DOJOLVI®
TRIHEPTANOIN
Oral Liquid

# UNDERSTANDING DOJOLVI DOSING

INDICATION

## WHAT IS DOJOLVI (triheptanoin)?

**DOJOLVI is indicated 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).**[1]

**DOJOLVI (triheptanoin) is the first and only FDA-approved treatment for all 6 LC-FAOD enzyme deficiency types and for patients of all ages diagnosed with LC-FAOD.**[1]

**LC-FAOD**

**CPT I** | **CACT** | **CPT II** | **VLCAD** | **TFP** | **LCHAD**

ENZYME DEFICIENCIES

LC-FAOD=long-chain fatty acid oxidation disorders.

## DOJOLVI is a unique, synthetic medium-chain triglyceride (MCT)[1]

DOJOLVI consists of three odd-chain, 7-carbon length **(C7)** fatty acids **(heptanoate)**. It provides a source of calories and fatty acids to bypass the long-chain FAOD enzyme deficiencies for **energy production and replacement**.[1]

**Dosing is individualized based on patient tolerability, medical needs, and other dietary requirements.**[2]

**Please see Important Safety Information provided throughout the brochure.**

# DOJOLVI DOSING IS INDIVIDUALIZED

**Dosing is individualized based on patient tolerability, medical needs, and other dietary requirements.**[2]

## The recommended target daily dosage of DOJOLVI is up to 35% of the patient's total prescribed daily caloric intake (DCI) divided into four or more doses and administered at mealtimes or with snacks.[1]

- To reach a target daily dosage, patients may require an **increase in their total fat intake**[1]
- All patients treated with DOJOLVI should be **under the care of a clinical specialist** who is knowledgeable in appropriate disease-related dietary management based upon current nutritional recommendations[1]
- If a patient is unable to achieve the target daily dosage during dosage titration, **maintain the patient at the maximum tolerated dosage**[1]
- Consider current nutritional recommendations when dosing the **neonatal population—this population may require higher fat intake and therefore an increased amount of DOJOLVI**[1]


### DAILY DOSE RANGES OF DOJOLVI

The daily dosage of DOJOLVI in Studies 1 and 2 ranged between **12% and 41% DCI** (which corresponds to 0.7 g/kg/day to 6.0 g/kg/day for pediatric patients and 0.5 g/kg/day to 1.3 g/kg/day for adult patients).[1*]

In Study 3, the daily dosage of triheptanoin ranged between **11% and 22% DCI** during the 4-month treatment.[3†]

## IMPORTANT SAFETY INFORMATION

### WARNINGS AND PRECAUTIONS

**Feeding Tube Dysfunction**

- Feeding tube dysfunction was reported in patients receiving triheptanoin. The contribution of DOJOLVI cannot be ruled out. Do not administer DOJOLVI in feeding tubes manufactured of polyvinyl chloride (PVC). Regularly monitor the feeding tube to ensure proper functioning and integrity.

**Intestinal Malabsorption in Patients with Pancreatic Insufficiency**

- Low or absent pancreatic enzymes may result in reduced absorption of heptanoate subsequently leading to insufficient supplementation of medium-chain fatty acids. Avoid administration of DOJOLVI in patients with pancreatic insufficiency.

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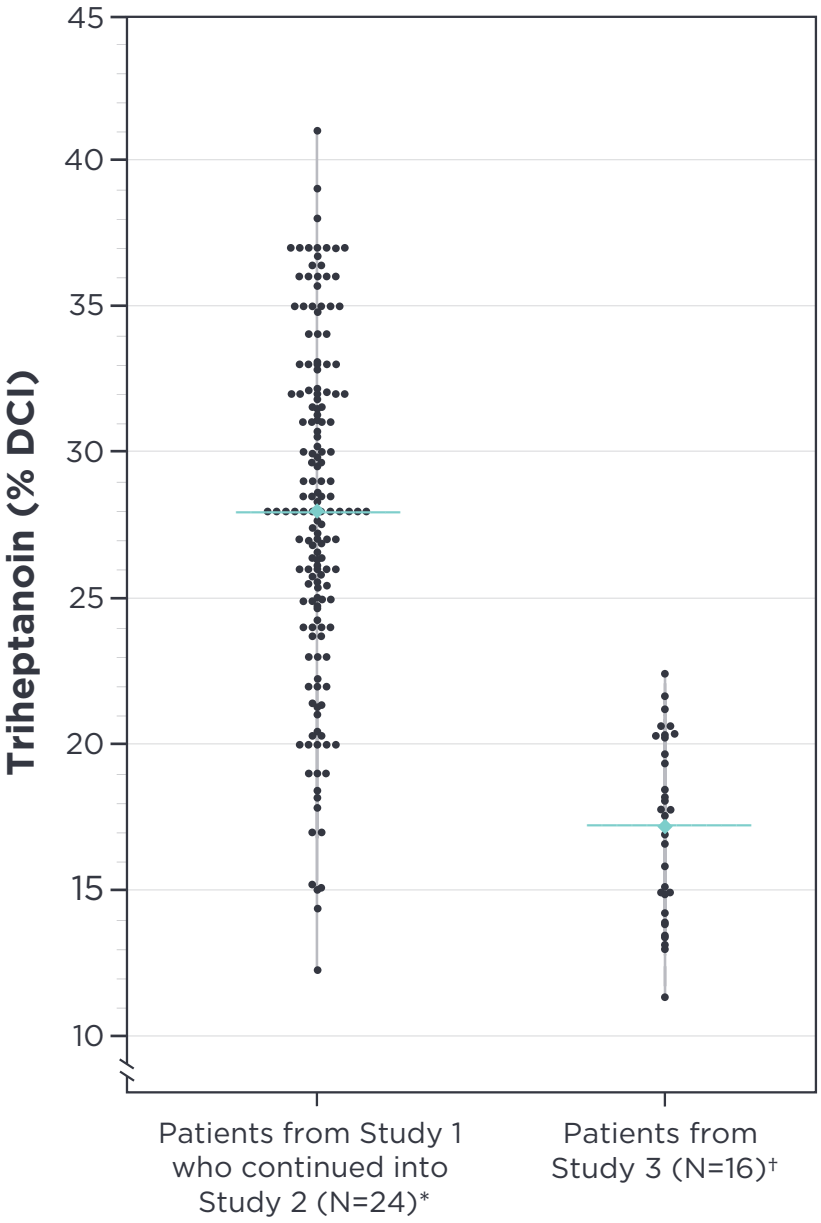
# DOJOLVI CLINICAL STUDIES—DOSE DETAILS AND STUDY DESIGN

**Actual Triheptanoin Daily Doses (%DCI) Among Patients from Study 1 who continued into Study 2* and Patients from Study 3† [Plots include multiple reported doses per patient][4]**




The teal line represents the mean of all reported triheptanoin daily doses.

Patients from Study 1 who continued into Study 2 (left): mean dose = 28.0% DCI

Patients from Study 3 (right): mean dose = 17.2% DCI

*Patients from Study 1 who continued into Study 2: This group includes the Study 1 patients who continued into Study 2, which is often referred to as the Rollover cohort. Data plots represent all reported triheptanoin daily doses among N=24 LC-FAOD patients. Patients had multiple doses reported throughout the treatment period, comprising of 160 total reported doses from baseline through Week 156.

†Patients from Study 3: Data plots represent all reported triheptanoin daily doses among N=16 LC-FAOD patients. Patients had multiple doses reported throughout the treatment period, comprising of 32 total reported doses of triheptanoin during the 4-month treatment.

## IMPORTANT SAFETY INFORMATION (continued)

### ADVERSE REACTIONS

**Gastrointestinal (GI)**

- The most common GI-related adverse reactions reported in the pooled safety population of Studies 1 and 2 were abdominal pain (abdominal discomfort, abdominal pain, abdominal distension, abdominal pain upper, GI pain) [60%], diarrhea [44%], vomiting [44%], and nausea [14%].

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# DOJOLVI CLINICAL STUDIES, CONTINUED

## STUDY DESIGN & BASELINE CHARACTERISTICS

### STUDY 1

- Total of N=29 LC-FAOD patients (10 months to 58 years of age) (mean age 12.06) received DOJOLVI[5]
- DOJOLVI was initiated with 10% DCI or the MCT oil-equivalent dose if patient had received MCT oil prior to study and gradually up-titrated every 2 to 3 days until the target dose range, 25%-35% DCI, was achieved[6]
- After titration, the majority of patients generally maintained 25%-35% DCI for 78 weeks, although the individual dose was continuously modified throughout the study[5]

### STUDY 2

- Total of N=75 LC-FAOD patients (0.3 to 64 years of age) received triheptanoin; 24 patients were rolled over from Study 1, 20 were triheptanoin-naïve, and 31 were rolled over from other triheptanoin studies[7]
- Rollover patients from the other triheptanoin studies continued the same triheptanoin dose received prior to rollover[8]
- For triheptanoin-naïve patients, initial dose and titration schemes were consistent with Study 1 patients[8]

### STUDY 3

- Triheptanoin was administered to N=16 LC-FAOD patients aged 7 to 64 years[3]
- Patients were instructed to consume 20% DCI of their total caloric needs and ended up taking between 11% to 22% DCI of triheptanoin during the 4-month treatment[3]

## IMPORTANT SAFETY INFORMATION (continued)

**DRUG INTERACTIONS**

**Pancreatic Lipase Inhibitors**

- Avoid co-administration due to potential for reduced clinical effect of DOJOLVI.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy and Lactation**

- 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. Advise women to report pregnancies to Ultragenyx Pharmaceutical Inc. at 1-888-756-8657.
- There are no data on the presence of triheptanoin or its metabolites in human or animal milk, the effects on the breastfed infant, or the effects on milk production.

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# SAFETY AND TOLERABILITY IN DOSING DOJOLVI

## ADVERSE REACTIONS

The most common adverse reactions to DOJOLVI reported in the pooled safety population of Study 1 and Study 2 were gastrointestinal (GI)-related, including[1]:

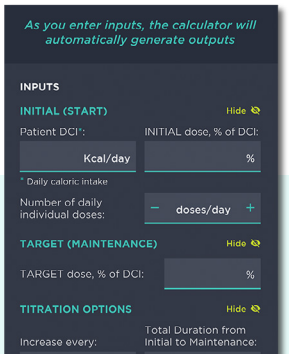
- abdominal pain (abdominal discomfort, abdominal pain, abdominal distension, abdominal pain upper, GI pain) [60%]
- diarrhea [44%]
- vomiting [44%]
- nausea [14%]

In Study 3, commonly reported adverse reactions with triheptanoin were similar to those reported in Study 1 and Study 2.[1]

## TOLERABILITY

- Monitor patients' total caloric intake during dosage titration, especially in patients with gastrointestinal adverse reactions, and adjust all components of the diet as needed[1]
- To avoid gastrointestinal upset, **mix or emulsify DOJOLVI thoroughly into the food or liquid**[1,9]
- If a patient has difficulty tolerating 1/4 of the total daily dosage at one time, more frequent, smaller doses may be considered[1]
- If GI distress occurs, consider dosage reduction until the gastrointestinal symptoms resolve. After gastrointestinal adverse reaction(s) resolve, you may be able to reinitiate titration[1,6]

SCAN HERE TO ACCESS THE DOSING CALCULATOR




For additional resources, visit **https://www.dojolvihcp.com/resources/**

## IMPORTANT SAFETY INFORMATION (continued)

### PATIENT COUNSELING INFORMATION

Advise and inform the patient or caregiver:

- To read the FDA-approved patient labeling, which includes information on the appropriate oral or feeding tube preparation, administration, and storage.
- To regularly inspect the feeding tube for proper functioning and integrity and report to the healthcare provider if any issues are identified.
- That pancreatic insufficiency may reduce the clinical effect of DOJOLVI and to report any known pancreatic insufficiency to the healthcare provider.

You may report side effects to Ultragenyx Pharmaceutical Inc. at 1-888-756-8657 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see full Prescribing Information, including the Patient Information Leaflet, for a complete discussion of the risks associated with DOJOLVI.

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# DOJOLVI ACCESS AND SUPPORT

## Have confidence in availability of DOJOLVI and access for your LC-FAOD patients

- **More than 400 patients in the US** with LC-FAOD have been prescribed DOJOLVI (since FDA approval in June 2020)[10]
- LC-FAOD patients prescribed in 2022 were able to receive DOJOLVI within an **average of less than 30 days**[10]

UltraCare®

**Ultragenyx is committed to patients with rare diseases,** which is why we created **UltraCare** for DOJOLVI—your patients' guide throughout their treatment journeys

- UltraCare is a support resource from Ultragenyx that provides ongoing assistance to patients and caregivers
- UltraCare helps patients obtain coverage and assists with financial support for medication and its administration
- UltraCare is designed to support patients in emergency situations

### IN SUMMARY

DOJOLVI dosing can be **individualized** to each patient and allows for **adaptability** to patients' needs.[2]

The recommended target daily dosage of DOJOLVI **is up to 35%** of the patient's total prescribed daily caloric intake (DCI) divided into **four or more doses** and administered **at mealtimes or with snacks**.[1]

The most common adverse reactions to DOJOLVI were gastrointestinal (GI)-related. To minimize gastrointestinal upset, **mix or emulsify DOJOLVI thoroughly into the food or liquid**.[1,9]

**Ultragenyx is committed to patients with rare diseases**, which is why **UltraCare** is available for DOJOLVI.


**REFERENCES**

1. DOJOLVI Prescribing Information, November 2021.
2. Data on file. Ultragenyx CL201 CSR. Ultragenyx Pharmaceutical Inc.; 2017.
3. Gillingham MB, Heitner SB, Martin J, et al. Triheptanoin versus trioctanoin for long-chain fatty acid oxidation disorders: a double blinded, randomized controlled trial. *J Inherit Metab Dis*. 2017; 40(6):831-843. doi:10.1007/s10545-017-0085-8.
4. Data on file. Graph distribution of daily doses of triheptanoin with % Daily Caloric Intake (%DCI). Ultragenyx Pharmaceutical Inc.; 2022.
5. Vockley J, Burton B, Berry GT, et al. Results from a 78-week, single-arm, open-label phase 2 study to evaluate UX007 in pediatric and adult patients with severe long-chain fatty acid oxidation disorders (LC-FAOD). *J Inherit Metab Dis*. 2019;42(1):169-177. doi:10.1002/jimd.12038.
6. Data on file. UX007-CL201 CSR Addendum. Ultragenyx Pharmaceutical Inc.; 2018.
7. Vockley J, Burton B, Berry G, et al. Effects of triheptanoin (UX007) in patients with long-chain fatty acid oxidation disorders: Results from an open-label, long-term extension study. *J Inherit Metab Dis*. 2021;44(1):253-263. doi:10.1002/jimd.12313.
8. Data on file. UX007-CL202 Protocol Amendment. Ultragenyx Pharmaceutical Inc.; 2015.
9. Hook DG, Marsden D, Gillingham MB, et al. Triheptanoin stability in foods, formulas, and emulsion. Ultragenyx Pharmaceutical Inc.; 2021.
10. Data on file. Ultragenyx Hub Data: Prescribed Patients. Ultragenyx Pharmaceutical Inc.; 2022.




MRCP-UX007-00615 09/2022


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**HIGHLIGHTS OF PRESCRIBING INFORMATION**
**These highlights do not include all the information needed to use DOJOLVI safely and effectively. See full prescribing information for DOJOLVI.**

**DOJOLVI® (triheptanoin) oral liquid**
**Initial U.S. Approval: 2020**

**----------INDICATIONS AND USAGE----------**
DOJOLVI is a medium-chain triglyceride indicated 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).

**----------DOSAGE AND ADMINISTRATION----------**
- Assess metabolic requirements by determining daily caloric intake (DCI) prior to calculating the dosage of DOJOLVI. (2.1)
- For patients receiving another medium-chain triglyceride product, discontinue prior to the first dose of DOJOLVI. (2.1)
- The recommended target daily dosage of DOJOLVI is up to 35% of the patient's total prescribed DCI divided into at least four doses and administered orally diluted with foods, liquids, or formula via a silicone or polyurethane feeding tube. (2.1, 2.3)
- See the full prescribing information for instructions on how to calculate the volume per dose; initiate and titrate the dosage to achieve the target; and prepare and administer DOJOLVI. (2.1, 2.2, 2.3)

**----------DOSAGE FORMS AND STRENGTHS----------**
Oral Liquid, 100% w/w of triheptanoin. (3)

**----------CONTRAINDICATIONS----------**
None.

**----------WARNINGS AND PRECAUTIONS----------**
- Feeding Tube Dysfunction: Regularly monitor the tube to ensure proper functioning and integrity. (5.1)
- Intestinal Malabsorption in Patients with Pancreatic Insufficiency: Low or absent pancreatic enzymes may reduce absorption of DOJOLVI. Avoid administration of DOJOLVI in patients with pancreatic insufficiency. (5.2)

**----------ADVERSE REACTIONS----------**
Most common adverse reactions are (≥10%): abdominal pain, diarrhea, vomiting, and nausea. (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact Ultragenyx Pharmaceutical Inc. at 1-888-756-8657 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

**----------DRUG INTERACTIONS----------**
- Pancreatic Lipase Inhibitors: Avoid co-administration due to potential for reduced clinical effect of DOJOLVI. (7.1)

**See 17 for PATIENT COUNSELING INFORMATION and FDA approved patient labeling.**

**Revised: 11/2021**

# FULL PRESCRIBING INFORMATION

## 1 INDICATIONS AND USAGE
DOJOLVI is indicated 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 DOSAGE AND ADMINISTRATION

### 2.1 Recommended Dosage
Assess the metabolic requirements of the patient by determining their daily caloric intake (DCI) prior to calculating the dose of DOJOLVI.

For patients receiving another medium-chain triglyceride (MCT) product, discontinue prior to the first dose of DOJOLVI.

The recommended target daily dosage of DOJOLVI is up to 35% of the patient's total prescribed DCI divided into at least four doses and administered at mealtimes or with snacks.

In order to reach a target daily dosage, patients may require an increase in their total fat intake. All patients treated with DOJOLVI should be under the care of a clinical specialist knowledgeable in appropriate disease-related dietary management based upon current nutritional recommendations.

The neonatal population may require higher fat intake and therefore an increased amount of DOJOLVI. Current nutritional recommendations should be considered when dosing the neonatal population.

The total daily dosage is converted to a volume of DOJOLVI to be administered in mL using the following calculation:

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

$$Total\ Daily\ Dose\ (\_\_\_mL) = \frac{Patients\ DCI\ (\_\_\_kcal)\ x\ Target\ \_\_\_\%\ dose\ of\ DCI}{8.3\frac{kcal}{mL}\ of\ DOJOLVI}$$

**2.2 Dosage Initiation and Titration**

For patients not currently taking a MCT product

Initiate DOJOLVI at a total daily dosage of approximately 10% DCI divided into at least four times per day and increase to the recommended total daily dosage of up to 35% DCI over a period of 2 to 3 weeks.

For patients switching from another MCT product

Discontinue use of MCT products before starting DOJOLVI.

Initiate DOJOLVI at the last tolerated daily dosage of MCT divided into at least four times per day. Increase the total daily dosage by approximately 5% DCI every 2 to 3 days until the target dosage of up to 35% DCI is achieved.

Tolerability

If a patient has difficulty tolerating 1/4 of the total daily dosage at one time, more frequent smaller doses may be considered *[see Adverse Reactions (6.1)]*.

Monitor patients' total caloric intake during dosage titration, especially in patients with gastrointestinal adverse reactions, and adjust all components of the diet as needed.

If a patient experiences gastrointestinal adverse reaction(s), consider dosage reduction until the gastrointestinal symptoms resolve *[see Adverse Reactions (6.1)]*. If a patient is unable to achieve the target daily dosage of up to 35% DCI during dosage titration, maintain the patient at the maximum tolerated dosage.

**2.3 Preparation and Administration Instructions**

Administer DOJOLVI mixed with semi-solid food or liquids orally or enterally via a silicone or polyurethane feeding tube. Do not administer DOJOLVI alone to avoid gastrointestinal upset.

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

DOJOLVI is not compatible with certain plastics. Do not prepare or administer DOJOLVI using containers, dosing syringes or measuring cups made of polystyrene or polyvinyl chloride (PVC) plastics.

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

Oral Preparation and Administration

- Use an oral syringe or measuring cup made of compatible materials as listed above to withdraw the prescribed volume of DOJOLVI from the bottle.
- DOJOLVI can be mixed into the following semi-solid foods and liquids:
  - plain or artificially sweetened fat free yogurt
  - fat free milk, formula, or cottage cheese
  - whole grain hot cereal
  - fat free low carbohydrate pudding, smoothies, applesauce, baby food, etc.
- Add the prescribed amount of DOJOLVI to a clean bowl, cup or container, made of the compatible materials as listed above, which contains an appropriate amount of semi-solid food or liquid that takes into consideration the age, size and average consumption of the patient in order to ensure administration of the full dose.
- Mix DOJOLVI thoroughly into the food or liquid.
- The mixture may be stored for up to 24 hours in refrigerated conditions.

Feeding Tube Preparation and Administration

DOJOLVI can be administered via oral or enteral feeding tubes manufactured of silicone or polyurethane. Do not use feeding tubes manufactured of polyvinyl chloride (PVC). Feeding device performance and functionality can degrade over time depending on usage and environmental conditions. Regularly monitor the feeding tube to ensure proper functioning and integrity *[see Warnings and Precautions (5.1)]*.

*Preparation and Administration Instructions*

- Use an oral syringe or measuring cup made of compatible materials as listed above to withdraw the prescribed volume of DOJOLVI from the bottle.
- Add the prescribed amount of DOJOLVI to a clean bowl, cup or container, made of compatible materials as listed above, which contains an amount of formula that takes into consideration the age, size and average consumption of the patient in order to ensure administration of the full dose.
- Mix DOJOLVI thoroughly into the formula.
- Draw up the entire amount of the DOJOLVI-formula mixture into a slip tip syringe.
- Remove the residual air from the syringe and connect the syringe directly into the feeding tube feeding port.
- Push the syringe contents into the feeding tube feeding port using steady pressure until empty.
- Flush the feeding tubes with between 5 mL to 30 mL of water. Flush volume should be modified based on specific patient needs and in cases of fluid restriction.
- Discard any unused portion of the DOJOLVI-formula mixture. Do not save for later use.

- Administer DOJOLVI over 15 to 20 minutes for patients receiving bolus delivery of enteral feeds. For patients receiving continuous feeds, administer DOJOLVI over 30 to 60 minutes alternating with formula alone.

Missed Doses
If a dose is missed, take the next dose as soon as possible with subsequent doses taken at 3 to 4-hour intervals. Skip the missed dose if it will not be possible to take all four doses in a day.

## 3 DOSAGE FORMS AND STRENGTHS
Oral liquid: clear, colorless to light yellow liquid supplied in 500 mL bottles containing 100% w/w of triheptanoin.

## 4 CONTRAINDICATIONS
None.

## 5 WARNINGS AND PRECAUTIONS
### 5.1 Feeding Tube Dysfunction
Feeding tube performance and functionality can degrade over time depending on usage and environmental conditions. In clinical trials, feeding tube dysfunction was reported in patients receiving triheptanoin. The contribution of DOJOLVI cannot be ruled out. Do not administer DOJOLVI in feeding tubes manufactured of polyvinyl chloride (PVC) *[see Dosage and Administration (2.3)]*. Regularly monitor the feeding tube to ensure proper functioning and integrity.

### 5.2. Intestinal Malabsorption in Patients with Pancreatic Insufficiency
Pancreatic enzymes hydrolyze triheptanoin and release heptanoate as medium-chain fatty acids in the small intestine. Low or absent pancreatic enzymes may result in reduced absorption of heptanoate subsequently leading to insufficient supplementation of medium-chain fatty acids. Avoid administration of DOJOLVI in patients with pancreatic insufficiency.

## 6 ADVERSE REACTIONS
### 6.1 Clinical Trial Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety population included 79 patients with LC-FAOD exposed to DOJOLVI in two studies: one open-label 78-week study of DOJOLVI in 29 patients (Study 1; NCT01886378) followed by an open-label extension study (Study 2; NCT02214160). Twenty-four patients from Study 1 continued into Study 2. Patients ranged from 4 months to 63 years of age and the population was 52% male. Of the 79 patients, 87% were white, 5% were black or African-American, 4% were Asian and 4% other. The daily dosage of DOJOLVI ranged between 12% and 41% DCI (which corresponds to 0.7 g/kg/day to 6.0 g/kg/day for pediatric patients and 0.5 g/kg/day to 1.3 g/kg/day for adult patients) for a mean duration of 23 months.

The most common adverse reactions to DOJOLVI reported in the pooled safety population of Study 1 and Study 2 were gastrointestinal (GI)-related, and included abdominal pain (abdominal discomfort, abdominal pain, abdominal distension, abdominal pain upper, GI pain) [60%], diarrhea [44%], vomiting [44%], and nausea [14%].

Gastrointestinal (GI) Adverse Reactions

In Study 1 and Study 2, median time to onset of a first occurrence of a GI adverse reaction was 7.3 weeks. GI adverse reactions led to dose reductions in 35% and 12% of patients in Study 1 and Study 2, respectively.

In Study 3 (NCT01379625), a 4-month double-blind randomized controlled study, commonly reported adverse reactions with triheptanoin were similar to those reported in Study 1 and Study 2.

## 7 DRUG INTERACTIONS

### 7.1 Pancreatic Lipase Inhibitors

Co-administration of triheptanoin with a pancreatic lipase inhibitor (e.g., orlistat) may reduce exposure to the triheptanoin metabolite, heptanoate, and reduce the clinical effect of triheptanoin *[see Clinical Pharmacology (12.3)]*. Avoid co-administration of DOJOLVI with pancreatic lipase inhibitors.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

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.

### 8.2 Lactation

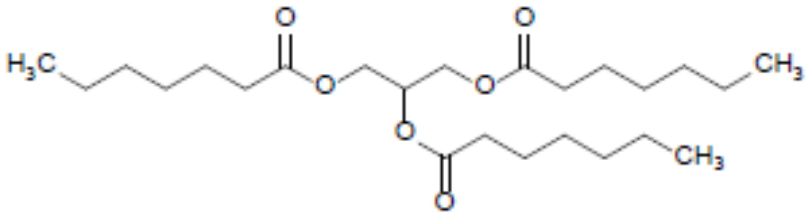
Risk Summary

There are no data on the presence of triheptanoin or its metabolites in human or animal milk, the effects on the breastfed infant, or the effects on milk production. Medium-chain triglycerides and other fatty acids are normal components of breastmilk and the composition of breastmilk varies within feedings, over stages of lactation, and between mothers and populations due to maternal factors including genetics, environment, and diet. The developmental and health benefits of breastfeeding should be considered along with the clinical need for 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)].*

**8.5 Geriatric Use**
Clinical studies of DOJOLVI did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients.

## 11 DESCRIPTION
DOJOLVI (triheptanoin) is a synthetic medium odd-chain (C7) triglyceride supplied as a colorless to light yellow clear oral liquid. The chemical name of triheptanoin is heptanoic acid, 1,1',1''-(1,2,3-propanetriyl) ester. The empirical formula is $C_{24}H_{44}O_6$ and its molecular weight is 428.6 g/mol. The chemical structure is:




The caloric value of triheptanoin is 8.3 kcal/mL.

## 12 CLINICAL PHARMACOLOGY
**12.1 Mechanism of Action**
Triheptanoin is a medium-chain triglyceride consisting of three odd-chain 7-carbon length fatty acids (heptanoate) that provide a source of calories and fatty acids to bypass the long-chain FAOD enzyme deficiencies for energy production and replacement.

**12.2 Pharmacodynamics**
No formal pharmacodynamic studies have been conducted with DOJOLVI.

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

Absorption
The pharmacokinetics of heptanoate in healthy adult subjects following an oral administration of DOJOLVI mixed with food are summarized in Table 1.

**Table 1: Summary of Pharmacokinetic Parameters of Heptanoate after Single and Multiple Oral Administration of DOJOLVI to Healthy Adults (N=13)**

| | DOJOLVI Dose | Mean (SD) $C_{max}$ (µmol/L) | Mean (SD) $AUC_{0-8h}$ (µmol*hr/L) | Time to First Peak Concentration* Median (range) (hours) |
|---|---|---|---|---|
| Single Dose | 0.3 g/kg | 178.9 (145) | 336.5 (223) | 0.5 (0.4 to 1.0) |
| | 0.4 g/kg | 259.1 (134) | 569.1 (189) | 0.8 (0.4 to 6.4) |
| Multiple Doses | 0.3 g/kg administered 4 times a day for 2 days (total daily dosage of 1.3 g/kg/day) | 319.9 (164) | 789.8 (346) | 1.2 (0.0 to 2.4) |

* After oral administration of DOJOLVI, more than one peak concentration of heptanoate is observed.

Distribution

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

Elimination

After a single dose of either 0.3 g/kg or 0.4 g/kg triheptanoin to healthy subjects, the mean apparent clearance (CL/F) of heptanoate was 6.05 and 4.31 L/hr/kg, respectively. Half-life (t1/2) of heptanoate could not be determined due to multiple peak concentrations of heptanoate observed.

*Metabolism*

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

*Excretion*

After single or multiple repeat doses of triheptanoin to healthy subjects, triheptanoin and its metabolites were minimally excreted in urine.

Drug Interaction Studies

*In Vitro Studies*

Heptanoate is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4. Heptanoate and BHP are not CYP substrates nor UGT substrates. Heptanoate increases the unbound fraction of valproic acid by approximately 2-fold.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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

Published studies with structurally similar triglycerides (i.e. MCTs) were also evaluated. In a 2-year dietary study of rats fed tricaprylin (C8 MCT) at dose levels up to 9.5 g/kg (approximately 1.2 times

the anticipated maximum clinical dose), there were increased incidences of pancreatic and forestomach hyperplasia and adenomas but not carcinomas. Chronic administration of a diet containing approximately 17% MCT was not shown to promote effects on colon tumor incidence in an azomethane-induced colon tumorigenicity rat model.

Mutagenesis

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

Impairment of Fertility

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

## 14 CLINICAL STUDIES

The efficacy of triheptanoin as a source of calories and fatty acids was evaluated in Study 3, a 4-month double-blind randomized controlled study comparing triheptanoin (7-carbon chain fatty acid) with trioctanoin (8-carbon chain fatty acid). The study enrolled 32 adult and pediatric patients with a confirmed diagnosis of LC-FAOD and evidence of at least one significant episode of rhabdomyolysis and at least two of the following diagnostic criteria: disease specific elevation of acylcarnitines on a new born blood spot or in plasma, low enzyme activity in cultured fibroblasts, or one or more known pathogenic mutations in *CPT2, ACADVL, HADHA*, or *HADHB*.

The dosage of study drug was titrated to a protocol-specified target of 20% DCI (actual mean daily dose achieved was 16% for triheptanoin and 14% for trioctanoin). The recommended target dosage of DOJOLVI is up to 35% of DCI *[see Dosage and Administration (2.1)]*. Patients ranged in age from 7 years to 64 years (median 24 years) and 12 were male.

Baseline cardiovascular function in both groups was normal and within test/retest variability normally observed in repeated echocardiograms. After 4 months, patients in both groups had similar mean changes from baseline in left ventricular ejection fraction and wall mass on resting echocardiogram and similar maximal heart rates on treadmill ergometry.

Five patients experienced 7 events of rhabdomyolysis in the triheptanoin group and 4 patients experienced 7 events of rhabdomyolysis in the trioctanoin group.

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

## 16 HOW SUPPLIED/STORAGE AND HANDLING

DOJOLVI (triheptanoin) oral liquid is supplied in glass bottles as follows:

| | |
|---|---|
| 500 mL bottle | NDC 69794-050-50 |

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) (see USP Controlled Room Temperature). Do not freeze.

Opened bottles of DOJOLVI can be used for up to 9 months after opening, but not beyond the expiration date on the bottle.

Do not dose or store using materials made of polystyrene or polyvinyl chloride (PVC) containers *[see Dosage and Administration (2.3)]*.

Pharmacist: Dispense only in Glass or HDPE bottles.

## 17 PATIENT COUNSELING INFORMATION

Advise the patient or caregiver to read the FDA-approved patient labeling (Patient Information).

Preparation and Administration
Instruct the patient or caregiver:

- To read the instructions in the *Patient Package Insert* on appropriate preparation and administration techniques for oral administration or via a feeding tube.
- To mix DOJOLVI thoroughly into semi-solid foods, liquids, or formula.
- That DOJOLVI is not compatible with certain plastics. Do not prepare or administer DOJOLVI using containers or utensils made of polystyrene or polyvinyl chloride (PVC) plastics.
- That if a dose is missed, to take the next dose as soon as possible with subsequent doses taken at 3 to 4-hour intervals. Skip the missed dose if it will not be possible to take all four doses in a day *[see Dosage and Administration (2.3)]*.

Storage
Instruct the patient or caregiver to store DOJOLVI at room temperature in the bottle in which it was dispensed *[see How Supplied/Storage and Handling (16)]*.

Feeding Tube Dysfunction
Advise the patient or caregiver to regularly inspect the feeding tube for proper functioning and integrity and report to the healthcare provider if any issues are identified *[see Warnings and Precautions (5.1)].*

Intestinal Malabsorption in Patients with Pancreatic Insufficiency
Inform the patient or caregiver that pancreatic insufficiency may reduce the clinical effect of DOJOLVI. Any known pancreatic insufficiency should be reported to the healthcare provider *[see Warnings and Precautions (5.2)].*

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.

Manufactured for:
Ultragenyx Pharmaceutical Inc.
60 Leveroni Court
Novato, CA 94949

**Patient Information**
**DOJOLVI (doh-johl-vee)**
**(triheptanoin)**
**Oral Liquid**

**What is DOJOLVI?**

DOJOLVI is a prescription medicine used to treat long-chain fatty acid oxidation disorders (LC-FAOD) in children and adults.

**Before taking DOJOLVI, tell your healthcare provider about all of your medical conditions, including if you:**

- are pregnant or plan to become pregnant. It is not known if DOJOLVI will harm your unborn baby. **Pregnancy Safety Study.** There is a pregnancy safety study for women who take DOJOLVI during pregnancy. The purpose of this study is to collect information about your health and your baby's health. You can talk to your healthcare provider or contact 1-888-756-8657 to enroll in this study or get more information.
- are breastfeeding or plan to breastfeed. It is not known if DOJOLVI passes into breast milk. Talk to your healthcare provider about the best way to feed your baby if you take DOJOLVI.
- are taking a pancreatic lipase inhibitor, such as orlistat, as it may affect how well DOJOLVI works.

**Tell your healthcare provider about all the medicines you take,** including prescription and over-the-counter medicines, vitamins, and herbal supplements.

**How should I take DOJOLVI?**

- See the detailed **"Instructions for Use"** at the end of this Patient Information Leaflet for instructions about how to mix and take DOJOLVI by mouth in soft foods or drinks or how to mix and give DOJOLVI through feeding tubes**.**
- Take DOJOLVI exactly as your healthcare provider tells you.
- Your healthcare provider may start you on a low dose of DOJOLVI and slowly increase your dose to help avoid side effects. **If you are taking another medium chain triglyceride (MCT) product, stop taking the MCT before starting DOJOLVI.**
- **Do not** mix or give DOJOLVI using containers, dosing syringes or measuring cups made of polystyrene (a type of plastic that can be solid or foam) or polyvinyl chloride (PVC), a solid plastic material.
- DOJOLVI should be taken at least 4 times a day with meals or snacks, and always mixed well with soft food or drink.

**What are the possible side effects of DOJOLVI?**

- **Feeding tube problems.** Feeding tubes may not work as well or stop working over time when taking DOJOLVI. **Do not use DOJOLVI in feeding tubes made of polyvinyl chloride (PVC).** Monitor the feeding tube to make sure it is working properly.
- **Intestinal absorption problems in patients with pancreatic insufficiency.** If you have pancreatic insufficiency, consult with your healthcare provider as it may affect how well DOJOLVI works.
- The most common side effects of DOJOLVI include:
    - stomach (abdominal) pain
    - diarrhea
    - vomiting
    - nausea

These are not all the possible side effects of DOJOLVI. Call your healthcare provider for medical advice about side effects. You may report side effects to Ultragenyx at 1-888-756-8657 or FDA at 1-800-FDA-1088.

**How should I store DOJOLVI?**

- Store DOJOLVI at room temperature between 68°F to 77°F (20°C - 25°C).
- Do not freeze DOJOLVI.
- When the bottle of DOJOLVI has been opened, use within 9 months or by the expiration date on the bottle, whichever comes first.
- Do not store DOJOLVI in containers made of polystyrene or polyvinyl chloride (PVC).

**General information about the safe and effective use of DOJOLVI.**

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information Leaflet. Do not use DOJOLVI for a condition for which it was not prescribed. Do not give DOJOLVI to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about DOJOLVI that is written for health professionals.

**What are the ingredients in DOJOLVI?**

DOJOLVI is made of 100% triheptanoin and contains no other ingredients.

Manufactured for:
Ultragenyx Pharmaceutical Inc.
60 Leveroni Court
Novato, CA 94949
For more information, go to www.dojolvi.com or call 1-888-756-8657.

This Patient Information has been approved by the U.S. Food and Drug Administration. Issued: 06/2020

**Instructions for Use**
**DOJOLVI (doh-johl-vee)**
**(triheptanoin)**
**Oral Liquid**

Read this Instructions for Use before you start taking DOJOLVI and each time you get a refill. There may be new information. This leaflet does not take the place of talking to your healthcare provider about your medical condition or treatment.

**Important information about DOJOLVI:**

- Use an oral syringe or measuring cup to measure your prescribed dose. Ask your healthcare provider or pharmacist to show you how to measure your prescribed dose.
- Mix or give DOJOLVI using containers, dosing syringes or measuring cups made of materials such as stainless steel, glass, or high-density polyethylene (HDPE), polypropylene, low density polyethylene, polyurethane and silicone (types of plastic materials).
- **Do not** mix or give DOJOLVI using containers, dosing syringes or measuring cups of polystyrene (a type of plastic that can be solid or foam) or polyvinyl chloride (PVC), a solid plastic material.
- DOJOLVI should be taken at least 4 times a day with meals or snacks, and always mixed well with soft food or drink.
- DOJOLVI can be mixed with the following soft food or drink:
  - ○ plain or artificially sweetened fat free yogurt
  - ○ fat free milk, formula or cottage cheese
  - ○ whole grain hot cereal
  - ○ fat free low carbohydrate pudding, smoothies, applesauce, or baby food
- The mixture may be stored for up to 24 hours in the refrigerator.
- Your healthcare provider may advise you on maintaining a proper diet when taking DOJOLVI.
- If you miss a dose, take the next dose as soon as possible. Take the following doses 3 to 4 hours apart. If it is not possible to take all the doses for the day, skip the missed dose.

**Taking DOJOLVI liquid by mouth:**

1. Use an oral syringe or measuring cup made of the materials listed above to measure the prescribed amount of DOJOLVI from the bottle.
2. Add the prescribed amount of DOJOLVI to a clean bowl, cup, or container, made of the materials listed above, containing the appropriate amount of soft food or drink as instructed by your healthcare provider.
3. Mix DOJOLVI well into the soft food or liquid and swallow the DOJOLVI mixture.
4. The DOJOLVI mixture may be stored for up to 24 hours in the refrigerator.

**Giving DOJOLVI liquid by feeding tube:**

1. **Do not** give DOJOLVI in feeding tubes made of polyvinyl chloride (PVC), a type of plastic. DOJOLVI can be given in feeding tubes made of silicone or polyurethane.
2. Use an oral syringe or measuring cup made of the materials listed above to measure the correct dose of DOJOLVI from the bottle and mix with formula.
3. Draw up the entire amount of the DOJOLVI-formula mixture into a slip tip syringe.
4. Remove the air from the syringe and connect the syringe directly into the feeding tube port.
5. Push the contents of the syringe (DOJOLVI-formula mixture) into the feeding tube port using steady pressure until empty.
6. Draw up about 5 mL to 30 mL of water with the slip tip syringe and flush the feeding tube feeding port with the water. Throw away any unused DOJOLVI-formula mixture. **Do not** save for later use.
7. Check the feeding tube often to make sure it is working properly.

**How should I store DOJOLVI?**

- Store DOJOLVI at room temperature between 68°F to 77°F (20°C to 25°C).
- **Do not** freeze DOJOLVI.
- When the bottle of DOJOLVI has been opened, use within 9 months or by the expiration date on the bottle, whichever comes first.
- **Do not** store DOJOLVI in containers made of polystyrene or polyvinyl chloride (PVC).

**Keep DOJOLVI and all medicines out of the reach of children.**

This Instructions for Use has been approved by the U.S. Food and Drug Administration.
Approved: 06/2020