Drug Monograph

Drug Name: **Dojolvi™ (triheptanoin) oral liquid**
Drug Class: **Nutritional Supplement/Anaplerotic Agent**
Prepared For: MO HealthNet
Prepared By: Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms:	Dojolvi is available as a 100% w/w oral liquid in a 500 mL bottle.
Manufacturer:	Manufactured for: Ultragenyx Pharmaceutical Inc., Novato, CA 94949.
Summary of Findings:	The efficacy of Dojolvi was demonstrated in 2 studies involving a total of 61 patients, one a 78-week open-label phase II study and the other a 4-month randomized, double-blind, controlled study. In the phase II study, there was a statistically significant improvement in the mean annualized event rates and the mean annualized duration rate. In the randomized, double-blind study, there was a statistically significant improvement in cardiac function, as evidenced by echocardiogram, and in exercise tolerance. The most common adverse reactions in patients taking Dojolvi (>10%) were abdominal pain, nausea, diarrhea, and vomiting.

Status Recommendation:	☐ Clinical Edit ☒ Open Access	☐ PA Required ☐ PDL
Type of PA Criteria:	☐ Appropriate Indications ☒ No PA Required	☐ Non-Preferred ☐ Preferred

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [1-3]

Fatty acid oxidation disorders (FAODs) are autosomal recessive errors of metabolism resulting in failure of mitochondrial beta-oxidation or the carnitine-based transport of fatty acids into mitochondria. FAODs lead to deficient energy production and produce widely variable clinical presentations ranging from mild hypotonia in adults to sudden death in infants. They can present at any age, with the most severe forms such as long-chain fatty acid oxidation disorders (LCFAODs), presenting in the first few days of life, their prevalence ranging from 1 in 100,000 to 1 in 2,000,000 in both males and females in all ethnic populations. Common presenting signs include hypoglycemia, hyperammonemia, liver disease and liver failure, cardiac and skeletal myopathy, rhabdomyolysis, and retinal degeneration. Part of the difficulty in treating LCFAODs is due to a lack of complete understanding of the pathophysiologic effects of the abnormal energy metabolism.

Dosage Form [4]

Dojolvi is available as a 100% w/w oral liquid of triheptanoin in a 500 mL bottle.

Manufacturer [4]

Manufactured for: Ultragenyx Pharmaceutical Inc., Novato, CA 94949.

Indication(s) [4]

Dojolvi is indicated as a source of calories and fatty acids for the treatment of pediatric and adult patients with molecularly confirmed LCFAODs.

Clinical Efficacy [4,5] (mechanism of action/pharmacology, comparative efficacy)

Dojolvi, a synthetic medium odd-chain (C7) triglyceride, provides a source of calories and fatty acids to bypass the LCFAOD enzyme deficiencies for energy production and replacement.

Pharmacokinetics:

Absorption	Mean time to first peak: • 0.3 g/kg dose: 0.5 hours (0.4-1) • 0.4 g/kg dose: 0.8 hours (0.4-6.4)
Metabolism	Hydrolyzed to heptanoate and glycerol by pancreatic lipases in the intestines which is then metabolized to beta-hydroxypentanoate (BHP) and beta-hydroxybutyrate (BHB) in the liver
Excretion	Urine: minimally as unchanged drug and metabolites
Half-life	N/A

Clinical Trials Experience[6,7]

STUDY 1 DESIGN	Open-label Phase II study (n = 29)

INCLUSION CRITERIA	• At least 6 months of age with severe LCFAOD as evidenced by any of the following significant clinical manifestations despite management:
	  ○ Chronic elevated creatine kinase (CK) with major clinical events
	  ○ Episodic elevate CK with reported muscle dysfunction
	  ○ Highly elevated CK but asymptomatic
	  ○ Frequent severe major medical episodes
	  ○ Severe susceptibility to hypoglycemia
	Evidence of functional cardiomyopathy

EXCLUSION CRITERIA	None listed
TREATMENT REGIMEN	Patients received triheptanoin at a target dose 25-35% of their daily caloric intake (DCI) over 78 weeks.
RESULTS	The frequency and duration of major clinical events (hospitalizations, emergency room visits, and emergency home interventions due to rhabdomyolysis, hypoglycemia, and cardiomyopathy) occurring during treatment was compared with the frequency and duration of events captured retrospectively from medical records for 78 weeks before treatment began. The mean annualized event rates decreased from 1.69 to 0.88 events/year following triheptanoin initiation (p=0.021; 48.1% reduction). The mean annualized duration rate decreased from 5.96 to 2.96 days/year (p=0.028; 50.3% reduction). All other results were statistically insignificant.
SAFETY	Discussed in the Adverse Effects section below.

STUDY 2 DESIGN	Double blinded, randomized controlled trial conducted at two sites (n = 32)
INCLUSION CRITERIA	• ≥7 years of age • Confirmed diagnosis of carnitine palmitoyltransferase-2, very long-chain acylCoA dehydrogenase, trifunctional protein or long-chain 3-hydroxyacylCoA dehydrogenase deficiencies (all LCFAODs)
EXCLUSION CRITERIA	• Anemia (hemoglobin < 10 g/dL • Peripheral neuropathy limiting the ability to walk • Pregnancy • Breastfeeding • History of myocardial infarction
TREATMENT REGIMEN	Patients were randomly assigned a diet containing 20% of the total DCI from either triheptanoin, an anaplerotic seven-carbon fatty acid triglyceride, or trioctanoin, an eight-carbon fatty acid triglyceride over 4 months.
RESULTS	The primary outcomes included changes in total energy expenditure (TEE), cardiac function by echocardiogram, exercise tolerance, and phosphocreatine recovery following acute exercise. Patients in the triheptanoin group showed increased left ventricular (LV) ejection fraction by 7.4% (p = 0.046) while experiencing a 20% (p = 0.041) decrease in LV wall mass on their resting echocardiogram. They also

	required a lower heart rate for the same amount of work during a moderate-intensity exercise stress test when compared to patients taking trioctanoin. There was no difference in TEE or phosphocreatine recovery.
SAFETY	Discussed in the Adverse Effects section below.

Contraindications [4,5]

- None

Warnings and Precautions [4,5]

- Feeding tube performance and functionality can degrade over time depending on usage and environmental conditions. Do not administer Dojolvi in feeding tubes manufactured of polyvinyl chloride (PVC). Regularly monitor the feeding tube to ensure proper functioning and integrity.
- 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.

Adverse Effects [4,5]

Most common, ≥ 1%	Dojolvi (n = 79) %
Most common, ≥ 1%	60
Abdominal pain[a]	44
Diarrhea	14
Nausea	44

a: Including abdominal distention, abdominal distress, gastrointestinal pain, upper abdominal pain.

Drug Interactions [4,5]

- Pancreatic lipase inhibitors: Co-administration may reduce exposure to heptanoate and reduce the clinical effect. Avoid co-administration with pancreatic lipase inhibitors (e.g., Orlistat).

Dosage and Administration [4,5]

- Assess the metabolic requirements of the patient by determining their DCI prior to calculating the dose of Dojolvi.
- For patients receiving another medium-chain triglyceride (MCT) product, discontinue prior the first dose of Dojolvi.
- 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 2-3 weeks.
- Calculate the total daily dosage of Dojolvi in mL by multiplying the patient's DCI in kcal by the target percentage dose of Dojolvi and then dividing by the caloric value of Dojolvi (8.3 kcal/mL).
- In order to reach a target daily dosage, patients may require an increase in their total fat intake. The neonatal population may require higher fat intake and therefore an increased amount of Dojolvi.
- If a patient has difficulty tolerating ¼ of the total daily dosage at one time, more frequent

smaller doses may be considered.
- If a patient experiences gastrointestinal (GI) adverse reaction(s), consider dosage reduction until the GI symptoms resolve.
- Monitor patients total caloric intake during dosage titration, especially in patients with GI adverse reactions, and adjust all components of the diet as needed.

Cost

Generic Name	Brand Name	Manufacturer	Dose	Cost**/ Month
Triheptanoin	Dojolvi	Ultragenyx Pharmaceutical Inc.	Varies depending on DCI	$4,875 per 500 mL bottle

** Wholesale Acquisition Cost

Conclusion

Dojolvi is indicated as a source of calories and fatty acids for the treatment of pediatric and adult patients with molecularly confirmed LCFAODs. The efficacy of Dojolvi was demonstrated in 2 studies involving a total of 61 patients, one a 78-week open-label phase II study and the other a 4-month randomized, double-blind, controlled study. In the phase II study, there was a statistically significant improvement in the mean annualized event rates and the mean annualized duration rate. In the randomized, double-blind study, there was a statistically significant improvement in cardiac function, as evidenced by echocardiogram, and in exercise tolerance. The most common adverse reactions in patients taking Dojolvi (>10%) were abdominal pain, nausea, diarrhea, and vomiting.

Recommendation

MO HealthNet Division recommends Open Access status for this product.

References

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