Medicines & Healthcare products Regulatory Agency

MHRA

**Early Access to Medicines Scheme – Treatment protocol – Information for healthcare professionals**

**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 information is intended for healthcare professionals and is provided by the pharmaceutical company that manufactures the EAMS medicine. This medicine, which does not yet have a licence (marketing authorisation), and the information is provided to assist physicians in prescribing this unlicensed medicine. Guidance on prescribing unlicensed medicines can be found on the GMC webpage:
https://www.gmc-uk.org/guidance/ethical_guidance/14327.asp
The scientific opinion is based on assessment of the information supplied to the MHRA on the benefits and risks of this promising new 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.

Healthcare professionals should also refer to the summary information on the pharmacovigilance system which is provided in the document 'Early Access to Medicines Scheme – Treatment protocol – Information on the pharmacovigilance system'.

Scientific opinion period: The MHRA will withdraw the EAMS positive scientific opinion when a marketing authorisation (drug licence) is issued for the EAMS product covering the EAMS indication, or if following scientific assessment, the EAMS criteria are considered to be no longer met.

Treatment protocol update(s): In case of substantial new efficacy or safety data, the treatment protocol may need to be updated.

Contact information regarding queries on using this EAMS medicine can be found at the end of this document.

**Information for the healthcare professionals**

## 1. NAME OF THE MEDICINAL PRODUCT

Triheptanoin 0.96 g/mL oral liquid

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of liquid contains 0.96 g of triheptanoin. This corresponds to a density of 0.96 g/mL.

## 3. PHARMACEUTICAL FORM

Oral liquid.
Clear, colourless to light yellow oral liquid.

## 4. CLINICAL PARTICULARS

### 4.1 EAMS therapeutic indication

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

### 4.2 Posology and method of administration

All patients treated with triheptanoin should be under the care of a clinical specialist knowledgeable in appropriate disease-related dietary management based upon current nutritional recommendations.

The patient's metabolic requirements should be assessed by determining their daily caloric intake (DCI) prior to calculating the dose of triheptanoin.

Posology

The recommended target daily dosage for adults and paediatric patients is 25-35% of the patient's total prescribed DCI divided into at least four doses and administered by mixing thoroughly into semi-solid food/liquid or medical food/formula at mealtimes or with snacks.

In order to reach a target daily dosage, patients may require an increase in their total fat intake.

*Paediatric population*
The neonatal population may require higher fat intake and therefore an increased amount of triheptanoin. Consider current nutritional recommendations when dosing the neonatal population.

*Total daily dose calculation*

The target daily dosage (%) is converted to a volume (mL) to be administered using the following calculation:

- Caloric value of triheptanoin = 8.3 kcal/mL
- Round the total daily dosage to the nearest whole millilitre.
- Divide the total daily dosage into at least four approximately equal individual doses.

$$Total\ Daily\ Dosage\ (\_\_\_mL) = \frac{Daily\ Caloric\ Intake\ (DCI)(\_\_\_kcal)\ x\ \_\_\%\ Target\ from\ triheptanoin}{8.3\frac{kcal}{mL}\ of\ triheptanoin}$$

*Missed doses*

If a dose is missed, the next dose should be taken as soon as possible with subsequent doses taken at 3- to 4-hour intervals. The patient should be advised not to take a double dose at one meal to make up for a missed dose. The missed dose should be skipped if it will not be possible to take all doses in a day.

*Dosage initiation and titration*

***For patients not currently taking an MCT product***
Triheptanoin should be initiated at a total daily dosage of approximately 10% DCI divided into at least four times per day. The dose should be increased to the recommended total daily dosage by approximately 5% DCI every 2 to 3 days until the target dose range of 25-35% DCI is achieved.

***For patients switching from another MCT product***
In clinical trials, triheptanoin was initiated at the last tolerated daily dosage of MCT. The safety and efficacy of the concomitant use of MCT and triheptanoin have not been evaluated.
Triheptanoin should be initiated at the last tolerated daily dosage (mL) of MCT divided into at least four times per day. The total daily dosage should be increased by approximately 5% DCI every 2 to 3 days until the target dose range of 25-35% DCI is achieved.

*Tolerability*

- More frequent smaller doses should be considered if a patient has difficulty tolerating a quarter of the total daily dosage at one time based on gastrointestinal adverse reactions (see section 4.8).
- The patient's total caloric intake should be monitored during dosage titration, especially for a patient with gastrointestinal adverse reactions, and all components of the diet should be adjusted as needed.
- If a patient experiences gastrointestinal adverse reaction(s), dosage reduction should be considered until the gastrointestinal symptoms resolve (see section 4.8).
- If a patient is unable to achieve the target daily dose range of 25-35% DCI during dosage titration, the patient should be maintained at the maximum tolerated dosage.

Method of administration

Triheptanoin should be mixed thoroughly with semi-solid food/liquids (oral administration) or medical food/formula (feeding tube administration). It should not be administered undiluted to avoid gastrointestinal upset and feeding tube degradation (see section 4.8).

For preparation and handling instructions, see section 6.6.

## 4.3 Contraindications

Hypersensitivity to the active substance.

## 4.4 Special warnings and precautions for use

Feeding tube dysfunction

Feeding tube performance and functionality can degrade over time depending on usage and environmental conditions. In clinical trials, feeding tube dysfunction was reported in patients receiving triheptanoin. The contribution of triheptanoin to these events cannot be ruled out. This product must not be administered in feeding tubes manufactured of polyvinyl chloride (PVC) (see section 6.6). The feeding tube should be regularly monitored to ensure proper functioning and integrity.

Intestinal malabsorption in patients with exocrine pancreatic insufficiency

Pancreatic enzymes hydrolyse triheptanoin and release heptanoate as medium-chain fatty acids in the small intestine. Low or absent pancreatic enzymes may result in reduced absorption of heptanoate subsequently leading to insufficient supplementation of medium-chain fatty acids. For patients with

exocrine pancreatic insufficiency, pancreatic enzyme replacement therapy (PERT) may be needed to allow digestion and absorption of Dojolvi.

### 4.5 Interaction with other medicinal products and other forms of interaction

Pancreatic Lipase Inhibitors

Concomitant use of triheptanoin with pancreatic lipase inhibitors may reduce the systemic exposure of heptanoate and lead to reduced efficacy. Co-administration with pancreatic lipase inhibitors should be avoided.

### 4.6 Fertility, pregnancy, and lactation

Fertility

No human data are available on the effect of triheptanoin on fertility. Animal studies (Seg I fertility in rodents, Seg II embryofoetal development in rodents and rabbits, and Seg III pre/post-natal development studies in rodents) do not indicate harmful effects with respect to male and female fertility (see section 5.3).

Pregnancy

There are a limited amount of data from the use of triheptanoin in pregnant women. In animal reproduction studies conducted in pregnant rats and rabbits administered triheptanoin during the period of organogenesis, the primary toxicological effect (reduced body weight gain) was considered to be specific to decreased food consumption related to taste aversion in animals.

Animal studies do not indicate risk of reproductive toxicity due to the pharmacology of triheptanoin or its metabolites (see section 5.3).

Triheptanoin should only be used during pregnancy after careful consideration of the benefits and risks of treatment to the patient. Healthcare professionals should consider the risks associated with the disease itself and the risk of discontinuing triheptanoin treatment.

Lactation and Breastfeeding

There are no data on the presence of triheptanoin or its metabolites in human or animal milk, the effects on the breastfed infant, or the effects on milk production. A risk to newborns/infants cannot be excluded. Medium-chain triglycerides and other fatty acids are normal components of breastmilk and the composition of breastmilk varies within feedings, over stages of lactation, and between mothers and populations due to maternal factors including genetics, environment, and diet. The developmental and health benefits of breastfeeding should be considered along with the clinical need for triheptanoin and any potential adverse effect on the breastfed infant from triheptanoin or from the underlying condition.

### 4.7 Effects on ability to drive and use machines

Not relevant.

### 4.8 Undesirable effects

The assessment of adverse reactions was based on a safety population that included 99 patients with LC-FAOD exposed to triheptanoin from 2 clinical studies: one open-label 78-week study of triheptanoin in 29 patients (Study 1 [UX007-CL201]) followed by an open-label extension study (Study 2 [UX007-CL202]). Twenty-four patients from Study 1 continued into Study 2 and the remaining patients were treatment naïve (n = 33) or rolled over from investigator sponsored trials (IST)/another trial (n = 37). Patients ranged from 4 months to 63 years of age and received triheptanoin at daily doses ranging from 8% to 49% DCI (which corresponds to 0.7 g/kg/day to 6.0 g/kg/day for paediatric patients and 0.5 g/kg/day to 1.6 g/kg/day for adult patients) for a mean duration of 3.64 years.

The most common treatment-related adverse reactions reported in the pooled safety population of Study 1 and Study 2 were gastrointestinal (GI)-related, and included abdominal pain (abdominal

discomfort, abdominal distension, abdominal pain, abdominal pain upper, GI pain) [45.5%], diarrhoea [45.5%], vomiting [13.1%], and nausea [8.1%].

Study 3 was a 4-month, double-blind, randomized, controlled study comparing triheptanoin (7-carbon chain fatty acid) with trioctanoin (8-carbon chain fatty acid) in 32 adult and paediatric patients with a confirmed diagnosis of LC-FAOD. Commonly reported adverse reactions with triheptanoin were similar to those reported in Study 1 and Study 2.

Tabulated list of adverse reactions

Table 1 lists the adverse reactions reported from clinical trials, Study 1 and Study 2, in which 99 patients were treated with triheptanoin. All adverse reactions were gastrointestinal in nature based on integrated safety data from Study 1 and Study 2.

Adverse reactions are presented by system organ class, preferred term, and frequency. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), and very rare (< 1/10 000).

**Table 1: Treatment-related adverse reactions reported in patients treated with triheptanoin**

| MedDRA system organ class | MedDRA preferred term (PT) | Frequency |
|---|---|---|
| Gastrointestinal disorders | Abdominal pain [a] | Very common |
| | Diarrhoea | Very common |
| | Vomiting | Very common |
| | Nausea | Common |

[a] Abdominal Pain includes the following grouped terms: Abdominal discomfort, Abdominal distension, Abdominal pain, Abdominal pain upper, and Gastrointestinal pain.

Description of selected adverse reactions

*Gastrointestinal (GI) adverse reactions*
Gastrointestinal adverse reactions were mild (80%) to moderate (19%) in severity and led to dose reductions in 27% of patients in the pooled safety data from Study 1 and Study 2. In Study 1 and Study 2, median time to onset of a first occurrence of a gastrointestinal adverse reaction across the pooled population was 3.7 weeks. The median time to resolution of gastrointestinal adverse reactions across the pooled population was 4 days with 21.4% that resolved within 3 days and 27.6% that resolved in 1 day.

Paediatric population

Of the 99 patients included in Studies 1 and 2, 36 patients were aged between 6 and 18 years and 39 patients were below 6 years of age (including 3 patients between 0-1 years old and 29 patients between 1-6 years old in Study 2). Treatment-related adverse reactions occurred in a greater proportion of patients below 18 years old than in the older age group (80.0% and 58.3%, respectively), although the type and severity of adverse reactions were similar to those observed in adults.

Post-marketing Experience
Post-marketing safety experience with triheptanoin remains consistent with that observed in clinical trials.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals (physicians, pharmacists, and nurses) involved with the EAMS are required to report all adverse events (AEs) (serious or non-serious) occurring in patients receiving triheptanoin via this EAMS programme by completing and emailing the Triheptanoin EAMS Adverse Event Report Form to ultragenyx@primevigilance.com. Serious adverse events should be reported within 24 hours of awareness. Non-serious adverse events should be reported within 3 days of awareness.

Any pregnancy which occurs during the EAMS period (from the start of the first dose of triheptanoin) should be reported to Ultragenyx within 24 hours of learning of the pregnancy. The Triheptanoin EAMS Pregnancy Notification Form should be completed and emailed to ultragenyx@primevigilance.com.

Where AEs/Human Safety Information are considered related to any other medicinal product that the patient may be receiving whilst in the EAMS program, healthcare professionals should report these events to the MHRA via the Yellow Card scheme website: www.https://yellowcard.mhra.gov.uk or search for MHRA Yellow Card in the Google Play or Apple App Store.

### 4.9 Overdose

The overdose potential of triheptanoin has not been evaluated in human studies. In case of overdose, appropriate treatment should be initiated according to the patient's clinical signs and symptoms.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other alimentary tract and metabolism products, ATC code: A16AX17

Mechanism of action

Triheptanoin is a medium odd chain triglyceride consisting of three 7-carbon length fatty acids (heptanoates). Each molecule of heptanoate provides two molecules of acetyl-CoA and one molecule of propionyl CoA, bypassing the long chain FAOD enzyme deficiencies and replenishing TCA cycle intermediates for energy production (anaplerosis).

Pharmacodynamic properties

No formal pharmacodynamic studies have been conducted with triheptanoin.

Clinical efficacy and safety

*Study UX007-CL201 (Study 1) and Study UX007-CL202 (Study 2)*

Study UX007-CL201 (Study 1) was a 78-week, single-arm study of 29 paediatric and adult patients with serious clinical manifestations of LC-FAOD (as defined by evidence of chronic or acute metabolic crises, periodic elevations of creatine kinase (with or without symptoms), exercise intolerance, and/or frequent muscle fatigue) who were receiving conventional management (including MCT and dietary control) and crossed over to triheptanoin. Patients received triheptanoin at a dose titrated to a target of 25%–35% of the DCI or a maximum tolerated dose (prescribed daily dose ranged from 16.6% to 35%).

Study UX007-CL202 (Study 2) was an open-label study that included long-term follow-up (median of 50.7 additional months) of 24 patients who completed Study 1. It also included a cohort of 33 triheptanoin-naïve paediatric and adult patients ranging in age from 0.3 to 48.6 years (median 6.4 years of age) with LC-FAOD who had failed conventional therapy and who were treated for a median of 21.9 months. Patients received triheptanoin at a dose titrated to a target of 25%–35% of the DCI or a maximum tolerated dose. The prescribed daily dose in the triheptanoin-naïve cohort ranged from 15.6% to 34.6%.

*Major Clinical Events*
In Study 1, the efficacy of triheptanoin was assessed based on the frequency (a key efficacy endpoint) and duration of acute metabolic crises, evaluated as major clinical events (MCEs), including those that resulted in hospitalisations, over 78 weeks of treatment, compared to a retrospective 78-week period prior to triheptanoin treatment. MCEs included rhabdomyolysis, hypoglycaemia, and cardiomyopathy events, resulting in any hospitalisation, visit to the emergency room/acute care, or emergency intervention. During the 78-week pre-triheptanoin period, a total of 70 MCEs were reported, of which 57 events (81.4%) led to hospitalisation. During the 78-week triheptanoin treatment period, 39 MCEs were reported, of which 29 events (74.4%) lead to hospitalisation. The mean annualised event rate was reduced by 48.1% and the mean annualised event duration reduced by 50.3% during the

78 weeks of treatment (see Table 2). The annualised hospitalisation rate was reduced by 53.1%, from 1.39 events/year to 0.65 events/year. The annualised MCE hospitalisation days was reduced by 51.6% from 5.66 days/year to 2.74 days/year.

**Table 2: Major clinical events annualised event rate and annualised event duration during Study 1 through 78 weeks (N = 29)**

| | Annualised event rate (events/year) (N = 29) | | | | Annualised event duration[a] (days/year) (N = 29) | | | |
|---|---|---|---|---|---|---|---|---|
| | Pre-trihep Period[b] | Study 1 Treatment Period | % Change[c] | P-value[d] | Pre-trihep Period[b] | Study 1 Treatment Period | % Change[c] | P-value[d] |
| **Total Events** | | | | | | | | |
| **Mean** (SD) | 1.69 (1.608) | 0.88 (1.142) | -48.1 | 0.0208 | 5.96 (6.078) | 2.96 (3.973) | -50.3 | 0.0284 |
| **Median** (Q1, Q3) | 1.33 (0.67, 2.2) | 0.66 (0.00, 1.31) | -50.6 | – | 5.33 (0.67, 8.67) | 1.24 (0.00, 4.67) | -76.7 | – |
| **Hospitalisations** | | | | | | | | |
| **Mean** (SD) | 1.39 (1.345) | 0.65 (1.008) | -53.1 | 0.0160 | 5.66 (6.109) | 2.74 (3.941) | -51.6 | 0.0316 |
| **Median** (Q1, Q3) | 1.15 (0.00, 2.00) | 0.00 (0.00, 0.68) | -100.00 | – | 4.33 (0.00, 8.00) | 0.00 (0.00, 4.16) | -100.00 | – |

SD = standard deviation; trihep = triheptanoin

[a] Defined as total duration in days resulting from clinical events (major clinical events) in a year, averaged across all years and all patients.

[b] Data is derived from a retrospective chart review.

[c] Percent change values were based on mean (and median) values prior to rounding.

[d] P-values were calculated using a two-tailed Student's t-test.

Rhabdomyolysis events were reduced from 55 events to 37 events (36.1% reduction from a mean (standard deviation [SD]) pre-triheptanoin rate of 1.30 (1.508) events/year to 0.83 (1.151) events/year, p-value = 0.1189), hypoglycaemic events were reduced from 12 events to 1 event (a mean (SD) pre-triheptanoin rate of 0.32 (0.910) events/year to 0.02 (0.122) events/year, p-value = 0.0677) and there were fewer cardiomyopathy events (3 events pre-triheptanoin to 1 event).

In Study 2, the primary efficacy endpoint was the difference in the annualised rate of MCEs in the triheptanoin treatment period compared to the 78 weeks prior to triheptanoin treatment. Study 1 and Study 2 both demonstrated statistically significant reductions in annualised event rate meeting the primary endpoint in Study 2. Both studies also showed clinically meaningful reductions in annualised event duration; a key efficacy endpoint in Study 1 and a key secondary endpoint in Study 2.

Secondary endpoints included the annualised rate of MCEs that resulted in hospitalisations, and the difference in annualised duration of MCEs and associated hospitalisations. Among the 24 patients who continued from Study 1 into Study 2, the mean annualised MCE rate was reduced by 44% (p = 0.035) from 1.8 to 1.0 events/year in the combined triheptanoin treatment period. The median annualised MCE days was reduced by 45% (p = 0.81). The mean annualised hospitalisation rate was reduced by 44% (p = 0.044) from 1.4 to 0.8 events/year (see Table 3).

**Table 3: Major clinical events annualised event rate and annualised event duration from initiation of triheptanoin treatment through median follow-up of 68.5 months in patients who participated in Study 1 and Study 2 (N = 24)**

| | Annualised event rate (events/year) (N = 24) | | | | Annualised event duration[a] (days/year) (N = 24) | | | |
|---|---|---|---|---|---|---|---|---|
| | Pre-trihep period[b] | Study 1 + Study 2 Treatment period | % Change | P-value[c] | Pre-trihep period[b] | Study 1 + Study 2 Treatment period | % Change | P-value[d] |
| **Total events** | | | | | | | | |
| Mean (SD) | 1.76 (1.640) | 1.00 (1.00) | -43.5% | 0.0347 | 6.31 (6.35) | 7.92 (13.02) | 25.5% | –[f] |
| Median (Q1, Q3) | 1.53 (0.33, 2.72) | 0.62 (0.17, 1.75) | -59.6% | –[e] | 5.33 (0.33, 9.00) | 2.93 (0.47, 8.16) | -45.1% | 0.8139 |
| **Hospitalisations** | | | | | | | | |
| Mean (SD) | 1.43 (1.323) | 0.80 (0.96) | -43.8% | 0.0437 | 5.98 (6.380) | 7.73 (13.07) | 29.3% | –[f] |
| Median (Q1, Q3) | 1.33 (0.00, 2.12) | 0.35 (0.08, 1.49) | -73.7% | –[e] | 4.8 (0.0, 8.7) | 2.2 (0.2, 7.7) | -54.2% | 1.0000 |

SD = standard deviation; trihep = triheptanoin

[a] Defined as total duration in days resulting from major clinical events in a year, averaged across all years and all patients.

[b] Data is derived from a retrospective chart review of the 18 months prior to triheptanoin initiation.

[c] Statistical analysis performed using the paired t-test.

[d] Statistical analysis performed using the Wilcoxon matched pairs test.

[e] Not reported because data conformed to a normal distribution.

[f] Not reported because data deviated from a normal distribution.

The results of Study 2 were consistent with the results observed in Study 1. For the 33 patients who began triheptanoin treatment in Study 2, the median annualised MCE rate was reduced by 86% (p = 0.034), from 2.0 events/year prior to triheptanoin treatment to 0.3 events/year during triheptanoin treatment. The median annualised MCE duration decreased by 91% (p = 0.0325) from 8.7 days/year to 0.8 days/year. The median annualised rate of hospitalisations for MCEs decreased by 85.1% (p = 0.0643) from 1.3 to 0.2 events/year. The median annualised duration of hospitalisations for MCEs decreased (p = 0.0405) from 8.0 to 0.8 days/year, a reduction of 90.1% (see Table 4).

**Table 4: Major clinical events annualised event rate and annualised event duration from initiation of triheptanoin treatment throughout Study 2, triheptanoin-naïve cohort (N = 33)**

| | Annualised event rate (events/year) (N = 33) | | | | Annualised event duration[a] (days/year) (N = 33) | | | |
|---|---|---|---|---|---|---|---|---|
| | Pre-trihep period[b] | Treatment period | % Change | P-value[c] | Pre-trihep period[b] | Treatment period | % Change | P-value[c] |
| **Total events** | | | | | | | | |
| Mean (SD) | 2.49 (2.66) | 5.52[d] (21.43) | 121.7% | – | 15.59 (23.64) | 19.26[d] (67.20) | 23.54% | – |
| Median (Q1, Q3) | 2.00 (0.33, 2.73) | 0.28 (0.0, 1.62) | -85.9% | 0.0343 | 8.66 (3.33, 18.66) | 0.80 (0.0, 5.48) | -90.8% | 0.0325 |
| **Hospitalisations** | | | | | | | | |
| Mean (SD) | 2.03 (1.97) | 5.45[d] (21.44) | 168.5% | – | 15.13 (23.62) | 19.12[d] (67.22) | 26.37% | – |
| Median (Q1, Q3) | 1.33 (0.67, 3.33) | 0.20 (0.00, 1.43) | -85.1% | 0.0643 | 8.0 (1.33, 18.66) | 0.80 (0.00, 5.48) | -90.1% | 0.0405 |

SD = standard deviation; trihep = triheptanoin

[a] Defined as total duration in days resulting from major clinical events in a year, averaged across all years and all patients.

[b] Data is derived from a retrospective chart review.

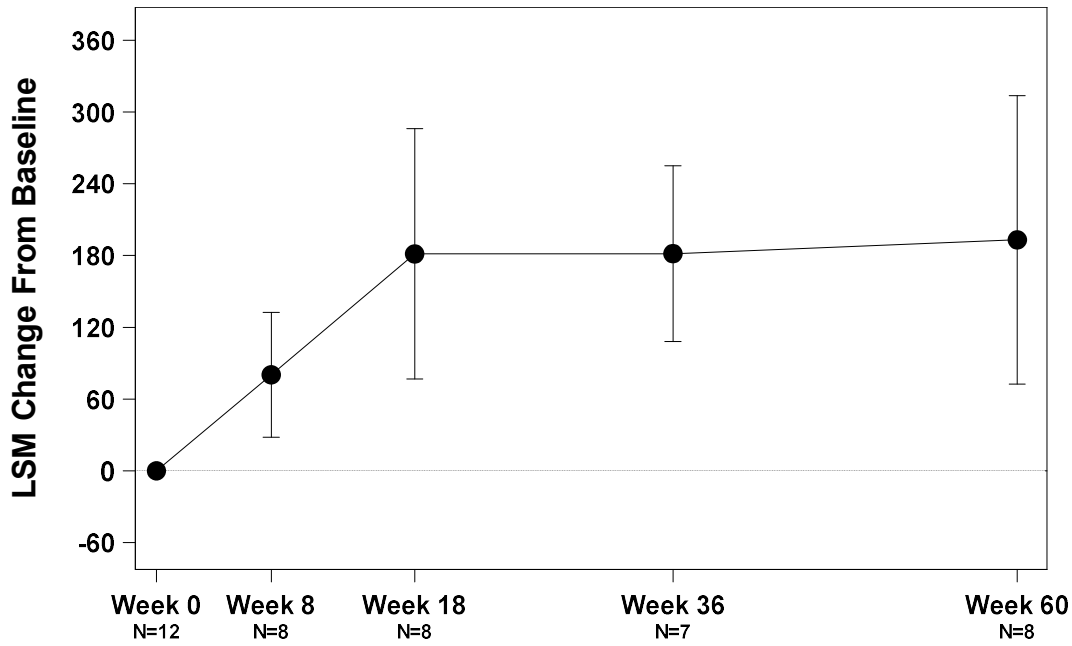
[c] Statistical analysis performed on median values using the Wilcoxon matched pairs test because the data were not normally distributed.

[d] One patient was hospitalized for the same duration as their enrollment duration in the study (3 days), resulting in outlier values for annualised MCE rate and duration (121.8 events/year and 365.3 days/year, respectively).

Twelve-minute walk test

In Study 1, 8 patients who were ⩾ 6 years of age performed a 12-minute walk test (12MWT) to assess the efficacy of treatment with triheptanoin on exercise tolerance and muscle function. At baseline, the patients' mean total distance walked was 673.4 m. After 18 weeks of treatment, total distance walked increased by a least-squares (LS) mean (standard error [SE]) change of +181.9 (106.2) m (p = 0.0868) (see Figure 1). A separate analysis at Week 60 demonstrated sustained increase in total distance walked by an LS mean (SE) change of +193.1 (120.5) m (p = 0.1090). The sample size was too small to reach statistical significance.

**Figure 1: 12-minute walk test from baseline to Week 60 in Study 1**




LSM = least-squares mean

Study NCT01379625 (Study 3)

The efficacy of triheptanoin was evaluated in Study NCT01379625 (Study 3), a 4-month, double-blind, randomised, controlled study comparing triheptanoin (7 carbon chain fatty acid) with trioctanoin (8 carbon chain fatty acid). Study 3 enrolled 32 adult and paediatric patients with a confirmed diagnosis of LC-FAOD and evidence of at least 1 significant episode of rhabdomyolysis and at least 2 of the following diagnostic criteria: disease specific elevation of acylcarnitines on a newborn blood spot or in plasma, low enzyme activity in cultured fibroblasts, or 1 or more known pathogenic mutations in CPT2, ACADVL, HADHA, or HADHB. The recommended target dosage of triheptanoin is up to 35% of DCI.

The treatment dosage was titrated to a target of 20% DCI (actual mean daily dose achieved was 16% for triheptanoin and 14% for trioctanoin). Patients ranged in age from 7 years to 64 years (median 22.5 years) and 12 were male.

*Cardiac function*

After 4 months, patients in the triheptanoin group had a left ventricular ejection fraction mean fold change from baseline of 1.04 compared to 0.97 in patients treated with trioctanoin, a difference of 7.4% ($p = 0.046$) and left ventricular wall mass mean fold change from baseline of 0.92 compared to 1.15, respectively ($p = 0.041$), on resting echocardiogram.

The triheptanoin group performed the same workload at a lower maximal heart rate (7 beats per minute lower at Month 4 vs. baseline, $p = 0.04$) on treadmill ergometry; no change in maximal heart rate was observed in the trioctanoin-treated group after 4 months of treatment.

Because cardiovascular function of the patients was within normal range at baseline, interpretation of these changes is limited.

*Rhabdomyolysis and associated peak creatinine kinase*

In Study 3, 5 patients experienced 7 events of rhabdomyolysis in the triheptanoin treatment group, and 4 patients experienced 7 events of rhabdomyolysis in the trioctanoin treatment group. Patients treated with triheptanoin had a lower average peak creatinine kinase associated with rhabdomyolysis events than the trioctanoin-treated patients. The mean peak creatinine kinase value in triheptanoin-treated

patients was 17,101 U/L (median: 14,440 U/L, n = 7 events) compared to 46,042 U/L in trioctanoin-treated patients (median: 35,519 U/L, n = 7 events).

*Blood metabolic markers*

No differences were observed between the triheptanoin and trioctanoin groups in blood markers of metabolism including glucose, insulin, lactate, total serum, ketones, acylcarnitines, and serum free fatty acid concentrations.

Expanded Access Programme and Named Patient Programmes

Patients with LC-FAOD treated in an Expanded Access programme were also evaluated to support the efficacy of triheptanoin.

A retrospective case series (18 patients with LC-FAOD in France; median treatment duration of 22 months) included observed benefits of decreased mean number of emergency hospitalisations per patient, decreased cumulative annual number of days of emergency home care, decreased mean number of emergency home care events, reduced annual mean rhabdomyolysis episodes, and reduced fatigue and myalgia in the majority of patients.

Data from 12 Austrian patients with LC-FAOD (median treatment duration of 3.9 years) demonstrated that triheptanoin was well tolerated. Total hospitalisation days per year decreased by 82%; rhabdomyolysis events reduced by 45%; liver function returned to normal for patients with hepatopathy; and cardiac function returned to normal in 6 of the 8 patients who presented with cardiomyopathy.

A retrospective study (51 critically ill patients with LC-FAOD) showed that 76% of patients experienced improvements in both short-term health and long-term LC-FAOD manifestations. In addition, 73% of patients with cardiomyopathy (16 of 22) showed improvement in their cardiac function and acute cardiomyopathy with treatment.

## 5.2 Pharmacokinetic properties

Following oral administration, triheptanoin is extensively hydrolysed to heptanoate and glycerol by pancreatic lipases in the intestines. The exposure of triheptanoin in human plasma is minimal. The pharmacokinetics of heptanoate exhibit high inter-patient variability. Heptanoate exposure increases greater than dose-proportional in the dose range between triheptanoin 0.3 and 0.4 g/kg.

Absorption

The pharmacokinetics of heptanoate in healthy adult patients following an oral administration of triheptanoin mixed with food are summarised in Table 5.

**Table 5: Summary of pharmacokinetic parameters of heptanoate after single and multiple oral administration of triheptanoin to healthy adults (N = 13)**

| | Triheptanoin dose | Mean (SD) $C_{max}$ (µmol/L) | Mean (SD) $AUC_{0-8h}$ (µmol*hr/L) | Time to first peak concentration[a] Median (range) (hours) |
|---|---|---|---|---|
| Single dose | 0.3 g/kg | 178.9 (145) | 336.5 (223) | 0.5 (0.4 to 1.0) |
| | 0.4 g/kg | 259.1 (134) | 569.1 (189) | 0.8 (0.4 to 6.4) |
| Multiple doses | 0.3 g/kg administered 4 times a day for 2 days<br>(total daily dosage of 1.3 g/kg/day) | 319.9 (164) | 789.8 (346) | 1.2 (0.0 to 2.4) |

SD = standard deviation

[a] After oral administration of triheptanoin, more than one peak concentration of heptanoate is observed.

Distribution

The plasma protein binding of heptanoate is approximately 80% and is independent of total concentration.

Metabolism

Heptanoate, formed by hydrolysis of triheptanoin, can be metabolised to beta-hydroxypentanoate (BHP) and beta-hydroxybutyrate (BHB) in the liver.

Elimination

After a single dose of either 0.3 g/kg or 0.4 g/kg triheptanoin to healthy patients, the mean apparent clearance (CL/F) of heptanoate was 6.05 and 4.31 L/hr/kg, respectively. Half-life ($t_{½}$) of heptanoate could not be determined due to multiple peak concentrations of heptanoate observed.

Pharmacokinetics in specific/special populations

Results of population pharmacokinetic analyses indicate that gender, race, and age do not influence the pharmacokinetics of triheptanoin. Limited pharmacokinetic data are available in non-White patients with LC-FAOD.

Patients with hepatic impairment

No studies have been conducted to evaluate the pharmacokinetics of triheptanoin and its metabolites in patients with hepatic impairment. Fatty acid beta-oxidation can occur in any tissues and organs with mitochondria, and it is unlikely that hepatic impairment would affect the pharmacokinetics of triheptanoin and its metabolites.

Patients with renal impairment

No studies have been conducted to evaluate the pharmacokinetics of triheptanoin and its metabolites in patients with renal impairment. Based on the minimal excretion of triheptanoin and its metabolites in the urine, it is not likely that the pharmacokinetics of triheptanoin and its metabolites is affected by renal impairment.

Drug interaction studies

Triheptanoin is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4. Heptanoate and BHP are not CYP substrates nor UGT substrates. In vitro studies have shown heptanoate increases the unbound fraction of valproic acid by approximately 2-fold. This interaction is not expected to be clinically meaningful because valproic acid is a very low extraction ratio drug.

### 5.3 Preclinical safety data

Nonclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction and development.

Nonclinical toxicology studies

Nonclinical studies evaluating tolerability to triheptanoin and its metabolites in mice, rats, and guinea pigs have been published, and studies to further support the safety of triheptanoin in rats, rabbits, and minipigs have been performed. These studies also provide data on the absorption, metabolism, and toxicity of triheptanoin when administered intravenously (IV) and orally at doses up to 50% the recommended caloric intake.

Acute toxicity
Single-dose toxicity was assessed in rats administered food-grade triheptanoin by oral gavage at doses up to 5 mL/kg (or 4.75 g/kg) with no deaths or signs of toxicity observed in this study.

Chronic toxicity
In repeat-dose studies, triheptanoin was well tolerated at the highest dose level tested in chronic 9-month GLP dietary toxicity studies conducted in rats (up to 1.14 g/kg) and juvenile minipigs (50% DCI equivalent to 10 g/kg).

Developmental and Reproductive Toxicity Studies

Embryofoetal developmental studies have been conducted with triheptanoin in rats and rabbits following oral administration of 10% (3.2 g/kg), 30% (9.7 g/kg), and 50% (16 g/kg) DCI in rats and 10% (1.2 g/kg), 20% (2.3 g/kg), and 30% (3.5 g/kg) DCI in rabbits during the period of organogenesis. Reduced body weight gain, associated with decreased food consumption, was observed in pregnant rats and rabbits following administration of triheptanoin food mixture and was attributed to taste aversion. The no-observed-adverse-effect-level (NOAEL) for this maternal toxicity (reduced body weight gain) was 10% DCI for both rats and rabbits. Administration of dietary triheptanoin to pregnant rats at doses approximately 2 times above, and pregnant rabbits approximately equal to the targeted clinical dose of 35% DCI, resulted in increased incidence of skeletal malformations and decreased litter weights in both species and reduced number of viable litters in rabbits. The adverse effects on rat and rabbit embryofoetal development were associated with the reduced body weight gain observed in pregnant animals. The NOAEL for embryofoetal development toxicity was 30% and 20% DCI for rats and rabbits, respectively. In a pre- and post-natal developmental study in rats, reduced birthweights and delayed sexual maturation in pups were observed at 50% DCI and were considered secondary to the reductions in body weight gain in pregnant rats.

Impairment of fertility

Triheptanoin had no effect on fertility or any other parameters of mating performance in rats exposed to repeat dietary administration of triheptanoin at dose levels equivalent to up to 50% daily caloric intake (16 g/kg) that resulted in systemic drug exposure (AUC) of heptanoate approximately equal to the maximum recommended human dose.

Carcinogenesis

Nonclinical animal studies evaluating long-term administration of triheptanoin have not been conducted to assess carcinogenic potential. In a published chronic 9-month dietary study conducted in rats, daily administration of triheptanoin at dose levels up to 1.14 g/kg was associated with atrophy or hyperplasia of the intestinal villa. In a chronic 9-month dietary study conducted in juvenile minipigs, treatment with triheptanoin at dose levels up to 10 g/kg was well tolerated with no changes in histopathology suggestive of any carcinogenic potential.

Published studies with structurally similar triglycerides (i.e., MCTs) were also evaluated. In a 2-year dietary study of rats fed tricaprylin (C8 MCT) at dose levels up to 9.5 g/kg (approximately 1.2 times the anticipated maximum clinical dose), there were increased incidences of pancreatic and forestomach hyperplasia and adenomas but not carcinomas. Chronic administration of a diet containing approximately 17% MCT was not shown to promote effects on colon tumour incidence in an azomethane-induced colon tumorigenicity rat model.

Mutagenesis

Triheptanoin was not genotoxic in a battery of genotoxicity tests including the *in vitro* bacterial reverse mutation in *S. typhimurium* and *E. coli* test, *in vitro* mammalian chromosomal aberration test in human peripheral blood lymphocytes, and the *in vivo* mammalian erythrocyte micronucleus test in rat bone marrow.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

None.

### 6.2 Incompatibilities

Triheptanoin is not compatible with certain plastics and should not be dosed or stored using materials made of polystyrene or polyvinyl chloride (PVC).

### 6.3 Shelf life

4 years.

After first opening:
9 months

### 6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.
Store in the original container.
Do not freeze.

### 6.5 Nature and contents of container

500 mL oral liquid in an amber, Type III glass bottle with a white polypropylene (PP) and high-density polyethylene (HDPE) child-resistant closure and a foil-sealed liner.

Pack size: 1 bottle. Also contains one low density polyethylene (LDPE) press-in bottle adaptor and two 10 mL polypropylene oral syringes with 1 mL graduations.

### 6.6 Special precautions for disposal and other handling

Prepare or administer triheptanoin using containers or oral syringes made of compatible materials such as stainless steel, glass, high density polyethylene (HDPE), polypropylene, low density polyethylene, polyurethane, and silicone.

Do not prepare or administer triheptanoin using containers or oral syringes made of polystyrene or polyvinyl chloride (PVC) plastics.

Regularly monitor the containers, dosing components, or utensils that are in contact with triheptanoin to ensure proper functioning and integrity.

<u>Oral preparation and administration</u>

1. Use the provided measuring syringe to withdraw the prescribed volume of triheptanoin from the bottle.

   Triheptanoin can be mixed with soft food or liquid such as:
   - plain or artificially sweetened fat-free yogurt
   - fat-free milk, formula, or cottage cheese
   - whole grain hot porridge
   - fat-free low carbohydrate custard, smoothies, applesauce, or baby food

2. Add the prescribed amount of triheptanoin to a clean bowl, cup, or container made of the compatible materials as listed above, which contains an appropriate amount of semi-solid food or liquid that takes into consideration the age, size, and fluid needs of the patient to ensure administration of the full dose.

3. Mix triheptanoin thoroughly into the food or liquid.

   Any unused mixture may be stored for up to 24 hours in refrigerated conditions. If not used within 24 hours, discard the triheptanoin mixture in household waste. Do not pour down the sink. Do not save for later use.

4. Check the items used to take triheptanoin often to make sure they are working properly and are not breaking down. Each of the measuring syringes provided with triheptanoin can be used for up to 60 doses. Throw away the syringe once it has been used for 60 doses.

Feeding tube preparation and administration

Triheptanoin is administered as an oral or enteral bolus medication. Do not add triheptanoin to the feeding bag, as the feeding equipment may degrade over time.

Triheptanoin can be administered via oral or enteral feeding tubes manufactured of silicone or polyurethane. Do not use feeding tubes manufactured of PVC. Feeding device performance and functionality can degrade over time depending on usage and environmental conditions. Regularly monitor the feeding tube to ensure proper functioning and integrity (see section 4.4).

1. Use the provided measuring syringe to withdraw the prescribed volume of triheptanoin from the bottle.

2. Add the prescribed amount of triheptanoin to a clean bowl, cup, or container made of compatible materials as listed above, which contains an amount of medical food or formula that takes into consideration the age, size, and fluid needs of the patient to ensure administration of the full dose.

3. Mix triheptanoin thoroughly into the medical food or formula prior to administering via feeding tube, y-connector, or feeding tube extension set made of silicone or polyurethane.

4. Draw up the entire amount of the triheptanoin mixture into a slip tip syringe (used for the feeding tube; not provided).

5. Remove the air from the syringe and connect the syringe directly into the feeding tube port.

6. Push the contents of the syringe into the feeding tube port using steady pressure until empty.

7. Flush the feeding tube port with between 5 mL to 30 mL of water. Flush volume should be modified based on specific patient needs and in cases of fluid restriction.

8. Discard any unused triheptanoin mixture in household waste. Do not pour down the sink. Do not save for later use.

9. Check the feeding tube and other items used to give triheptanoin often to make sure they are working properly and are not breaking down. Each of the measuring syringes provided with triheptanoin can be used for up to 60 doses. Throw away the syringe once it has been used for 60 doses.

## 7. SCIENTIFIC OPINION HOLDER

Ultragenyx Netherlands B.V.
Unit 104, Evert Van De Beekstraat 1
Schiphol, 1118 CL
Netherlands

## 8. EAMS NUMBER(S)

41104/0001

## 9. DATE OF SCIENTIFIC OPINION

DD/MM/YYYY

**Additional Information**
Physicians or pharmacists (HCPs) interested in enrolling a patient in the triheptanoin EAMS must first contact UX007_EarlyAccess@ultragenyx.com to begin the registration process. Full details on instructions to HCPs is provided in the document entitled Triheptanoin EAMS – Treatment Protocol – Information on the Pharmacovigilance (PV) System and Requirements for Reporting Safety Data.

Registered HCPs will submit the necessary information for each individual patient. The following documents will be provided to HCPs via email:

- Triheptanoin EAMS – Drug Registry
- Triheptanoin EAMS – Treatment Protocol – Information for Healthcare Professionals (HCPs)
- Triheptanoin EAMS – Treatment Protocol – Information for Patients
- Triheptanoin EAMS – Treatment Protocol – Information on the Pharmacovigilance (PV) System and Requirements for Reporting Safety Data
- Triheptanoin EAMS – Safety Training and Reporting Responsibilities
- Triheptanoin EAMS – Safety Training Acknowledgment Form
- Triheptanoin EAMS – Drug Supply Request Form
- Triheptanoin EAMS – Agreement (Contract)
- Triheptanoin EAMS – Treatment Start Date Form
- Triheptanoin EAMS – Informed Consent Form (ICF)
- Triheptanoin EAMS – Adverse Event Report Form
- Triheptanoin EAMS – Pregnancy Report Form

Reporting adverse events (AEs) after administration of the medicinal product is mandatory within the EAMS. Prescribers will be provided with guidance on reporting adverse events (see Triheptanoin EAMS – Treatment Protocol – Information on the Pharmacovigilance (PV) System and Requirements for Reporting Safety Data, for more details).

**Contact information:**
Email**:** ultragenyx@primevigilance.com
Fax: +1-415-930-4033