RXADVANCE
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NEW DRUG APPROVAL

Brand Name	Dojolvi™
Generic Name	triheptanoin
Drug Manufacturer	Ultragenyx Pharmaceutical Inc

New Drug Approval

FDA Approval Date: June 6, 2020
Review Designation: Standard, Orphan
Type of Review: New drug application 213687

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Long-chain fatty acid oxidation disorders (LC-FAOD) are a group of autosomal recessive genetic disorders characterized by metabolic deficiencies in which the body is unable to convert long-chain fatty acids into energy.

Newborn screening and early intervention have reduced mortality, but most patients continue to experience frequent hospitalizations and significant morbidity despite treatment. The deficient energy state can cause serious liver, muscle, and heart disease, and may be associated with an increased risk of sudden death. Triheptanoin is a medium odd-chain fatty acid. Anaplerotic metabolites of triheptanoin have the potential to replace deficient tricarboxylic acid (TCA) cycle intermediates, resulting in net glucose production as a novel energy source for the treatment of LC-FAOD.

LC-FAOD affect an estimated 2,000 to 3,500 children and adults in the United States. The estimated incidence of FAODs is approximately one in every 5000 to 10,000 live births. The most common FAOD is medium-chain acyl-CoA dehydrogenase deficiency (MCADD), with a prevalence of 1 in 20,000. Other FAODs range from 1 in 100,000 to 1 in 2,000,000. These autosomal recessive disorders are seen in both males and females in all ethnic populations.

Efficacy

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. 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.

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Safety

ADVERSE EVENTS

Most common adverse reactions are (≥10%): abdominal pain, diarrhea, vomiting, and nausea.

WARNINGS & PRECAUTIONS

Feeding Tube Dysfunction: Regularly monitor the tube to ensure proper functioning and integrity.

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.

CONTRAINDICATIONS

None

Clinical Pharmacology

MECHANISMS 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.

Dose & Administration

ADULTS

Assess metabolic requirements by determining daily caloric intake (DCI) prior to calculating the dosage of DOJOLVI.

- For patients receiving another medium-chain triglyceride 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 orally diluted with foods, liquids, or formula via a silicone or polyurethane feeding tube

PEDIATRICS

The safety and effectiveness of DOJOLVI have been established in pediatric patients aged birth and older.

GERIATRICS

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

RENAL IMPAIRMENT

None

HEPATIC IMPAIRMENT

None

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Oral liquid available in 500 mL bottles containing 100% w/w of triheptanoin.