PrDOJOLVI™

Triheptanoin Oral Liquid

Liquid, 100% w/w triheptanoin, Oral

Medium Chain Triglyceride, A16AX17

Product Monograph

Including Patient Medication Information

ultragenyx pharmaceutical

RECENT MAJOR LABEL CHANGES

Not Applicable.

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

DOJOLVI™ (triheptanoin) is indicated as a source of calories and fatty acids for the treatment of adult and pediatric patients with long-chain fatty acid oxidation disorders (LC-FAOD).

1.1 Pediatrics (<18 years)

Based on the data submitted and reviewed by Health Canada, the safety and efficacy of DOJOLVI in pediatric patients have been established; therefore, Health Canada has authorized an indication for pediatric use. (see ADVERSE REACTIONS and CLINICAL TRIALS)

1.2 Geriatrics (≥65 years of age)

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

2 CONTRAINDICATIONS

Triheptanoin is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient or component of the container. For a complete listing, see Dosage Forms, Strengths, Composition and Packaging.

3 DOSAGE AND ADMINISTRATION

3.1 Dosing Considerations

- Assess the metabolic requirements of the patient by determining their daily caloric intake (DCI) prior to calculating the dose of DOJOLVI.
- The neonatal and infant population may require higher fat intake and therefore an increased amount of DOJOLVI. Current nutritional recommendations should be considered when dosing the neonatal or infant population.

3.2 Recommended Dose and Dosage Adjustment

The recommended target daily dosage of DOJOLVI is up to 35% of the patient's total prescribed DCI divided into at least four doses, administered at mealtimes or with snacks, at 3 to 4 hour intervals or as directed by the healthcare provider.

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

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.

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

Dosage Initiation and Titration

For patients not currently taking a medium-chain triglyceride (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.

Monitor patients' DCI 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. Maintain the patient at the maximum tolerated dosage up to 35% DCI.

3.3 Administration

Administer DOJOLVI mixed with semi-solid food or liquids orally or enterally. Do not administer DOJOLVI alone to avoid gastrointestinal upset.

DOJOLVI is not compatible with certain plastics. 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.

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 syringes or measuring cups 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 semi-solid foods and liquids.
- 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 PVC. Feeding tube performance and functionality can degrade over time depending on usage and environmental conditions.

Regularly monitor the feeding tube to ensure proper functioning and integrity.

- 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.

3.4 Missed Dose

If a dose (one of the portions taken throughout the day) is missed, take the next dose as soon as possible. Skip the missed dose if it will not be possible to take all doses in a day.

4 OVERDOSAGE

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

For management of a suspected drug overdose, contact your regional poison control centre.

5 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1: Dosage Forms, Strengths, Composition and Packaging

Route of Adminstration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
oral	Liquid, 100% w/w	N/A

DOJOLVI (triheptanoin) is a colorless to light yellow clear liquid supplied in 500 mL bottles containing 100% w/w of triheptanoin active ingredient.

6 WARNINGS AND PRECAUTIONS

General

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 DOJOLVI. The contribution of DOJOLVI to these events cannot be ruled out. Do not administer DOJOLVI in feeding tubes manufactured of PVC. Regularly monitor the feeding tube to ensure proper functioning and integrity.

Hepatic/Biliary/Pancreatic

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 reduce absorption of heptanoate leading to insufficient supplementation of medium-chain fatty acids. Avoid administration of DOJOLVI in patients with pancreatic insufficiency.

6.1 Special Populations

6.1.1 Pregnant Women

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. (see TOXICOLOGY – Reproduction and Development)

6.1.2 Breast-feeding

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.

6.1.3 Pediatrics

The safety and efficacy of DOJOLVI in pediatric patients have been established.

6.1.4 Geriatrics

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

6.1.5 Hepatic Insufficiency

No studies have been conducted to evaluate the PK of triheptanoin and its metabolites in patients with hepatic impairment.

6.1.6 Renal Insufficiency

No studies have been conducted to evaluate the PK of triheptanoin and its metabolites in patients with renal impairment.

7 ADVERSE REACTIONS

7.1 Adverse Reaction Overview

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 distension, abdominal pain, abdominal pain upper, GI pain) [60%], diarrhea [44%], vomiting [44%], and nausea [14%].

In the pooled safety population (Study 1 and Study 2) 5 (6%) subjects had TEAEs leading to dose discontinuation including myalgia, gastroesophageal reflux disease, pain, diarrhea, vomiting and rhabdomyolysis, the latter 3 considered related to triheptanoin.

Dose reductions occurred in 20 subjects (25.3%) including 12 subjects (41%) in Study 1 and 9 subjects (12%) in Study 2. Of these, GI adverse reactions led to dose reductions in 35% and 12% of patients in Study 1 and Study 2, respectively and included abdominal pain (28%), diarrhea (24%), and nausea (3%) in Study 1 and diarrhea (7%), and abdominal pain (5%) in Study 2.

Dose interruptions were made to triheptanoin in 16 subjects (20%) including 10 subjects (34%) in Study 1 and 8 subjects (11%) in Study 2. Of these, GI adverse reactions led to dose interruptions in 3 subjects (10%) in Study 1 for diarrhea (7%), abdominal pain (7%), nausea (3%) and vomiting (3%) and 5 subjects (7%) in Study 2 for vomiting (5%) and diarrhea (1%).

7.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The assessment of adverse reactions was based on a safety population that included 79 patients with LC-FAOD exposed to DOJOLVI in two studies: one open-label single arm 78-week study of DOJOLVI in 29 patients (Study 1 [UX007-CL201]) followed by an open-label extension study (Study 2 [UX007-CL202]). Twenty-four patients from Study 1 continued into Study 2 and the remaining patients were treatment naïve (n=19) or rolled over from investigator sponsored trials (IST)/another trial (n=31). 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 mean average daily dosage of DOJOLVI per patient was 25% DCI (ranged between 5% and 40% DCI) which corresponds to 0.3 g/kg/day to 5.2 g/kg/day for pediatric patients and 0.1 g/kg/day to 1.2 g/kg/day for adult patients for a mean duration of 30 months.

The most common adverse reactions from the pooled safety population of Study 1 and Study 2 were gastrointestinal (GI) in nature (Table 2).

Table 2: Adverse Reactions Reported in Patients with LC-FAOD from Study 1 and Study 2

Adverse Reaction	DOJOLVI N=79 (%)
Abdominal Pain[a]	60
Diarrhea	44
Vomiting	44
Nausea	14

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

Gastrointestinal (GI) Adverse Reactions

GI adverse reactions were severe (1%), moderate (22%) and mild (77%) in severity.

In Study 3, a 4-month double-blind randomized controlled study in 32 adult and pediatric patients with a confirmed diagnosis of LC-FAOD, commonly reported adverse reactions with triheptanoin were similar to those reported in Study 1 and Study 2.

7.3 Less Common Clinical Trial Adverse Reactions

Not applicable.

7.4 Clinical Trial Adverse Reactions (Pediatrics)

The safety profile of triheptanoin in the pediatric population appears to be similar to that observed in the adult population.

7.5 Post-Market Adverse Reactions

No post-market data are available.

8 DRUG INTERACTIONS

8.1 Overview

In vitro studies show that 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.

8.2 Drug-Drug Interactions

Pancreatic Lipase Inhibitors

Concomitant use of triheptanoin with pancreatic lipase inhibitor (e.g., orlistat) may reduce the systemic exposure of heptanoate (metabolite of triheptanoin) and may reduce the efficacy of triheptanoin. Avoid co-administration of DOJOLVI with pancreatic lipase inhibitors.

8.3 Drug-Food Interactions

Interactions with food have not been established.

8.4 Drug-Herb Interactions

Interactions with herbal products have not been established.

8.5 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

9 ACTION AND CLINICAL PHARMACOLOGY

9.1 Mechanism of Action

Triheptanoin is a medium chain triglyceride consisting of three odd-chain 7-carbon length fatty acids (heptanoates) that provide a source of odd-chain fatty acids to bypass the long-chain FAOD enzyme deficiencies for energy production and replacement.

9.2 Pharmacodynamics

No formal pharmacodynamic studies have been conducted with DOJOLVI.

9.3 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 patients following an oral administration of DOJOLVI mixed with food are summarized in Table 4.

Table 4: Summary of Pharmacokinetic Parameters of Heptanoate after Single and Multiple Oral Administration of DOJOLVI to Healthy Adults (N=13)

	DOJOLVI Dose	C_{max} (uM) Mean (SD)	T_{max} (h) Median (range)	Time to[a] First peak concentration (h) Median (range)	AUC_{0-8h} (uM*h) Mean (SD)	CL/F (L/h/kg) Mean (SD)
Single dose	0.3 g/kg	178.9 (145)	0.67 (0.42-6.47)	0.50 (0.42 – 0.97)	336.5 (223)	6.05 (2.80)
	0.4 g/kg	259.1 (134)	1.17 (0.42 – 8.33)	0.82 (0.42 – 6.40)	569.1 (189)	4.31 (1.02)
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)	1.42 (0 – 8.42)	1.17 (0 – 2.42)	789.8 (346)	NA

[a] After oral administration of DOJOLVI, multiple peak concentrations of heptanoate are observed.

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

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

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

10 STORAGE, STABILITY AND DISPOSAL

Store bottle upright at 15° to 30°C.

Once the bottle of DOJOLVI has been opened, use within 9 months or by the expiration date on the bottle, whichever is earlier.

Do not freeze.

Pharmacists should dispense only in glass or HDPE bottles.

Do not dose or store using materials made of polystyrene or polyvinyl chloride (PVC) containers.

PART II: SCIENTIFIC INFORMATION

11 PHARMACEUTICAL INFORMATION

Drug Substance

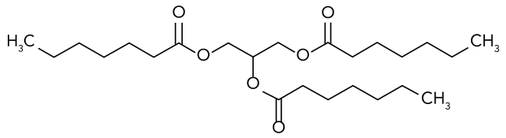
Proper/Common name: Triheptanoin

Chemical name: heptanoic acid, 1,1',1"-(1,2,3-propanetriyl) ester

Molecular formula and molecular mass: $C_{24}H_{44}O_6$

Molecular Weight: 428.6 g/mol

Structural formula:



Physicochemical properties:

Physical form: Clear, colorless to light yellow liquid

Solubility: Water solubility: < 0.05 mg/L at 20 C

pH and pKa values: N/A

Partition coefficient (n-octanol/water): Log P_{ow}: 8.86 at 20 °C and pH 6

Melting point/freezing point: ~ -25 °C at ~1013 hPa[1]

Boiling point: 232.4 °C at ~101 kPa[2]

Optical rotation: N/A

Refractive index: 1.4440 - 1.4465

Hygroscopicity: N/A

UV absorption maxima and molar absorptivity: N/A

[1] hPa = hectopascal
[2] kPa = kilopascal

12 CLINICAL TRIALS

12.1 Trial Design and Study Demographics

Table 5: Summary of Patient Demographics for Clinical Trials

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Age Mean (Range)[a]	Sex
Study 3	Phase 2 Double-blind randomized controlled study	Target Dose: 20% DCI, oral liquid, 16 weeks	32	24.8 years (7.0 – 64.0)	12 Male 20 Female

12.2 Study Results

Study 3

The efficacy of triheptanoin as a source of odd-chain 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). Study 3 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 newborn 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 target of 20% DCI (actual mean daily dose achieved was 16% for triheptanoin and 14% for trioctanoin). Patients ranged in age from 7 years to 64 years (median 22.5 years) and 12 were male.

Cardiac Function

After 4 months, patients in 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. Because cardiovascular function of the patients was within normal range at baseline, interpretation of these changes is limited.

Rhabdomyolysis

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

Blood Metabolic Markers

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.

13 NON-CLINICAL TOXICOLOGY

General Toxicology

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

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

Carcinogenesis

The 2-year rat carcinogenicity study has not been conducted with triheptanoin. 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.

Genotoxicity

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.

Reproductive and Developmental Toxicology

Embryo-fetal development studies were performed in rats and rabbits during organogenesis. In pregnant animals, the maternal toxicity (attributed to taste aversion which resulted in reduced maternal body weight and lower corrected total gain) was observed following oral administration of triheptanoin at dose levels equivalent to DCI of ≥30% (in rats) and ≥20% (in rabbits). The no-observed-adverse-effect level (NOAEL) of triheptanoin for maternal toxicity was 10% DCI for both rats and rabbits.

Based on increased incidence of skeletal malformations along with reduced litter weights following oral administration of triheptanoin at higher dose levels (50% DCI in rats and 30% DCI in rabbits), the NOAEL for developmental toxicity was 30% DCI in rats and 20% DCI in rabbits. The developmental toxicity was likely secondary to the maternal toxicity.

In a pre- and postnatal development study in rats, triheptanoin-related effects during F1 generation postweaning phase at 50% DCI were reductions in mean body weights and body weight gains along with delay in sexual maturation. These were likely secondary effects related to maternal toxicity in rats.

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

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

DOJOLVI™
Triheptanoin oral liquid

Read this carefully before you start taking **DOJOLVI** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **DOJOLVI.**

What is DOJOLVI used for?

Dojolvi is used as a source of calories and fatty acids to treat adults and children with long-chain fatty acid oxidation disorders (LC-FAOD).

How does DOJOLVI work?

The body usually uses glucose (sugar) for energy; however, when all the glucose is used up, the body also gets energy from fat. People with LC-FAOD cannot use long-chain fat for energy. DOJOLVI is a source of medium chain fatty acids. It can provide energy to the body in two ways:

1. by working around the process to break down long chain fatty acids into energy; and
2. by providing another source of energy.

What are the ingredients in DOJOLVI?

Medicinal ingredients: Triheptanoin
Non-medicinal ingredients: None

DOJOLVI comes in the following dosage forms:

Liquid: 100% w/w of triheptanoin

Do not use DOJOLVI if:

- you are allergic to triheptanoin or to any other ingredients in this medicine including components of the container.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take DOJOLVI. Talk about any health conditions or problems you may have, including if:

- you have feeding tube problems. Feeding tubes can breakdown over time. It is possible that using DOJOLVI with a feeding tube might also contribute to its breakdown. Check the feeding tube regularly to ensure it is not damaged and is working properly;
- you have pancreatic insufficiency. This is a condition where the pancreas does not make enough enzymes to help digest food properly;
- you or your partner are pregnant or planning to get pregnant;
- you are breastfeeding or plan to breastfeed.

Other warnings you should know about:

Visits with your healthcare professional: You should have regular visits with this healthcare professional so they can:

- determine how DOJOLVI is working for you,
- make adjustments to your dose, and
- talk to you about your diet.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with DOJOLVI:

- Medicines called pancreatic lipase inhibitors, which act on enzymes in the gastrointestinal tract. An example is the medicine orlistat.
- A medicine used to treat seizures, bipolar disorder or migraines called valproic acid.

How to take DOJOLVI:

- Take DOJOLVI:
  - exactly as directed by your healthcare professional.
  - by mouth or give through a feeding tube. Follow the step-by-step instructions listed below. If you are not sure, contact your healthcare professional.
  - 4 or more times throughout the day with a meal or snack. You will take DOJOLVI about every 3 to 4 hours.
  - Mix it with liquid or soft food. Taking DOJOLVI on its own may cause side effects.
- Tracking your doses, especially as you start taking DOJOLVI, can help you get used to and continue with your treatment plan. It can also help your healthcare professional decide if changes to your dose are needed.
- If you are taking another medium-chain triglyceride (MCT) product, you must stop before your first dose of DOJOLVI.
- Your healthcare professional will tell you:
  - how much DOJOLVI to take;
  - how much liquid or soft food to use.
  - They may also recommend that you increase the amount of fats that you eat in your diet.

- Do not mix or give DOJOLVI with plastic items made of polystyrene or polyvinyl chloride (PVC).
- Only use DOJOLVI with supplies (including feeding tubes) made of:
  - stainless steel,
  - glass,
  - high or low density polyethylene,
  - polypropylene,
  - polyurethane, and
  - silicone.
  - Check all your supplies (including the feeding tube, if applicable) regularly. This is to ensure they are not broken or damaged in any way and that the feeding tube is working properly.

Preparing and taking DOJOLVI by mouth:

1. Gather the required supplies and information, including:
   - the amount of liquid or soft food needed, as directed by your healthcare professional.
   - DOJOLVI bottle
   - an oral syringe or measuring cup
   - a clean bowl, cup or container made of one of the materials listed above.
2. Measure out:
   - the required amount of DOJOLVI using the oral syringe or measuring cup; and
   - the required amount of liquid or soft food and place in the bowl, cup, or container
3. Add DOJOLVI to the liquid or soft food. Mix well.
4. Swallow the DOJOLVI mixture.
5. The DOJOLVI mixture may be stored for up to 24 hours in the refrigerator.

Preparing and giving a dose of DOJOLVI through a feeding tube:

1. Gather the required supplies and information, including:
   - the amount of prepared tube feeding formula needed, as directed by your healthcare professional.
   - DOJOLVI bottle
   - an oral syringe
   - a clean bowl, cup or container made of one of the materials listed above.
   - a slip tip syringe
2. Measure out:
   - the required amount of DOJOLVI using the oral syringe or measuring cup; and
   - the required amount of prepared tube feeding formula and place in the bowl, cup or container.

3. Add DOJOLVI to the required amount of prepared tube feeding formula. Mix well.
4. Using a slip tip syringe, draw up all of the DOJOLVI-formula mixture.
5. Remove all air from the syringe.
6. Connect the syringe into the feeding tube port.
7. Push the mixture into the feeding tube port until the syringe is empty.
8. Flush out the feeding tube port using about 5 mL to 30 mL of water in the slip tip syringe. You may need more or less water to do this. Your healthcare professional will tell you how much water to use.
9. Throw away any leftover DOJOLVI-formula mixture. **Do not** save this for later.

Usual dose:

The usual dose of DOJOLVI is different for everyone and will depend on how many calories you usually get from your food.

Your healthcare professional will tell you how much DOJOLVI to take. They may start you on a lower dose of DOJOLVI and increase the dose slowly over a few days or weeks. Babies may need a higher dose of DOJOLVI, since they may need more fats in their diet.

If you experience certain side effects, your healthcare professional may lower the dose of DOJOLVI.

Overdose:

If you think you have taken too much DOJOLVI, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose (one of the portions taken throughout the day), take the next dose as soon as possible. If it is not possible to take all the doses for the day, skip the missed dose.

What are possible side effects from using DOJOLVI?

These are not all the possible side effects you may feel when taking DOJOLVI. If you experience any side effects not listed here, contact your healthcare professional.

- Abdominal pain
- Diarrhea
- Vomiting
- Nausea

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
UNKNOWN FREQUENCY			
Feeding tube problems: mechanical issues, softening, breaking, failure, or other malfunction of the feeding tube. Feeding tubes may not work as well or stop working over time when taking DOJOLVI.		X	
Intestinal absorption problems in patients with pancreatic insufficiency: diarrhea, stools that appear greasy or oily, abdominal bloating, gas, weight loss.		X	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store the DOJOLVI bottle upright between 15 - 30°C. **Do not** freeze.
- Once the bottle of DOJOLVI has been opened, use it within 9 months or by the expiration date on the bottle, whichever is earlier. There is a place on the DOJOLVI labels to write the date the bottle is opened.
- **Do not** use or store DOJOLVI in containers made of polystyrene or PVC.

Keep out of reach and sight of children.

If you want more information about DOJOLVI:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada.html); the manufacturer's website (https://www.ultragenyx.com) or by calling 1-833-388-5872.

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