSI that are considered by the prescribing HCP to be related to treatment after triheptanoin discontinuation should be reported as described above.

Once marketing authorisation has been granted for the EAMS indication, AE/safety information for triheptanoin should be reported to Ultragenyx by following the standard pathway for reporting spontaneous postmarketing AEs/SAEs (ie, via the MHRA via the Yellow Card scheme: https://yellowcard.mhra.gov.uk or directly to Ultragenyx).

All AEs/SAEs should be submitted using the AE/SAE Reporting Form via email to ultragenyx@primevigilance.com or faxed to +1 415 930-4033.

Ultragenyx will have clear oversight of safety reporting and overall safety data at all times throughout the duration of the triheptanoin EAMS programme.

The Scientific Opinion Holder is required to send ADRs suspected to be related to EAMS products to the MHRA within the agreed timelines ().

As per Human Medicines Regulations 170(3), all serious suspected adverse drug reactions (ADRs) in EAMS patients are to be reported to MHRA within 15 calendar days of receipt by Ultragenyx from the EAMS HCP. All suspected ADRs with a fatal outcome in an EAMS patient are to be reported to the MHRA within 7 calendar days of receipt by Ultragenyx, with additional information to be provided within 8 calendar days.

Ultragenyx will generate an EAMS periodic update report to summarise EAMS patient safety data and usage of triheptanoin, per the EAMS requirements. The EAMS periodic report will be submitted to MHRA according to the agreed upon periodicity in the EAMS Risk Management Plan for triheptanoin the periodic reporting cycle is 3-monthly.

Training for Healthcare Professionals

Once the prescribing HCP has registered their intent to participate in the triheptanoin EAMS programme, the HCP will receive training materials at each centre likely to be involved in the EAMS programme, which will include the process for reporting AEs/HSI together with information on recognising and managing AEs associated with triheptanoin treatment as described in the Information for Healthcare Professionals (HCPs) Treatment Protocol. The HCP will need to acknowledge that they have reviewed and understood their reporting responsibilities prior to any drug shipment.

Ultragenyx will email the HCP the Safety Training and Reporting Requirement Instructions as part of the start-up package. The HCP will be required to sign an Acknowledgement of Receipt form confirming receipt, reading, and understanding of the training information (see initial request process described above).

Additional Risk Minimisation Materials

Not applicable

Additional Information

Drug Registry

The Drug Registry Protocol is intended to specify which information is to be collected about patients as part of the EAMS programme for triheptanoin for the treatment of LC-FAOD.

Mandatory Data

The following patient information will be collected as part of the triheptanoin EAMS programme:

At Baseline:

- Date of birth
- Gender, race and ethnicity
- LC-FAOD subtype and basis for diagnosis
- Medical history, including all hospitalisations (indication and dates) in the past 18 months
- Concomitant medications
- Prescribed nutritional regimen, including any specialised formulas and prescribed daily intake of medium-chain triglycerides

After treatment initiation:

- Prescribed dose, frequency, route; dates and duration of treatment
- All AEs/safety information

Additional Data

No additional data are planned to be collected as part of the triheptanoin EAMS programme.

Periodic Reports

Data on the safety and usage of triheptanoin will also be provided to the MHRA by Ultragenyx via 3-monthly periodic reports, which will be prepared and submitted.

Contact Details

For initial request to participate in the triheptanoin EAMS programme:

UX007_EarlyAccess@ultragenyx.com

For AE/SAE reporting:

ultragenyx@primevigilance.com

Fax number +1 (415) 930-4033