

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

213687Orig1s000

OTHER REVIEW(S)

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: June 26, 2020
Requesting Office or Division: Division of Rare Diseases and Medical Genetics (DRDMG)
Application Type and Number: NDA 213687
Product Name and Strength: Dojolvi (triheptanoin) oral liquid, 100 % w/w
Applicant/Sponsor Name: Ultragenyx Pharmaceutical
OSE RCM #: 2019-1652-2
DMEPA Safety Evaluator: Sarah K. Vee, PharmD
DMEPA Team Leader: Ashleigh Lowery, PharmD, BCCCP

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on April 21, 2020 for Dojolvi. We review the revised container label and carton labeling for Dojolvi (Appendix A) to determine if it is acceptable from a medication error perspective. Ultragenyx revised the container label and carton labeling to include incompatible container materials (polystyrene or polyvinyl chloride) to be consistent with the prescribing information.

2 CONCLUSION

The proposed revisions are acceptable from a medication error perspective and we have no additional recommendations at this time.

2 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

SARAH K VEE
06/26/2020 11:25:20 AM

ASHLEIGH V LOWERY
06/26/2020 11:29:03 AM



**Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency Templates
Version: 2018-01-24**

Date: June 10, 2020

Reviewer/Team Leader: Catherine Callahan, PhD, MA
Division of Epidemiology I

Deputy Division Director: CAPT Sukhminder K. Sandhu, PhD, MPH, MS
Division of Epidemiology I

Subject: ARIA Sufficiency Memo for Pregnancy Safety Concerns

Drug Name: Triheptanoin (DOJOLVI)

Application Type/Number: NDA 213687

Sponsor: Ultragenyx

OSE RCM #: 2020-861



Expedited ARIA Sufficiency Template for Pregnancy Safety Concerns

1. BACKGROUND INFORMATION

1.1. Medical Product

Triheptanoin (DOJOLVI) is a medium-chain triglyceride with the proposed indication as a source of calories and fatty acids for the treatment of pediatric and adult patients with molecularly confirmed long-chain fatty acid oxidation disorders (LC-FAOD). The proposed dosage is up to 35% of the patient's total prescribed daily caloric intake divided into at least four doses and administered at mealtimes or with snacks. The mean apparent clearance (CL/F) of heptanoate was 6.05 L/hr/kg and 4.31 L/hr/kg, respectively, following single oral dose of triheptanoin 0.3125 g/kg and 0.375 g/kg.¹ The proposed labelling for triheptanoin has warnings and precautions for feeding tube dysfunction and intestinal malabsorption in patients with pancreatic insufficiency. The most commonly reported adverse events in the triheptanoin development program were abdominal pain, diarrhea, vomiting, and nausea.

1.2. Describe the Safety Concern

The Division of Gastroenterology and Inborn Errors Products (DGIEP, now the Division of Rare Diseases and Medical Genetics (DRDMG)) requested that the Division of Epidemiology (DEPI) assess the sufficiency of ARIA for broad-based signal detection studies of triheptanoin exposure during pregnancy.

Safety during pregnancy due to drug exposure is a concern for women who are pregnant or of childbearing potential. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.² Currently there are few documented reports of pregnancy outcomes with maternal LC-FAOD. As treatments for LC-FAOD improve, there is a need to better understand the impact of these treatments on fetal outcomes.³

There are no adequate and well-controlled studies that investigated adverse pregnancy outcomes after triheptanoin exposure and a lack of pregnancy studies generally. Pregnant women were excluded from triheptanoin clinical studies and there were no pregnancies observed in the clinical studies. In animal studies, 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 adverse effects on rat and rabbit embryofetal development (increased incidence of skeletal malformations and decreased litter weights in both species and reduced number of viable litters in rabbits) were associated with the reduced body weight gain observed in pregnant animals.

In the proposed labeling, as of June 1, 2020 the Risk Summary in Section 8.1 states:

8.1 Pregnancy

¹ Triheptanoin Draft Integrated Review, as of June 1, 2020.

² Dinatale M. Division of Pediatric and Maternal Health, FDA. The pregnancy and lactation labeling rule (PLLR). <https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM520454.pdf> Accessed February 11, 2020

³ Triheptanoin Draft Integrated Review, as of June 1, 2020.

Risk Summary

There are no available data on triheptanoin use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. 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, and therefore is not relevant to clinical use in the intended populations.

Advise women to report pregnancies to Ultragenyx Pharmaceutical Inc. at 1-888-756-8657.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

Embryofetal 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 NOAEL for this maternal toxicity (lack of 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 embryofetal development were associated with the reduced body weight gain observed in pregnant animals. The NOAEL for embryofetal development toxicity was 30% and 20% DCI for rats and rabbits, respectively. In a pre- and postnatal 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.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

- Please ensure that the selected purpose is consistent with the other PMR documents in DARRTS

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)

Assess a known serious risk	X
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

- Specific FDA-approved indication in pregnant women exists and exposure is expected
- No approved indication, but practitioners may use product off-label in pregnant women
- No approved indication, but there is the potential for inadvertent exposure before a pregnancy

is recognized

- No approved indication, but use in women of child bearing age is a general concern

2.2. Regulatory Goal

- Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision and certainty
- Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty. †
- Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review). †

† **If checked, please complete General ARIA Sufficiency Template.**

2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

- Pregnancy registry with internal comparison group
- Pregnancy registry with external comparison group
- Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)
- Electronic database study with chart review
- Electronic database study without chart review
- Other, please specify: Single-arm pregnancy safety study, which enrolls exposed pregnancies into a protocol-driven observational cohort study for descriptive analyses and collects follow-up data, including detailed case narratives. These studies do not require inferential analyses and do not have the sample size requirements of a traditional pregnancy registry. A single-arm pregnancy safety study is appropriate because this drug is indicated for a rare disease and a study sufficiently powered for a comparative analysis is not required.

2.4. Which are the major areas where ARIA not sufficient, and what would be needed to make ARIA sufficient?

- Study Population
- Exposures
- Outcomes
- Covariates
- Analytical Tools

For any checked boxes above, please describe briefly:

Outcomes: ARIA lacks access to detailed narratives. Given that the study for broad-based surveillance being considered is descriptive, without sample size requirements, and without a comparison group, having detailed narratives are deemed necessary to identify and validate outcomes, assess exposure-outcome temporality, and to conduct causality assessments.

Analytical tools: ARIA analytic tools are not sufficient to assess the regulatory question of interest because data mining methods have not been tested for birth defects and other

pregnancy outcomes.

2.5. Please include the proposed PMR language in the approval letter.

The following language has been proposed by DGIEP, as of June 10, 2020, for the PMR related to pregnancy outcomes:

3858-1 Conduct a worldwide, single-arm, pregnancy safety study in women exposed to DOJOLVI during pregnancy to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Infant outcomes will be assessed through at least the first year of life. Results will be analyzed and reported descriptively.

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/s/

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Clinical Inspection Summary

Date	March 20, 2020
From	Zana Marks, M.D., M.P.H. Ying- Min Ning, M.D., Ph.D. Kassa Ayalew, M.D., M.P.H. GCPAB/OSI/CDER/FDA
To	Dina Zand, M.D. Katie Donohue, M.D. DGIEP/OND/FDA
NDA #	213687
Applicant	Ultragenyx Pharmaceutical Inc.
Drug	Triheptanoin
NME (Yes/No)	No
Therapeutic Classification	Triheptanoin is a medium chain triglyceride consisting of three 7-carbon fatty acids on a glycerol backbone
Proposed Indication	(b) (4) for the treatment of adults and pediatric patients with long-chain fatty acid oxidation disorders (LC-FAOD) (b) (4)
Consultation Request Date	September 25, 2019
Summary Goal Date	March 30, 2020
Action Goal Date	July 31, 2020
PDUFA Date	July 31, 2020

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from an open-label phase 2 study was submitted as a 505(b)(2) supplement to NDA 213687 to the Agency in support of the above proposed indication for triheptanoin. Three clinical investigators, Dr. Kimberly Chapman (Site 136), Dr. John Phillips (Site 119), and Dr. Gerard Vockley (Site 108) were selected for clinical inspections. The clinical sites were chosen primarily based on numbers of enrolled subjects and those sites with the most growth records.

The inspections verified the reported primary efficacy measures with source data at the clinical investigator sites. Dr. Vockley's site (Site 108) was found to have a few protocol deviations as described in Section III of this summary. One subject (Subject (b) (6)) was found not to have met the eligibility criteria, which was not reported to the sponsor as a protocol violation

Overall, the data generated by these clinical investigator sites, which were submitted by the sponsor, appear to be acceptable and supportive of this NDA.

II. BACKGROUND

Triheptanoin is a medium-chain triglyceride consisting of three 7-carbon fatty acids on a glycerol backbone. LC-FAOD is a group of six rare and life-threatening autosomal recessive disorders caused by defects in genes that encode mitochondrial enzymes critically involved in the conversion of dietary long-chain fatty acids into energy. Patients with LC-FAOD can experience acute metabolic crises during times of increased energy demand, such as common infections or moderate exercise. These metabolic crises (captured as major clinical events) may manifest as rhabdomyolysis, hypoglycemia, or cardiomyopathy and can be unpredictable, precipitous, and life-threatening requiring emergency medical management. Between these episodic events, patients with LC-FAOD may have periods of relatively normal function, however, many patients experience impaired exercise tolerance and reduced quality of life due to the avoidance of activities that might induce metabolic crises.

There are no approved therapies for the treatment of LC-FAOD. Current management of these disorders typically includes avoidance of fasting, maintenance of a low fat/high carbohydrate diet, and/or ingestion of commercially available medium chain triglyceride formulations (MCT) consisting primarily of 8- and 10-carbon fatty acids to bypass the defect in the long-chain fatty acid metabolizing enzymes.

To support the proposed indication in this NDA, the Applicant submitted clinical data from Study UX007-CL 201 (NCT018863). The design and conduct of this study are summarized below.

Protocol UX007-CL 201

Study Title: An open-label phase 2 study to assess safety and clinical effects of UX007 in subjects with long-chain fatty acid oxidation disorders (LC-FAOD)

Primary Objective

The primary objective of this study was to evaluate the impact of UX007 on acute clinical pathophysiology associated with LC-FAOD following 24 weeks of treatment.

Secondary Objective

The secondary objectives of this study were to evaluate the safety of UX007 treatment in subjects with LC-FAOD and to evaluate the effect of UX007 on energy metabolism in LC-FAOD. The objective of the Treatment + Extension Periods (following 78 weeks of treatment) of the study was to evaluate the impact of UX007 on major clinical events associated with LC-FAOD.

Methodology

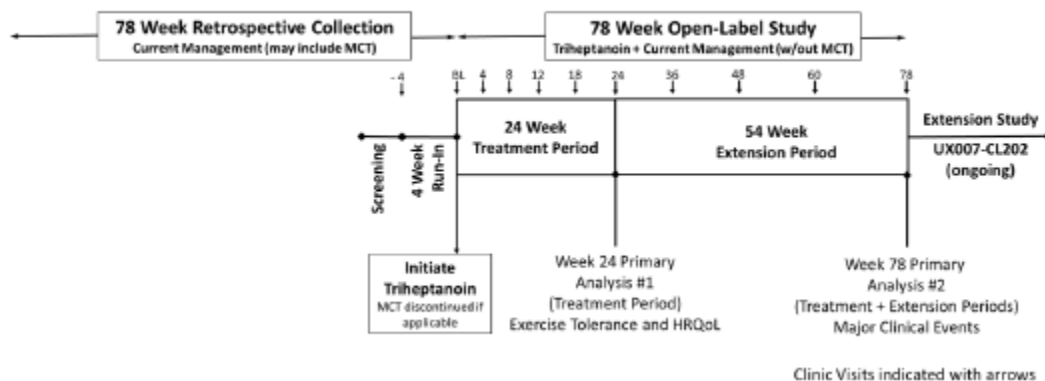
The study was a prospective, interventional, open-label Phase 2 study of UX007 treatment in 29 subjects with LC-FAOD (at least 6 months of age) exhibiting serious clinical manifestations of LC-FAOD despite current management.

At the Screening visit, available medical history of major clinical events during the prior 18-24 months was tabulated from medical records to assess the inclusion criteria (up to 24 months) and establish a pre-UX007 comparison (18 months or 78 weeks).

Given the heterogeneity of LC-FAOD clinical manifestations, the retrospective data collection was intended to provide a within-subject comparison for major clinical events (MCEs) so that each individual served as his/her own control comparing the 78 weeks on conventional LC-FAOD management (pre-UX007) to the 78-week UX007 period. Enrolled subjects continued current management during a 4-week Run-in Period to establish a stable baseline. Subjects discontinued use of MCT at the Baseline visit and began treatment with UX007 after the completion of the 4-week Run-in period. UX007 dosing was titrated to a target of 25% to 35% daily caloric intake (DCI) or maximum tolerated dose and followed for 24 weeks (Treatment Period), then continued treatment in the Extension Period for an additional 54 weeks for a total of 78 weeks.

The effects of UX007 treatment on MCEs were assessed over 78 weeks of study during the Treatment and Extension Periods and compared with that subject's available medical history for the pre-UX007 period. See study schema below:

Figure 2.1: UX007-CL201 Study Schema



Source: CSR NDA213687 page 8.

Number of Subjects (planned and analyzed)

The study planned to include 30 subjects with severe LC-FAOD; 29 patients were analyzed.

Inclusion Criteria

Inclusion criteria for study participation included the following: confirmed diagnosis of one of the four most common LC-FAOD disorders (carnitine palmitoyltransferase [CPT II] deficiency, very long chain acyl-CoA dehydrogenase [VLCAD] deficiency, long chain- 3-hydroxy-acyl-CoA dehydrogenase [LCHAD] deficiency, and trifunctional protein [TFP] deficiency); at least 6 months of age; currently managed on a stable treatment regimen

(including diet); willing to provide written informed consent or assent (where appropriate) with consent by a legally authorized representative; willing and able to provide access to medical records charting the last 18-24 months of care; no history of serious adverse reactions or known hypersensitivity to triheptanoin; severe LC-FAOD as evidenced by any of the following significant clinical manifestations despite management: chronic elevated CK with major clinical events, episodic elevated CK with reported muscle dysfunction (patient report of frequent muscle fatigue, exercise intolerance, or limitation of exercise), highly elevated CK but asymptomatic, frequent severe major medical episodes, severe susceptibility to hypoglycemia and/or evidence of functional cardiomyopathy (echocardiogram within 90 days documenting poor ejection fraction and requiring ongoing medical management).

Study Treatments

UX007 was to be administered orally (PO) mixed into food or drink (including formula) or by gastrostomy tube at least four times per day (breakfast, lunch, dinner, and before bed), titrated up to a target dose comprising up to 25% to 35% daily caloric intake (DCI) or maximum tolerated dose as indicated in the administration guideline.

Duration of Treatment

During the Run-in Period of the study (4 weeks), subjects continued on their current standard management regimen for LC-FAOD, including MCT if used. Following the Run-in Period, subjects entered the Treatment Period (24 weeks), where they discontinued MCT after the Baseline visit and began treatment with daily open-label UX007 while maintaining their other dietary restrictions. Following completion of assessments at Week 24, subjects continued treatment in the Extension Period for an additional 54 weeks (total of 78 weeks treatment).

Primary Efficacy Endpoint

The effect of UX007 on LC-FAOD was assessed by evaluating critical variables of disease impacting 3 clinical areas of focus (rhabdomyolysis and muscle function impairment, hypoglycemia and liver assessments, and cardiomyopathy and cardiac function), along with relevant biomarkers. The key efficacy endpoints included comparisons of major clinical events through 78 weeks of UX007 treatment compared with the pre-UX007 period.

Study Conduct

The study was conducted from February 6, 2014 (date of first subject consent and Screening Visit) to August 25, 2016 (date of last subject's last visit). A total of 29 subjects were enrolled from 10 study sites in the United States (U.S.) and the United Kingdom. Eight-three percent of subjects were from the U.S.

Rationale for Selection of Investigator

Three clinical investigators, Dr. Kimberly Chapman (Site 136), Dr. John Phillips (Site 119), and Dr. Gerard Vockley (Site 108) were selected for clinical inspections. These clinical sites were chosen primarily based on numbers of enrolled subjects. Drs. Chapman and Phillips had no previous inspection. Dr. Vockley had one FDA inspection conducted in February 2015.

RESULTS

1. Dr. Kimberly Chapman (Site 136)

Children's National Health System
111 Michigan Avenue, NW
Washington, DC, 20010

This clinical investigator was inspected on November 18-21, 2019. This was the first FDA inspection for this investigator.

The site screened 4 subjects and enrolled 2 of them into the study. The enrolled subjects received triheptanoin titrated to an effective dose that was 25-35% of the patient's total caloric intake. The records for the two enrolled subjects (Subjects (b) (6)) were reviewed.

The two subjects' source records were reviewed and compared with the submitted data listings to this NDA for the site. The reviewed source records included but were not limited to the signed informed consent, eligibility forms, documentation and reporting of adverse events, completion and documentation of study procedures, protocol adherence, and drug accountability. The inspection also examined the IRB's approvals and oversight of the study and reviewed relevant regulatory documents, including the signed Form FDA 1572s, financial disclosures, training records, sponsor's monitoring visits, and retention of study records at the site.

The inspection revealed no significant deficiencies, with no Form FDA 483 issued to the investigator. In general, the submitted data listings, including the primary endpoint data, for the 2 enrolled subjects were verifiable. There was one discrepancy in a hepatology report date for Subject (b) (6). The original date of the liver sonogram was (b) (6). This was read as normal. Six months later a repeat liver sonogram showed positive findings of mild hepatomegaly and slight parenchymal inhomogeneity. A third sonogram, performed six months after the second sonogram, revealed findings that were consistent with the second sonogram. The Chief of Academic Affairs had the sonograms re-read and concluded the initial sonogram in (b) (6) showed mild hepatomegaly as well. Therefore, the initial sonogram was then reported as an adverse event citing mild hepatomegaly. The data listings only listed the 2 subsequent sonograms. However, Notes to File matched the timeline of events related to the sonograms. There were no additional unreported adverse events identified in the inspection.

The protocol stated subjects with severe LC-FAOD were to be enrolled and their available history of major clinical events during the prior 18-24 months were to be

tabulated. Dr. Chapman provided a note to file that explained the treatment prior to and after enrollment for the major clinical events of hypoglycemia, rhabdomyolysis, and cardiomyopathy. Subject (b) (6) experienced cardiomyopathy in (b) (6). The PreTreatment Major Medical Events Worksheet did not list cardiomyopathy as a major clinical event (MCE). Dr Chapman explained that the echocardiogram was a part of a routine visit requiring no hospitalization. Additionally, it was noted that the subject was followed by cardiology regularly during the study and his cardiac findings were considered normal for his underlying condition. The sponsor agreed with the investigator that for Subject (b) (6), this and subsequent cardiomyopathy events are not considered a MCE as defined by the related reference manual.

Based on the protocol schedule, the initial three-day diet history recorded prior to the first run-in visit were to be reviewed by the site to establish daily caloric intake. Subjects and/or caregivers were required to maintain a record of daily diet in a diary for three days prior to each milestone visit (run-in, baseline, weeks 12, 24, 48, and 78). The diet dairies were to be reviewed with the site staff upon each indicated visit. During the review of Subject (b) (6) dietary history, the inspector noted that the percentage of calories provided by triheptanoin fell below what was recommended in the protocol for Week 24 (23.7%) ; Week 48 (15.1%) and Week 78 (17.8%). The sponsor consented to allow reducing the target dosage to 25% of the total calories, citing there was no efficacy shown for dosages below this level. The sponsor stated that dosing outside the targeted range was not considered a protocol deviation because the protocol specifically stated the need to adjust the dose of triheptanoin depending on the patient's tolerability. No formal documentation was available for the follow-up with the sponsor when the dose was decreased from 25 to 17.8% of the caloric intake.

Reviewer's Comment(s): The aforementioned findings (i.e. major clinical events, adverse/serious adverse events, and diet diary review) provided post inspectional discussion points. The clinical investigator team provided adequate documentation to provide context for the site inspector's queries. In general, the inspection revealed adequate adherence to the regulations and the investigational plan. No serious objectionable findings were discovered during this inspection. Overall, the data generated by this clinical investigator site, appear to be acceptable and supportive of this NDA.

2. Dr. John Phillips (Site 119)

Vanderbilt Medical Center
1161 21st Avenue SMCNDD-2205
Nashville, TN 37232

This clinical investigator was inspected on February 18-19 and 24-27, 2020. This was the first FDA inspection for this investigator.

This investigator site screened and enrolled 5 subjects into the study. All 5 subjects completed the study, with triheptanoin treatment titrated to an effective dose that was 25-35% of the patient's total caloric intake. The records for the 5 enrolled patients were reviewed. The source data for the 5 subjects records was presented to the investigator and reviewed in full.

The inspector reviewed the source documents related to informed consent, inclusion/exclusion criteria, and adverse events for the 5 enrolled subjects. The reviewed source records included but were not limited to the signed informed consent, eligibility forms, documentation and reporting of adverse events, completion and documentation of study procedures, protocol adherence, and drug accountability.

The inspection also examined the IRB's approvals and oversight of the study and reviewed relevant regulatory documents, including the signed Form FDA 1572s, financial disclosures, training records, sponsor's monitoring visits, and retention of study records at the site.

The inspection revealed no significant deficiencies, with no Form FDA 483 issued to the investigator. The submitted data listings for the 5 subjects were verifiable at the site, with no significant discrepancies identified or reported. The primary efficacy data were verified with the site's documented major clinical events (e.g. rhabdomyolysis, cardiomyopathy, and hypoglycemia). There were no unreported adverse events identified in the inspection.

Reviewer's Comment: The data generated by this clinical investigator site, appear to be acceptable and supportive of this NDA.

3. Dr. Gerard Vockley (Site 108)

Children's Hospital of Pittsburgh of UPMC
4401 Penn Avenue
Pittsburgh, PA 15224

This clinical investigator was inspected on January 13-17, 2020, 1/21-22, 2020, and the close out inspection visit occurred on 1/29/2020.

This investigator was inspected previously in February 2015 for study protocol 401.13.001, entitled "Open-Label Study of Uridine Triacetate in Pediatric Patients with Hereditary Orotic Aciduria". At that time, a Form FDA 483, Inspectional Observations, was issued for failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation. The investigator provided his written response to the inspection findings and stated plans to implement actions to prevent the recurrence of the inspection findings.

For the current inspected study, the site screened 8 subjects and enrolled all 8 into the study. With these subjects received triheptanoin titrated to an effective dose that was 25-35% of the patient's total caloric intake. Of the 8 subjects enrolled, 6 subjects completed the study at this site. The other 2 subjects (Subjects (b) (6)) transferred to a study site at Vanderbilt University early in the study.

The inspector reviewed all of the source records for the 8 subjects and verified the data listings submitted with the NDA with the source records at the site for these subjects. The reviewed source records included but were not limited to the signed informed consent, eligibility forms, , documentation and reporting of adverse events, completion and documentation of study procedures, protocol adherence, and drug accountability.

The inspection also examined the IRB's approvals and oversight of the study and reviewed relevant regulatory documents, including the signed Form FDA 1572s, financial disclosures, training records, sponsor's monitoring visits, and retention of study records at the site.

A Form FDA 483 was issued to the investigator citing the following 2 observations:

- 1) Not all changes in research activity were approved by an Institutional Review Board prior to implementation.

The clinical investigator screened and enrolled an infant weighing (b) (6) kg (Subject (b) (6)). The IRB had recently lowered the minimum weight for study participants to 8 kgs. The following day the same subject was re-weighed for the Run-In visit and the weight was (b) (6) kg. The Run-In visit included collection of blood for Fasting Serum Glucose, Creatine Kinase and Plasma Acylcarnitines/Carnitine testing. The investigator did not obtain IRB approval to deviate from the newly imposed weight restriction for the study.

- 2) An investigation was not conducted in accordance with the investigational plan.

The clinical investigator screened and enrolled Subject (b) (6) based on the inclusion criteria that stated "episodic elevated CK with reported muscle dysfunction. This was defined in the protocol as "Episodes of elevated CK levels over the last 6 months - 1 year (defined as > 2X upper limit of age/gender-matched normal or > 500 units/L (if age-matched reference is not established), AND patient report of frequent muscle fatigue, exercise intolerance, or limitation of exercise"

Subject (b) (6)'s records showed only one episode of elevated CK during the specified time frame, 6 months-1 year.

The clinical investigator acknowledged that documentation of the Subject (b) (6)'s eligibility was incomplete by charting one episode of elevated CK. He further explained that the subject had severe LC-FAOD that was treated at home without confirming the CK levels. He produced a note to file dated 1/17/20 where he explained the rationale for approving the eligibility of the subject. That note was also signed by a sponsor representative. Dr Vockley confirmed the study monitor never questioned the eligibility of this subject and the incidence was not documented as a protocol violation.

There were no other discrepancies between the submitted data listings and the source documents for the 6 subjects for whom data verification was performed. Specifically, the primary endpoint efficacy data was verifiable for all the 6 subjects.

Reviewer's Comment: The inspection of Dr. Vockley identified and confirmed that Subject (b) (6) at the study site did not meet the eligibility criteria. Although his note to file explaining his rationale for approving the subject was signed by a sponsor representative at the time of this inspection, the incident was not formally reported as a protocol violation prior to the submission of this NDA. This appears to be an isolated event that did not affect the reliability and integrity of the data.

{ See appended electronic signature page }

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Office of Scientific Investigations

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Central Doc. Rm. NDA 208051-S05
Review Division /Associate Division Director/B Nikhar
Review Division /Project Manager/C Cherry-France
Review Division/Clinical Reviewer/R Mehta
OSI/Office Director/D Burrow
OSI/DCCE/ Division Director/N Khin
OSI/DCCE/Branch Chief/K Ayalew
OSI/DCCE/Acting Team Leader/YM Ning
OSI/DCCE/GCP Reviewer/ZH Marks
OSI/ GCP Program Analysts/ Joseph Peacock/Yolanda Patague
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Division of Pediatric and Maternal Health Review

Date: March 19, 2020 **Date Consulted:** August 6, 2019

From: Jeanine Best, MSN, RN, PNP, Senior Clinical Analyst, Maternal Health
Division of Pediatric and Maternal Health

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health
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Shetarra Walker, MD, Acting Team Leader, Pediatrics
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health

To: Division of Gastroenterology and Inborn Errors Products (DGIEP)

Drug: Dojolvi (triheptanoin) liquid, for oral use

NDA: 213687

Applicant: Ultragenyx

Subject: Pregnancy and Lactation, and Pediatric Use Labeling

Indication: “as a source of calories and fatty acid acids for the treatment of pediatric and adult patients diagnosed with molecularly confirmed long-chain fatty acid oxidation disorders (LC-FAODs)”

Materials Reviewed:

- Applicant’s NDA submission and proposed labeling, July 31, 2019

Consult Question: “DGIEP would like DPMH to assist with labeling review.”

INTRODUCTION AND BACKGROUND

On July 31, 2019, Ultragenyx submitted NDA 213687 for Dojolvi (triheptanoin) liquid, for oral use, for initial FDA approval. The Division of Gastroenterology and Inborn Errors Products (DGIEP) consulted the Division of Pediatrics and Maternal Health (DPMH) on August 16, 2019 to assist with the *Pregnancy, Lactation, and Pediatric* subsections of labeling.

Regulatory History

- July 23, 2013: IND 117053 submitted for UX007 (triheptanoin).
- April 15, 2015: Orphan Drug Designation (ODD) granted to for triheptanoin for the treatment of fatty acid oxidation disorders.
- March 29, 2019: Rare Pediatric Disease Designation (RPDD) granted for triheptanoin for the treatment of long-chain fatty acid oxidation disorders (LC-FAODs).
- July 31, 2019: NDA submitted for the proposed indication of treatment of adult and pediatric patients with LC-FAOD [REDACTED] (b) (4) [REDACTED].¹
- July 31, 2019: Request for Rare Pediatric Disease Priority Review Voucher submitted.

Triheptanoin Drug Characteristics²

- An oral synthetic medium-chain triglyceride (MCT)³ consisting of three odd-chain (C7) fatty acids on a glycerol backbone to be used as a source of calories and fatty acids as a substrate for energy replacement in patients with LC-FAOD (marketed MCT supplements contain even chain, C8, fatty acids). Even chain fatty acids produce two molecules of acetyl CoA and odd chain fatty acids produce two molecules of acetyl CoA and propionyl CoA in the final round of degradation.⁴
- Following oral administration, triheptanoin is extensively hydrolyzed to heptanoate and glycerol by pancreatic lipases in the intestines; exposure of triheptanoin in plasma is minimal; plasma protein binding of heptanoate is approximately 80%; heptanoate can be metabolized to beta-hydroxypentanoate (BHP) and beta-hydroxybutyrate (BHB) in the liver (see Figure 1 on page 3).
- Pharmacokinetics of heptanoate exhibits high inter-subject variability.
- Molecular weight is 428.6 g/mol.
- Caloric value is 8.3 kcal/mL.
- Mean terminal half-life is ~ 1.7 hours.
- Triheptanoin and its metabolites are minimally excreted in urine.
- Supplied as a pure oral liquid; contains no excipients or inactive ingredients.

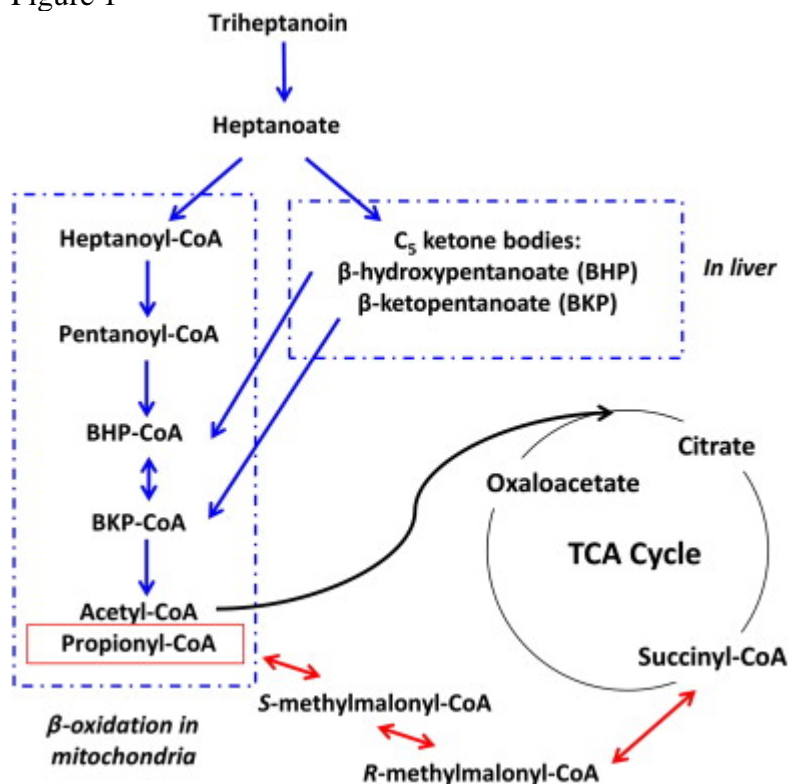
¹ DGIEP will be proposing the precedent indication of: “as a source of calories and fatty acids for the treatment of pediatric and adult patients with molecularly confirmed long-chain fatty acid oxidation disorders (LC-FAOD)”

² Refer to proposed labeling, 7/31/2019

³https://www.micromedexsolutions.com/micromedex2/librarian/CS/D66F7E/ND_PR/evidencexpert/ND_P/evidencexpert/DUPLICATIONSHIELDSYNC/D64FC7/ND_PG/evidencexpert/ND_B/evidencexpert/ND_AppProduct/evidencexpert/ND_T/evidencexpert/PFActionId/evidencexpert.IntermediateToDocumentLink?docId=29826-f&contentSetId=30&title=Triheptanoin&servicesTitle=Triheptanoin, accessed 12/12/2019

⁴ https://en.wikipedia.org/wiki/Odd-chain_fatty_acid

Figure 1⁵



REVIEW

Long-Chain Fatty Acid Oxidation Disorders

Long-chain fatty acid oxidation disorders (LC-FAODs) are rare autosomal recessive genetic inborn errors of metabolism and include defects that affect the carnitine cycle or fatty acid β-oxidation (fatty acids are mainly metabolized through fatty acid oxidation pathways). Fatty acids are important energy sources in catabolic conditions, including fasting, illness, and exercise. The heart and skeletal muscle depend on long-chain fatty acids as their primary energy source. LC-FAOD phenotypes range from asymptomatic to severe morbidity and mortality. Patients with a severe phenotype present with hyperammonemia, transient hypoglycemia, metabolic acidosis, cardiomyopathy, and sudden death in the neonatal period. The infantile-onset type presents in infancy or childhood with intermittent episodes of lethargy and vomiting associated with intercurrent illness and leads to hepatic dysfunction, hypokinetic hyperglycemia, encephalopathy, rhabdomyolysis, or sudden death. Patients can also present with progressive neuropathy, myopathy and retinopathy. The adolescent and adult-onset myopathic disease type presents with episodes of muscle weakness, myalgia, rhabdomyolysis, and risk of renal damage.

The current U.S prevalence of LC-FAODs is estimated at approximately 2,500 to 3,000 persons with approximately 65 to 95 children born annually with a LC-FAOD.⁶

⁵ Tan KN; McDonald TS; Borges K. Bioactive Nutraceuticals and Dietary Supplements in Neurological and Brain Disease, Chapter 48 Metabolic dysfunctions in epilepsy and novel metabolic treatment approaches. Prevention and Therapy, 2015: 461-473

⁶ Refer to the OOPD RPD designation review dated 2/6/2019

All U.S. states now include testing for FAODs in newborn screening programs using mass spectrometry (MS/MS) or blood spots. Early diagnosis and treatment are improving outcomes in patients with FAODs. Current treatment, which is individualized to each patient, includes prevention of catabolism with dietary modifications including sufficient caloric intake, restriction of dietary intake of long-chain and very long-chain fat, providing nutritional supplementation with medium chain triglycerides (MCTs) and docosahexaenoic acid (DHA), and providing supportive care during metabolic crises. Use of MCT supplementation provides fat as an energy source that bypasses the need to metabolize the long chain fats and are more easily absorbed through the gastrointestinal tract.^{7,8} MCT supplements contain a mixture of C6, C8, C10, and C12 triglycerides. Because MCT products are not regulated by FDA, the composition of each specific fatty acid may vary between products. Some plant oils, including coconut and palm kernel oil are comprised of medium chain triglycerides.

Pediatrics

For NDA 213687, the Applicant is seeking approval for Dojolvi (triheptanoin) liquid for oral use in any patient with LC-FAOD, regardless of age. The applicant received orphan drug designation, rare pediatric disease designation, and has submitted a request for a Rare Pediatric Disease Priority Review Voucher. Because of the ODD, triheptanoin is exempt from the study requirement under the Pediatric Research Equity Act (PREA), 21 U.S.C. 355c. Supportive data for pediatric use is summarized below.

Nonclinical⁹

Triheptanoin was well tolerated in general toxicological studies (single-dose and 9-month (chronic) conducted in juvenile rats and minipigs and no significant safety concerns were identified.

Pharmacokinetics¹⁰

There are no pharmacokinetic (PK) data from pediatric patients. Refer to the INTRODUCTION AND BACKGROUND section (Triheptanoin Drug Characteristics) of this review for detailed PK characteristics of the drug.

Dosage Form

Triheptanoin is a pure liquid oil for use and contains no excipients or inactive ingredients.

⁷ Vishwanath VA. Fatty acid beta-oxidation disorders: a brief review. *Ann Neurosci*, 2016;23:51-55

⁸ Merritt JL, Norris M, et al. Fatty acid oxidation disorders. *Ann Transl Med*, 2018;6(24):473-487

⁹ Refer to the final Nonclinical review and final Triheptanoin Integrated Review

¹⁰ Refer to the final Clinical Pharmacology review and final triheptanoin Integrated Review

Dosage and Administration¹¹

Dosage

No dose finding studies were conducted with triheptanoin. The recommended target daily dosage of triheptanoin is up to 35% of a patient's total prescribed daily calorie intake (DCI) divided into four doses and administered with food. The starting dose should be initiated at 10% DCI and titrated over 2 to 3 weeks. If a patient is switching from another MCT product, the MCT product should be discontinued and triheptanoin initiated at the last tolerated dosage of the MCT product. The recommended neonatal starting dose and dose titration schedule will be submitted for review by the applicant.

Administration

Triheptanoin is diluted 1:1 with a liquid for oral administration or administration via a silicone or polyurethane gastrostomy tube.

Efficacy¹²

Evidence of triheptanoin efficacy as a source of calories and odd-chain fatty acids was based on the results from a published single-center, double-blind, randomized, controlled clinical trial and supported by scientific knowledge about medium chain triglycerides. The study enrolled 32 patients with LC-FAOD ages ≥ 7 years. Patients (n=16 in each group) were administered triheptanoin (C7, an odd chain fatty acid) or trioctanoin (C8, an even chain fatty acid). The food-grade triheptanoin used in this study was comparable regarding safety and efficacy to MCT oil; although the study was underpowered for non-inferiority. DGIEP determined that the food-grade triheptanoin used in this study is similar to the to-be-marketed pharmaceutical grade product. This study was conducted under IND 113386 and published by Gillingham, et al. (2017);¹³ right of reference and the data were provided to the applicant for NDA 213687.

Safety¹⁴

The following studies were used as evidence of triheptanoin safety as a source of calories and odd-chain fatty acids:

- UX007-CL201 (Multinational) (Study 1): An Open-Label Phase 2 Study (single-arm, non-randomized) to Assess Safety and Clinical Effects of UX007 in Subjects with long-chain fatty acid oxidation disorders (LC-FAOD), n=29; ages ≥ 6 months
- UX007-CL202 (multinational) (Study 2): An Open-Label Long-Term Safety and Efficacy Extension Study in Subjects with LC-FAOD previously enrolled in UX007 or triheptanoin studies, n=75; ages ≥ 6 months (25/29 patients from Study 1 continued in this study)
- IND 113386, the Gillingham, et al. (2017) study used also as evidence of effectiveness.
- Expanded Access Program [patients treated under emergency IND, compassionate use, or nominative Temporary Authorization for Use (France only)], n=67; six patients < 6 months of age, one patient treated 1st day of life

¹¹ Refer to the final approved triheptanoin labeling

¹² Refer to the final triheptanoin Integrated Review

¹³ Gillingham M, Heitner S, et al. Triheptanoin versus trioctanoin for long-chain fatty acid oxidation disorders: a double blinded, randomized controlled trial. *J Inherit Metab Dis*, 2017;40:831-843

¹⁴ Refer to the final triheptanoin Integrated Review

- Expanded Access Program which included 11 narratives of molecularly confirmed infants who initiated triheptanoin from birth to 12 months after they were diagnosed with cardiomyopathy related to LC-FAOD. Two neonates were treated with triheptanoin on their 1st day of life

Adverse reactions reported in these studies were gastrointestinal-related, including abdominal pain, diarrhea, vomiting, and nausea. Gastrointestinal adverse reactions were defined as adverse events reported in patients who did not demonstrate signs or symptoms of disease exacerbation (e.g., creatine kinase elevation, hypoglycemia, cardiomyopathy). Triheptanoin was generally tolerated in LC-FAOD patients aged birth and older.

Pregnancy

Pregnancy and Fatty Acid Oxidation Disorders

One publication was located that described the management of a pregnant patient with Long-Chain 3-Hydroxyacyl-CoA Dehydrogenase Deficiency (LCHADD). Van Eerd, et al. (2017)¹⁵ describe the first report of a pregnancy in a patient with LCHADD. A 34 year female with LCHADD who suffered from severe exercise intolerance and was receiving medium chain triglyceride (MCT) supplementation became pregnant for the first time. After an uneventful first 32 weeks of pregnancy, the patient developed sinus tachycardia and increased levels of lactate and creatine kinase. MCT supplementation, both dose and frequency of administration, was increased which resulted in lowered heart rate and decreased lactated and creatine kinase levels. At 34 weeks gestation, the patient's heart rate rose again, and the decision was made to deliver the infant via cesarean section. Both mother and baby were reported well postpartum.

Although not related to the use of MCT supplementation in a pregnant women, pregnancies of mothers heterozygous for fatty acid oxidation disorders, including short, medium, or long-chain fatty acid oxidation disorders, carrying fetuses with a fatty acid oxidation disorder, have been associated with development of severe pre-eclampsia, acute fatty liver of pregnancy (ALFP) and HELLP syndrome (hemolysis, elevated liver enzymes, low platelets) in mothers and intrauterine growth retardation in infants.^{16,17} Studies have demonstrated that if a woman has HELLP or ALFP syndromes during pregnancy, there is 2% and 15-20%, respectively, risk of a long-chain fatty acid oxidation disorder in a fetus. And if considering all fatty acid oxidation disorders, the risks of a fetus with a fatty acid oxidation disorder are likely higher.¹⁸

Nonclinical Experience¹⁹

Findings from animal reproduction studies conducted in pregnant rats and rabbits with triheptanoin administration during organogenesis are not relevant to clinical use because the primary toxicological effect of reduced body weight gain in the animals was considered to be specific to decreased food consumption related to taste aversion.

¹⁵ Van Eerd DCD, Brusse IA, et al. Management of an LCHADD patient during pregnancy and high intense exercise. *JIMD Reports*, 2017; 32:95-100

¹⁶ Ibdah J, Bennet M, et al. A fetal fatty acid oxidation disorder as a cause of liver disease in pregnant women. *NEJM*, 1999;340(22):1723-1731

¹⁷ Browning MF, Levy HL, et al. Fetal fatty acid oxidation defects and maternal liver disease in pregnancy. *Obstet Gynecol*, 2006; 107(1):115-120

¹⁸ https://genetics.emory.edu/documents/resources/Emory_Human_Genetics_HELHP_AFLP_FAOD.PDF

¹⁹ Refer to the final Nonclinical review and final Triheptanoin Integrated Review

Clinical Experience

Triheptanoin is not currently approved as a drug product in any country. There are no reported pregnancies with the use of triheptanoin in clinical studies and no published reports with the use of triheptanoin in pregnant women in either PubMed, Embase, REPROTOX, or TERIS.

REPROTOX discusses the use of medium chain triglycerides during pregnancy and concludes that based on data from animal studies, treatment with medium chain triglycerides during pregnancy is not expected to increase the incidence of congenital malformations.²⁰ A published study in pregnant rats with a high dose intravenous infusion of medium chain triglycerides reported no teratogenic effects. The same study conducted in rabbits demonstrated decreased food consumption due to intolerance to the MCT infusion.²¹ Feeding a diet enriched with MCTs to pregnant sows during late pregnancy and lactation resulted in improved survival of low birth weight piglets.²² Lastly, adding a medium chain fatty acid to the culture medium may improve preimplantation development in mouse embryos *in vitro*.²³

Lactation

Nonclinical Experience²⁴

Studies were not conducted in animals to assess for the presence of triheptanoin in milk; however, in a pre- and postnatal developmental study in rats, detectable levels of triheptanoin or its metabolites could not be measured in the plasma of rat pups nursing from mothers administered food admixtures containing triheptanoin at levels approximately 2 times the targeted clinical dose of 35% daily calorie intake (DCI).

Clinical Experience

Triheptanoin is not currently approved as a drug product or as a medicinal food in any country. There is no information found on the use of triheptanoin during lactation in the following databases or published literature; PubMed, Embase, REPROTOX, TERIS, LactMed, or in Thomas Hale's book²⁵ (*Medications and Mothers' Milk*).

REPROTOX²⁶ discusses the use of medium chain triglycerides (MCTs) during lactation and states that MCTs are a normal component of breastmilk and the amount of these fatty acids vary

²⁰https://www.micromedexsolutions.com/micromedex2/librarian/CS/840EEB/ND_PR/evidencexpert/ND_P/evidencexpert/DUPLICATIONSHIELDSYNC/E729FC/ND_PG/evidencexpert/ND_B/evidencexpert/ND_AppProduct/evidencexpert/ND_T/evidencexpert/PFActionId/evidencexpert.IntermediateToDocumentLink?docId=4433&contentSetId=35&title=MEDIUM+CHAIN+TRIGLYCERIDES&servicesTitle=MEDIUM+CHAIN+TRIGLYCERIDES, accessed 2/19/2020

²¹ Henwood S, Wilson D, et al. Developmental toxicity study in rats and rabbits administered an emulsion containing medium chain triglycerides as an alternative caloric source. *Fundam Appl Toxicol*, 1997; 40(2):185-190

²² Azain M. Effects of adding medium chain triglycerides to sow diets during late gestation and early lactation on litter performance. *J Animal Sci*, 1993; 71(11):3011-3012

²³ Yarmada M, Takanashi K, et al. Adding a medium chain fatty acid as an alternative energy source in mouse preimplantation development. *Science Rep 2 Article 930*, 2012

²⁴ Refer to the final Nonclinical Review and final Integrated Review

²⁵ Hale T. *Medications and Mothers' Milk*. Springer Publishing Co. 2017

²⁶https://www.micromedexsolutions.com/micromedex2/librarian/CS/840EEB/ND_PR/evidencexpert/ND_P/evidencexpert/DUPLICATIONSHIELDSYNC/E729FC/ND_PG/evidencexpert/ND_B/evidencexpert/ND_AppProduct/evidencexpert/ND_T/evidencexpert/PFActionId/evidencexpert.IntermediateToDocumentLink?docId=4433&contentSetId=35&title=MEDIUM+CHAIN+TRIGLYCERIDES&servicesTitle=MEDIUM+CHAIN+TRIGLYCERIDES, accessed 2/19/2020

in breastmilk with gestational timing of delivery and maturity of breastmilk. Milk from mothers with preterm births contain two to three times the concentration of MCTs compared to the milk from mothers with term births. In addition, higher concentrations of MCTs are found at postnatal days 40 to 45 compared to colostrum. Mature milk contains similar MCT concentrations irrespective of birth status (preterm, term).^{27,28}

Females and Males of Reproductive Potential

Nonclinical Experience²⁹

There was no observed impact on fertility in male or female rats with administration of triheptanoin up to 50% daily calorie intake (DCI); however, animal body weights were significantly reduced.

Clinical Experience

Triheptanoin is not currently approved as a drug product in any country. There was no information on fertility effects with the use of triheptanoin found in PubMed, Embase, REPROTOX, or TERIS.

REPROTOX³⁰ reported on a study conducted in mice in which dietary long-chain triglycerides were replaced with MCTs and resulted in improved spermatogenesis and the maturation process of epididymal sperm.³¹

DISCUSSION AND CONCLUSIONS

Pediatrics

The data submitted with NDA 213687, Dojolvi (triheptanoin) liquid, for oral use, establish safety and effectiveness of the product in pediatric patients ages birth and older for the indication of “as a source of calories and fatty acid acids for the treatment of pediatric and adult patients diagnosed with molecularly confirmed long-chain fatty acid oxidation disorders (LC-FAODs).”

Therefore, pediatric use information should be appropriately distributed throughout Dojolvi labeling. DPMH recommends that the Pediatric Use subsection contain a pediatric use statement that safety and effectiveness were established in pediatric patients ages birth and older with cross-references to the ADVERSE REACTIONS and CLINICAL STUDIES sections. Dosing

²⁷ Molto-Puigmarti C, Castellote A, et al. Differences in fat content and fatty acid proportions among colostrum, transitional, and mature milk from women delivering very preterm, preterm, and term infants. *Clin Nutr*; 2011;30(1):300-312

²⁸ Gibson R, Kneebone G, et al. Fatty acid composition of human colostrum and mature breastmilk. *Am J Clin Nutr*, 1981;34:252-257

²⁹ Refer to the final Nonclinical Review and final Integrated Review

³⁰https://www.micromedexsolutions.com/micromedex2/librarian/CS/840EEB/ND_PR/evidencexpert/ND_P/evidencexpert/ND_T/evidencexpert/PFActionId/evidencexpert.IntermediateToDocumentLink?docId=4433&contentSetId=35&title=MEDIUM+CHAIN+TRIGLYCERIDES&servicesTitle=MEDIUM+CHAIN+TRIGLYCERIDES, accessed 2/19/2020

³¹ Kim N, Nakamura H, et al. Effect of lipid metabolism on male fertility. *Biochem Res Commun*, 2017;485(6):686-692

and administration information for all patients will appear in section the DOSAGE AND ADMINISTRATION section.

Pregnancy

There are no human data with the use of triheptanoin, a synthetic medium chain triglyceride (MCT), in pregnant women with long-chain fatty acid oxidation disorders (LC-FAODs) and the animal data were not considered relevant to clinical use in the intended populations. Due to the rarity of LC-FAODs, there is only one published report detailing a pregnancy outcome in a woman with an LC-FAOD treated with MCT supplementation (MCT oil). Avoidance of catabolism and individualized dietary modifications including sufficient caloric intake, restriction of dietary intake of long-chain and very long-chain fat, and nutritional supplementation with MCTs have become the standard of care to control LC-FAOD morbidity and mortality. Extra energy is required during pregnancy for the growth and maintenance of the fetus, placenta, and maternal tissues; therefore, it is important that a pregnant woman with a LC-FAOD receive sufficient caloric intake, including sufficient triheptanoin or other MCT supplementation to meet the increased energy requirements of pregnancy to avoid catabolism.

Triheptanoin is a synthetic medium chain triglyceride product and there are no data with the use of the product in pregnant women with a LC-FAOD to assess for any adverse maternal or fetal outcomes. Furthermore, there is only one published pregnancy outcome with use of MCT supplementation in a pregnant woman with a LC-FAOD. There will likely be some pregnancies occurring in women using triheptanoin, especially in women with mild or moderate disease presentation. Due to the rarity of LC-FAODs and the paucity of data with use of MCT supplementation in pregnant women with a LC-FAOD, DPMH recommends a postmarketing requirement for the applicant to conduct a single-arm pregnancy safety study in women exposed to Dojolvi (triheptanoin) during pregnancy to assess for risks of pregnancy complications and adverse effects on the developing fetus and neonate. Dose adjustment information and drug tolerability information could also be collected in this pregnancy safety study to better inform Dojolvi pregnancy labeling. Refer to FDA Draft Guidance for Industry: Post Approval Pregnancy Safety Studies, published May 8, 2019, <https://www.fda.gov/media/124746/download>. Although enrollment is expected to be low in this postmarketing pregnancy study, due to the disease rarity, any pregnancy use data would be informative for labeling.

The Pregnancy subsection of Dojolvi labeling should state the lack of human pregnancy data; the animal reproduction data are not relevant for clinical use; and contain the Pregnancy and Lactation Labeling Rule background risk statement.

Lactation

There are no data on the presence of triheptanoin in the milk of humans or animals. However, in a pre- and post-natal animal study, detectable levels of triheptanoin or its metabolites could not be measured in the plasma of rat pups nursing from mothers administered food admixtures containing triheptanoin at levels approximately 2 times the targeted clinical dose of 35% daily calorie intake (DCI).

Triheptanoin is a medium chain triglyceride (MCT). MCTs are normal components of breastmilk. Fatty acids in breastmilk originate from recent maternal fatty acid dietary intake, from release of fatty acids from maternal adipose tissue, from de novo synthesis in maternal mammary glands, and/or further metabolism of dietary fatty acids in the maternal liver.³² Unlike infant formula which has standard composition, breastmilk composition changes dynamically within a feeding, with time of day, over stage of lactation, and between mothers and populations. In addition, as previously mentioned in this review, there is a higher concentration of MCTs in the breastmilk of mothers who have preterm births. Breastmilk composition can be influenced by genetic and environmental factors, infant sex and infection status, maternal lifestyle and diet.³³ Nasser, et al. (2010)³⁴ studied the effect of maternal dietary fat manipulation (prospective cross-over study) on the fat composition of breastmilk and found that the concentration of medium chain fatty acids increased in breastmilk with a maternal low fat diet and decreased with a maternal high fat diet; however, the absolute changes in breast milk medium chain fatty acids was approximately 2% with dietary manipulation (13.6% with low fat diet; 11.4% with high fat diet). Furthermore, preterm infants often receive supplementation with MCTs (up to 40% of daily calorie intake) to meet energy needs for growth. MCTs are a quick and easy source of energy due to their gastrointestinal absorbability.^{35,36} Triheptanoin safety and effectiveness have been established in patients aged birth and older with doses up to 35% of daily calorie intake and the most common adverse reactions reported were gastrointestinal-related.

DPMH does not recommend a postmarketing requirement for a lactation study for Dojolvi at this time for the following reasons:

- Dosing and safety information are available with use of triheptanoin in infants and the amount of MCTs used a source of calories in infants is likely much higher than the amount of MCTs delivered to a breastfed infant through breastmilk.
- Triheptanoin is a synthetic medium chain triglyceride (MCT); its main metabolite, heptanoate is 80% protein bound in plasma; and its pharmacokinetics demonstrate high inter-subject variability. Due to the disease rarity, it is unlikely that the applicant could enroll a significant sample size of lactating women to capture any variability of the drug's presence in breastmilk.
- MCTs are a normal component of breastmilk. Breastmilk composition dynamically changes within feedings, with time of day, over stage of lactation and between mothers and populations based on factors including maternal genetics, environment, lifestyle, and diet.

The standard lactation benefit/risk statement should be placed in the Lactation subsection of Dojolvi labeling.

³² Innis S. Human milk: maternal dietary lipids and infant development. *Proceedings of the Nutrition Society*, 2007;66:397-404

³³ Bravi F, Wiens F, et al. Impact of maternal nutrition on breastmilk composition: a systematic review. *Am J Clin Nutr*, 2016; 104(3):646-662

³⁴ Nasser, R, Stephen A. The effect of controlled manipulation of maternal dietary fat intake on medium and long-chain fatty acids in human breast milk in Sakatoon, Canada. *Internat Breastfeeding J*, 2010;5:3

³⁵ http://www.espgan.org/fileadmin/user_upload/guidelines_pdf/Guidelines_2404/Enteral_Nutrient_Supply_for_Preterm_Infants_.21.pdf

³⁶ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5209465/>

Females and Males of Reproductive Potential

There are no human fertility effect data with triheptanoin use in females and males of reproductive potential. In addition, no adverse fertility effects were observed in animal studies with triheptanoin. There are no pregnancy testing or contraception recommendations or requirements with triheptanoin use.

The Females and Males of Reproductive Potential subsection should be omitted from Dojolvi labeling.

RECOMMENDATIONS

1. Postmarketing Requirement Recommendation

DPMH recommends a postmarketing requirement (PMR) for the applicant to conduct a single-arm, pregnancy safety study in women exposed to DOJOLVI during pregnancy to assess risks of pregnancy complications and adverse effects on the developing fetus and neonate. Refer to FDA Draft Guidance for Industry: Post Approval Pregnancy Safety Studies, published May 8, 2019, <https://www.fda.gov/media/124746/download>. The following language is suggested for the PMR and was discussed with DGIEP on February 27, 2020:

Conduct a worldwide single-arm pregnancy safety study in women exposed to DOJOLVI during pregnancy to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Infant outcomes will be assessed through at least the first year of life. Results will be analyzed and reported descriptively. The study will collect information for a minimum of 10 years. The proposed methodology for data collection should be agreed upon with the Agency and submitted in a protocol.

PMR Schedule Milestones

Draft Protocol Submission:	01/2021
Final Protocol Submission:	01/2022
Study/Trial Completion:	07/2032
Interim:	07/2027
Interim:	07/2032
Final Report Submission:	07 2033

An interim report on the cumulative findings and analyses will be submitted after 5-years and every 5-years thereafter until the conclusion of the study. Data collected retrospectively will be analyzed separately and reported with the interim and final study reports.

2. Labeling Recommendations

DPMH revised subsections 8.1, 8.2, and 8.4, and section 17 of labeling (see below). DPMH discussed our labeling recommendations with the Division at labeling meetings on January 16 and February 27, 2020. DPMH recommendations are below and reflect discussions with DGIEP. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on DOJOLVI use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. 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, and therefore is not relevant to clinical use in the intended populations.

Advise women to report pregnancies to Ultragenyx Pharmaceutical Inc. at 1-888-756-8657 or at [add webpage].

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

Embryofetal 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 NOAEL for this maternal toxicity (lack of body weight gain) was 10% DCI for both rats and rabbits. Administration of triheptanoin at doses approximately 2 times the targeted clinical dose of 35% DCI in rats and equal to the targeted clinical dose in rabbits 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 embryofetal development were associated with the reduced body weight gain observed in pregnant animals. The NOAEL for embryofetal development toxicity was 30% and 20% DCI for rats and rabbits, respectively.

In a pre- and postnatal 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.

8.2 Lactation

Risk Summary

There are no data on the presence of triheptanoin or its metabolites in human or animal milk; the effects on a breastfed infant or the effects on milk production. Medium chain triglycerides (MCTs) 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 DOJOLVI and any potential adverse effect on the breastfed infant from DOJOLVI or from the underlying condition.

8.4 Pediatric Use

The safety and effectiveness of DOJOLVI have been established in pediatric patients aged birth and older [*see Adverse Reactions (6.1), Clinical Studies (14.1)*].

17 PATIENT COUNSELING INFORMATION

Pregnancy

Advise patients that there is a pregnancy safety study that collects pregnancy outcome data in women taking DOJOLVI during pregnancy. Pregnant patients can enroll in the study by calling 1-888-756-8657 and visiting [add webpage].

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/s/

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TAMARA N JOHNSON
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SHETARRA E WALKER
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LYNNE P YAO
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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: March 18, 2020

To: Regulatory Project Manager
Division of Gastroenterology and Inborn Error Products (DGIEP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Marcia Williams, PhD
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Kelly Jackson, PharmD
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Adewale Adeleye, PharmD, MBA
Regulatory Review Order
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)
and Instructions for Use (IFU)

Drug Name (established name): DOJOLVI (triheptanoin)

Dosage Form and Route: oral liquid

Application Type/Number: NDA 213687

Applicant: Ultragenyx Pharmaceutical Inc

1 INTRODUCTION

On July 31, 2019, Ultragenyx Pharmaceutical Inc submitted for the Agency's review an Original New Drug Application (NDA) with the proposed indication (b) (4) for the treatment of adult and pediatric patients with long-chain fatty acid oxidation disorders (LC-FAOD) (b) (4)

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Gastroenterology and Inborn Error Products (DGIEP) on January 24, 2020 and August 5, 2019 respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for DOJOLVI (triheptanoin) oral liquid.

2 MATERIAL REVIEWED

- Draft DOJOLVI (triheptanoin) PPI and IFU received on July 31, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 28, 2020.
- Draft DOJOLVI (triheptanoin) Prescribing Information (PI) received on July 31, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 28, 2020.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI and IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We reformatted the PPI and IFU document using the Arial font, size 10.

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI and IFU is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the PPI and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI and IFU is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

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**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: March 18, 2020

To: Jenny Doan, Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products (DGIEP)

From: Adewale Adeleye, Pharm.D., MBA, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP Labeling Comments for DOJOLVI (triheptanoin) oral liquid

NDA: 213687

In response to DGIEP consult request dated August 5, 2019, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), Instructions for Use (IFU), and carton and container labeling for the original NDA submission for DOJOLVI (triheptanoin) oral liquid.

PI and PPI/IFU: OPDP's comments on the proposed labeling are based on the draft PI that was available in SharePoint on February 28, 2020, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI and IFU were sent under separate cover on March 18, 2020.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling that was available in SharePoint on March 16, 2020, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Adewale Adeleye at (240) 402-5039 or adewale.adeleye@fda.hhs.gov.

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MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: February 26, 2020

Requesting Office or Division: Division of Gastroenterology and Inborn Errors Products (DGIEP)

Application Type and Number: NDA 213687

Product Name and Strength: Dojolvi (triheptanoin) oral liquid, 100 % w/w

Applicant/Sponsor Name: Ultragenyx Pharmaceutical

OSE RCM #: 2019-1652-1

DMEPA Safety Evaluator: Sarah K. Vee, PharmD

DMEPA Team Leader (Acting): Ashleigh Lowery, PharmD, BCCCP

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on February 14, 2020 for Dojolvi. We reviewed the revised container label and carton labeling for Dojolvi (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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^a Vee S. Label and Labeling Review for Dojolvi (NDA 213687). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JAN 28. RCM No.: 2019-1652.

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	January 28, 2020
Requesting Office or Division:	Division of Gastroenterology and Inborn Errors Products (DGIEP)
Application Type and Number:	NDA 213687
Product Name, Dosage Form, and Strength:	Dojolvi (trihexanoin) oral liquid, 100% w/w
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Ultragenyx Pharmaceutical
FDA Received Date:	July 31, 2019
OSE RCM #:	2019-1652
DMEPA Safety Evaluator:	Sarah K. Vee, PharmD
DMEPA Team Leader (Acting):	Ashleigh Lowery, PharmD, BCCCP

1 REASON FOR REVIEW

As part of the approval process for Dojolvi (triheptanoin) oral liquid, the Division of Gastroenterology and Inborn Errors Products (DGIEP) requested that we review the proposed Dojolvi prescribing information (PI), container label, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Ultragenyx submitted an NDA for Dojolvi (triheptanoin) oral liquid. We reviewed the prescribing information, carton labeling, and container label. We identified areas in the Dojolvi container label and carton labeling that can be improved to increase readability and prominence of important information.

4 CONCLUSION & RECOMMENDATIONS

DMEPA identified areas in the labeling that can be improved to increase readability and prominence of important information and promote the safe use of the product. We provide recommendations in Section 4.1 for the Applicant. For the PI, we recommend that specific type of enteral feeding tubes be added (i.e., tubes made of silicone or polyurethane) and to add specific volume of water to flush the tubing after administration.

4.1 RECOMMENDATIONS FOR ULTRAGENYX PHARMACEUTICAL

We recommend the following be implemented prior to approval of this NDA:

- A. General Comments (Container labels & Carton Labeling)

1. Replace the placeholder "TRADENAME" with the conditionally acceptable proprietary name, Dojolvi.
2. Add the dosage form under the established name.
3. Increase the prominence of the strength statement and relocate to the same line as the dosage form or on a separate line under the established name per 21 CFR 201.15(a)(6).
4. To ensure consistency with the Prescribing Information, revise the statement, "See package insert for full prescribing information" to read "Recommended Dosage: See prescribing information."
5. As currently presented, the format for the expiration date is presented as MM/YY. To minimize confusion and reduce the risk for deteriorated drug medication errors, FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
6. Include the statements "Date of first opening __/__/__. Discard unused portion 90 days after first opening." in bold font under storage information on the container label and carton labeling. The "__/__/__" statement will alert the users to write a complete date (month, day, and year) on the container label and carton labeling.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Dojolvi received on July 31, 2019 from Ultragenyx Pharmaceutical.

Table 2. Relevant Product Information for Dojolvi	
Initial Approval Date	N/A
Active Ingredient	triheptanoin
Indication	as a source of calories and fatty acid acids for the treatment of pediatric and adult patients diagnosed with molecularly confirmed long-chain fatty acid oxidation disorders (LC-FAOD)
Route of Administration	Oral or Gastrostomy Tube
Dosage Form	oral liquid
Strength	100% w/w
Dose and Frequency	The recommended target daily dose dosage is up to 35% of the patient's total prescribed daily caloric intake, converted to mL, divided four times per day, administered at mealtimes or with snacks.
How Supplied	500 mL (b) (4) glass bottle
Storage	Store at 20° - 25°C (68° - 77°F); excursions permitted to 15° - 30°C (59° - 86°F) (see USP Controlled Room Temperature). Do not freeze. Opened bottles can be used for up to 90 days after opening, but not beyond the expiration date on the bottle.

APPENDIX B. PREVIOUS DMEPA REVIEWS – N/A

APPENDIX C. HUMAN FACTORS STUDY – N/A

APPENDIX D. ISMP NEWSLETTERS – N/A

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS) – N/A

APPENDIX F. N/A

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^a along with postmarket medication error data, we reviewed the following Dojolvi labels and labeling submitted by Ultragenyx Pharmaceutical.

- Container label received on July 31, 2019
- Carton labeling received on July 31, 2019
- Prescribing Information (Image not shown) received on July 31, 2019, available from <\\cdsesub1\evsprod\nda213687\213687.enx>

G.2 Label and Labeling Images

(b) (4)



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^a Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: December 4, 2019

From: Interdisciplinary Review Team for Cardiac Safety Studies

Through: Christine Garnett, Pharm.D.
Clinical Analyst
Division of Cardiovascular and Renal Products /CDER

To: Jenny Doan, RPM
DGIEP

Subject: IRT Consult to NDA 213687 (SDN 010)

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 11/12/2019 regarding the sponsor's response to the Division's 74-day letter regarding the lack of a TQT study in the NDA submission. We reviewed the following materials:

- Sponsor's [request to waive a QT study](#) (Submission 0010);
- Proposed [label](#) (Submission 0001); and
- [Highlights of clinical pharmacology and cardiac safety](#) (Submission 0011).

1 IRT Response for the Division

The recommendations in the ICH E14 guideline generally apply to new drugs with systemic bioavailability. Triheptanoin is a NME drug, and the major metabolites (heptanoate, and its downstream metabolite, beta-hydroxypentanoate), are exogenous substances with substantial systemic bioavailability. Typically, a QT assessment should be conducted per the guideline.

In the current submission, the clinical studies do not appear to have included high quality ECG data (e.g., those obtain in replicate when subjects are resting in the supine position) and the timing of the ECGs relative to dosing is not known. These routine safety ECGs cannot be used to characterize the effects of triheptanoin on the QTc interval. Furthermore, the sponsor has not conducted any of the safety pharmacology studies to support a low risk for QTc prolongation. Therefore, the ECG data cannot be used as a substitute for a TQT study.

If your experience with this class of products (i.e., medium chain triglyceride) indicates a low proarrhythmic risk, and the clinical trial data confirms there are no significant cardiac adverse events, then you could waive a QT study. If, however, you would like the sponsor to conduct a QT study as a post-marketing requirement, please have the sponsor submit a protocol for our review and comments.

2 BACKGROUND

2.1 Product Information

Triheptanoin (MW: 428.6 g/mol) is a medium-chain, odd-carbon triglyceride consisting of 3 fatty acids with 7 carbons indicated (b) (4) for the treatment of adult and pediatric patients with long-chain fatty acid oxidation disorders (LC-FAOD) (b) (4). The product must be thoroughly mixed with food or drink before administration by mouth or via gastrostomy tube. The target daily dose is (b) (4)% of the patient's total prescribed daily caloric intake (DCI), converted to mL, and divided four times per day including at mealtimes or snacks. The recommended starting dose is 10% DCI, or for patients previously on medium chain triglyceride (MCT), the last tolerated dose of MCT. The dose is titrated up to reach the target.

After oral administration, triheptanoin is hydrolyzed in the gastrointestinal tract to heptanoate (MW: 130.1849 g/mol) and is absorbed. Systemic exposure of triheptanoin is minimal.

Reviewer's comments:

- According to the sponsor, the target (b) (4)% DCI dose is equivalent to approximately (b) (4) g/kg/day in a healthy adult.
- At the maximum recommended dose ((b) (4)% DCI in 4 divided doses), C_{max} of heptanoate is above (b) (4) uM and the C_{max} of the two downstream metabolites (i.e. BHB and BHP) are approximately (b) (4) uM, respectively. BHB (beta-hydroxybutyric acid) is an endogenous moiety. The normal range is less than 0.4-0.5 mM while levels above 1 mM requires further action.¹ Therefore, BHB level after drug treatment is considered to be within the normal range of an endogenous moiety and a QT assessment is not needed for BHB. The effect of heptanoate and BHP on the QT/QTc interval has not been evaluated in any approved drug products.

2.2 Sponsor's position related to the question

The Sponsor believes that the historical long-term use of even, medium-chain triglycerides (MCTs) and odd-chain triheptanoin, along with the Ultragenyx-Sponsored clinical trial data (including a review of electrocardiogram (ECG) data and relevant adverse events) are sufficient to conclude that triheptanoin does not affect the QTc interval and that there is no need for a Thorough QT (TQT) study.

Reviewer's comments:

- QT assessment results from a different drug in the same class cannot directly applied to the investigational drug.

¹ <https://emedicine.medscape.com/article/2087381-overview>

- *FDA approved fatty acids are even-carbon, omega-3 fatty acids which have a different metabolite fate to the investigational drug. Most of them were approved before 2004 or under a 505(b)(2) pathway based on bioequivalence to the reference product, therefore, they were not subject to the requirement of QT assessment.*
- *The sponsor did not provide evidence that triheptanoin, heptanoate, or BHP has a long history of wide use at the proposed therapeutic doses, either as a dietary supplement or for treatment purposes.*
- *The sponsor's clinical trials do not have quality ECG data for QT assessment purposes (see section 2.5).*
- *It has been reported that triheptanoin treatment increased left ventricular (LV) ejection fraction and decreasing LV wall mass on patients' resting echocardiogram.²*

2.3 Nonclinical Cardiac Safety

No safety pharmacology studies were conducted with triheptanoin.

2.4 Clinical Cardiac Safety

There is no evidence of an association of clinical events related to QT prolongation with triheptanoin treatment.

A search of the LC-FAOD data (Study CL201 and CL202; 79 subjects) did not identify any AEs associated with QT prolongation per ICH E14 guidance except 2 events of seizure; both considered unrelated to triheptanoin by the Investigator.

Additionally, a broader search using additional cardiac/QT prolongation search terms outside of ICH E14 guidance identified 8 subjects all of whom experienced events (arrhythmia, seizure, ventricular extrasystoles, cardio-respiratory arrest, cardiac arrest, long QT syndrome, electrocardiogram T wave abnormal, blood magnesium decreased, blood potassium decreased) considered unrelated to triheptanoin and/or had pre-existing cardiac abnormalities or confounding underlying disease and potentially confounding medications with the exception of 1 subject. This subject was a 4.7 year-old male with LCHAD who had a history of hepatic disease and hypovolemic shock 3 months prior to triheptanoin administration, and experienced an event of borderline left ventricular hypertrophy by ECG at Day 162 (possibly related to triheptanoin by Investigator) and an event of left ventricular dilatation at Day 1269 (not related).

2.5 Summary results of prior QTc assessments

The sponsor collected ECGs in UX007-CL201 and UX007G-CL201 (subjects with LC-FAOD, N=28 at Baseline and Week 24; subjects with Glucose Transporter Type 1 Deficiency Syndrome, N=36, at Screening, Week 8 and 52). No subjects had QTc > 480 ms or ΔQTc > 60 ms.

Reviewer's comments: The timing of ECG collection relative to dosing is not unknown in these two studies. The quality of the ECG acquisition and measurements are not known.

2.6 Relevant details of planned Phase 3 study

Not applicable.

² <http://www.ssiem.org/centralstore/garrod/ULLOKUNE107069-21-09-2018.pdf>

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cdcrpqt@fda.hhs.gov

3 Highlights of Clinical Pharmacology and Cardiac Safety

Therapeutic dose and exposure	Target therapeutic dose: (b) (4)% of daily caloric intake (DCI). PK Exposure at the steady state with the clinical dosing regimen in subjects with LC-FAOD (25-35% of DCI)	
Mean (%CV)	<ul style="list-style-type: none"> • Systemic exposure of triheptanoin in the human plasma is minimal (parent). • Heptanoate (major and pharmacologically-active metabolite): <ul style="list-style-type: none"> ○ plasma Cmax: (b) (4) in adults; (b) (4) in pediatrics ○ plasma AUC_{0-4hr}: (b) (4) in adults; (b) (4) in pediatrics 	
Maximum tolerated dose	Triheptanoin was well tolerated up to 35% DCI in subjects with LC-FAOD and the maximum tolerated dose has not been established.	
Principal adverse events	In the pooled LC-FAOD safety population, the most frequently reported adverse events were rhabdomyolysis (65.8% of subjects), upper respiratory tract infection (54.4%), diarrhea (44.3%), viral upper respiratory tract infection (44.3%) and vomiting (44.3%). Diarrhea and abdominal pain terms were the most frequently reported treatment-related adverse events (occurring in 27 (34.2%), and 25 (31.6%) of subjects, respectively).	
Maximum dose tested and exposure achieved	Single Dose	0.375 g/kg (equivalent to 1.5 g/kg/day) in healthy volunteers (HV) Heptanoate Cmax: 125 uM (123%); AUC _{0-8hr} : 289 uM*hr (68%)
	Multiple Dose	0.3125 g/kg, 4 times per day (equivalent to 1.25 g/kg/day) in HV Heptanoate Cmax: 275 uM (69%); AUC _{0-8hr} : 732 uM*hr (47%)
Range of linear PK	Linear PK within the dose range tested in the clinical studies (25-35% of DCI) based on the population PK analysis	
Accumulation at steady state ⁴	Apparent accumulation of heptanoate: 2.5-fold at 0.3125 g/kg, 4 times per day (equivalent to 1.25 g/kg/day) in HV. The apparent accumulation may have been confounded by diurnal PK difference caused by the time differences of the PK sampling between single-dose (SD) and multiple-dose (MD). Blood samples were collected in the morning following the administration of triheptanoin with breakfast during the SD phase, but those samples were collected in the night following the administration of triheptanoin with bedtime meals during the MD phase.	
Metabolites	Major circulating metabolite: heptanoate; Down-stream metabolites of heptanoate: beta-hydroxybutyrate (BHB) and beta-hydroxypentanoate (BHP)	
Absorption	Bioavailability	Absolute bioavailability is not determined. Relative bioavailability was similar between the oil and powder formulations of triheptanoin.
	Tmax	0.67 hr (0.42 – 6.5) for heptanoate
Distribution	Vd/F or Vd	Vd/F is estimated to be 6.09 L for heptanoate in subjects with LC-FAOD having a body weight of 58 kg (popPK)
	% bound	~80% of heptanoate is bound to plasma proteins.
Elimination	Route	Triheptanoin is extensively hydrolyzed to heptanoate in the GI tract. After intestinal absorption, heptanoate is distributed to the entire body through the blood stream and transferred to mitochondria in the respective tissues and organs, where it is completely metabolized to acetyl-CoA and propionyl-CoA by the beta-oxidation. Heptanoate and its metabolites are not anticipated to be excreted from the body.
	Terminal t _{1/2}	1.7 hr in subjects with LC-FAOD for heptanoate in plasma (popPK)
	CL/F or CL	Apparent CL/F is estimated to be 446 L/hr for heptanoate in subjects with LC-FAOD having a body weight of 58 kg (popPK)
Intrinsic Factors	Age, Sex, and Race	do not significantly affect heptanoate PK.
	Hepatic and renal Impairment	Hepatic impairment: no clinical study was conducted to assess the effect of hepatic impairment. No clinically significant effect expect because: <ul style="list-style-type: none"> • No involvement of hepatic metabolic enzymes in the hydrolysis of triheptanoin in the GI tract

		<ul style="list-style-type: none"> • The major metabolic pathway of heptanoate elimination (i.e., mitochondrial beta-oxidation) is not specific to the liver. • No involvement of CYPs and UGTs, the major hepatic metabolic enzymes in the metabolism of heptanoate • No effect of mild hepatic impairment in the PK of heptanoate, based on the population PK analysis <p>Renal impairment: no clinical study was conducted to assess the effect of renal impairment. No clinically significant effects are anticipated in subjects with renal impairment since the urinary excretion of triheptanoin metabolites is minimal.</p>
Extrinsic Factors	Drug interactions ⁸	<p>No clinically significant drug interactions with concomitant medications of substrates and inhibitors for CYPs and UGTs are anticipated based on the in vitro evaluations.</p> <p>In vitro, triheptanoin increases the unbound fraction of valproic acid by ~ 2-fold in plasma.</p>
	Food Effects	<p>In clinical studies, triheptanoin was always administered with foods.</p> <p>No clinical studies have been conducted to evaluate the effects of food on the PK of triheptanoin and its metabolites.</p>
Expected High Clinical Exposure Scenario	No clinically significant fold-change in C _{max} and AUC is anticipated since the PK of heptanoate is not likely affected by intrinsic or extrinsic factors.	

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