PDL DRUG REVIEW

Proprietary Name: Dojolvi®
Common Name: triheptanoin liquid
PDL Category: Electrolytes/Nutritionals

Summary

Pharmacology/Usage: Triheptanoin, the active ingredient of Dojolvi®, is a synthetic medium odd-chain (C7) triglyceride; it 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 fatty acid oxidation disorder enzyme deficiencies for energy production and replacement. Long-chain fatty acid oxidation disorders (LC-FAOD) are a group of rare inherited disorders where the body is not able to convert long-chain fatty acids into energy. Dojolvi® circumvents the enzyme deficiencies that cause LC-FAOD and provide a source of calories and fatty acids that can be converted to energy.

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)

There is no pregnancy category for this medication; however, the risk summary indicates that there are no available data on use in pregnant women to assess for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Advise women to report pregnancies to Ultragenyx Pharmaceutical at 1-888-756-8657. The safety and efficacy of use in the pediatric population aged birth and older have been established.

Dosage Form: Oral Liquid in 500ml bottles: 100% w/w (weight for weight) of triheptanoin.

Prepare or administer Dojolvi® using containers, dosing syringes, or measuring cups made of compatible materials such as stainless steel, glass, high density polyethylene, 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.

Recommended Dosage: Prior to the first dose/calculating the first dose:

- Assess the metabolic requirements of the patient by determining their daily caloric intake (DCI) prior to calculating the dose
- For patients receiving another medium-chain triglyceride (MCT) product, discontinue that treatment

The recommended target daily dose of Dojolvi® is up to 35% of the patient's total prescribed DCI divided into at least 4 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 thus 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 4 approximately equal individual doses

Thus, the total daily dose (ml)= patients DCI X target % dose of DCI divided by 8.3 kcal/ml of Dojolvi®.

Initiate Dojolvi® at a total daily dosage of approximately 10% DCI divided into at least 4 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, initiate Dojolvi® at the last tolerated daily dosage of MCT divided into at least 4 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.

Monitor patient's total caloric intake during dosage titration, especially in patients with GI adverse reactions, and adjust all components of the diet as needed. If a patient experiences GI adverse reactions, consider dosage reduction until the GI symptoms resolve. 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.

Administer Dojolvi® mixed with semi-solid food or liquids orally or enterally vial a silicone or polyurethane feeding tube. Do not administer Dojolvi® alone to avoid GI upset.

Drug Interactions: Co-administration of triheptanoin with pancreatic lipase inhibitors (e.g. orlistat) may reduce exposure to the triheptanoin metabolite (heptanoate) and reduce the clinical effect of triheptanoin. Thus, avoid coadministration of Dojolvi® with pancreatic lipase inhibitors.

Box Warnings: There is no box warning listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Dojolvi®). There was no placebo data in the prescribing information to compare with.* The most frequently reported adverse events in the pooled safety population 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%).

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

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. Thus, avoid administration of Dojolvi® in patients with pancreatic insufficiency.

Contraindications: There are no contraindications listed with this product.

Manufacturer: Ultragenyx Pharmaceuticals

Analysis: The efficacy of triheptanoin as a source of calories and fatty acids was assessed in a one study (Study 3), which was a 4-month double-blind, randomized controlled study that compared triheptanoin (7-carbon chain fatty acid) with trioctanoin (8-carbon chain fatty acid) that included 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 2 of the following diagnostic criteria: disease specific elevation of acylcarnitine 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.*

Included patients ranged in age from 7 years to 64 years (median 24 years) and 12 were male. The dosage of study drug was titrated to a protocol-specific target of 20% DCI, with the actual mean daily dose achieved being 16% for triheptanoin and 14% for trioctanoin. (The recommended target dosage of Dojolvi® is up to 35% of DCI). 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. In addition, there were 5 patients who experienced 7 events of rhabdomyolysis in the triheptanoin group and 4 patients who experienced 7 events of rhabdomyolysis in the trioctanoin group. Furthermore, no differences were observed between triheptanoin and trioctanoin groups in blood markers of metabolism, including glucose, insulin, lactate, total serum, ketones, acylcarnitine, and serum-free fatty acid concentrations.

Place in Therapy: Dojolvi® is an oral liquid 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). In one study, 4 months of triheptanoin (Dojolvi®) resulted in similar mean changes from baseline as trioctanoin in left ventricular ejection fraction and wall mass on resting echocardiogram, as well as similar maximal heart rates on treadmill ergometry in a population with LC-FAOD.

It is recommended that Dojolvi® should be non-preferred in order to confirm the appropriate diagnosis and clinical parameters for its use.

PDL Placement:
- ☐ **Preferred**
- ☒ **Non-Preferred**
- ☒ **Refer to DUR for PA Criteria**

References

[1] Dojolvi [package insert]. Novato, CA: Ultragenyx Pharmaceuticals; 2020.