BRITISH COLUMBIA | Ministry of Health

Drug Coverage Decision for B.C. PharmaCare

About PharmaCare B.C. PharmaCare is a government-funded drug plan. It helps British Columbians with the cost of eligible prescription drugs and specific medical supplies.

Details of Drug Reviewed

Drug	**triheptanoin**
Brand Name	Dojolvi™
Dosage Form(s)	Liquid, 100 percent w/w triheptanoin
Manufacturer	Ultragenyx Canada Inc.
Submission Type	**New Submission**
Use Reviewed	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).
Canadian Agency for Drugs and Technologies in Health (CADTH) Reimbursement Reviews (CRR)	Yes, the CRR recommended **to Reimburse with clinical criteria and/or conditions.** Visit the CRR website for more details.
Drug Benefit Council (DBC)	The DBC met on April 4, 2022. In their review, the DBC considered the following: the final reviews completed by the CRR of the Canadian Agency for Drugs and Technologies in Health (CADTH) on February 08, 2022, which included clinical and pharmacoeconomic evidence review material and the recommendations from the Canadian Drug Expert Committee (CDEC). The DBC also considered Patient Input Questionnaire responses from two patients, as well as patient input provided to the CRR, and a Budget Impact Assessment.

triheptanoin (Dojolvi™)

	The DBC recommended that triheptanoin not be listed as a source of calories and fatty acids for the treatment of adult and pediatric patients with LC-FAOD.
Drug Coverage Decision	**Case-by-Case Coverage Through the Expensive Drugs for Rare Diseases (EDRD) Process**
Date	May 23, 2023
Reason(s)	**Drug coverage decision is consistent with the CDEC recommendation.** • Evidence from three studies suggest that triheptanoin may lead to improvements in some aspects of the disease, such as a reduced yearly event rate, improved exercise tolerance, and improvement in some heart measures. • The majority of patients enrolled in the studies received prior treatment with medium-chain triglycerides (MCT). As such, there is no evidence to support the use of triheptanoin as a first-line treatment. • However, there is an unmet need for patients who experience an acute life-threatening episode and need an alternative to conventional MCT formulations. • Based on economic considerations and the submitted product price, the drug was not cost effective and did not offer optimal value for money. • BC participated in the pan-Canadian Pharmaceutical Alliance (pCPA) negotiations with the manufacturer and the pCPA was able to address the concerns identified by CADTH with respect to the cost-effectiveness and value for money. The negotiations concluded with an agreement on March 14, 2023.
Other Information	See the DBC Recommendation & Reasons

The Drug Review Process in B.C.

A manufacturer submits a request to the Ministry of Health (Ministry).

An independent group called the Drug Benefit Council (DBC) gives advice to the Ministry. The DBC looks at:

- whether the drug is safe and effective
- advice from a national group called the Canadian Agency for Drugs and Technologies in Health (CADTH) Reimbursement Reviews(CRR)
- what the drug costs and whether it is a good value for the people of B.C.
- ethical considerations involved with covering or not covering the drug
- input from physicians, patients, caregivers, patient groups and drug submission sponsors

The Ministry makes PharmaCare coverage decisions by taking into account:

- the existing PharmaCare policies, programs and resources
- the evidence-informed advice of the DBC
- the drugs already covered by PharmaCare that are used to treat similar medical conditions
- the overall cost of covering the drug

Visit The Drug Review Process in B.C. - Overview and Ministry of Health - PharmaCare for more information.

Appendix

Drug Benefit Council (DBC) Recommendation and Reasons for Recommendation

FINAL

Triheptanoin (Dojolvi™)
Ultragenyx Pharmaceutical Inc.

Description:

Drug review of **triheptanoin (Dojolvi™)** for the following:

> As source of calories and fatty acids for the treatment of adult and pediatric patients with acute life-threatening long-chain fatty acid oxidation disorders (LC-FAODs).

In their review, the DBC considered the following: the final reviews completed by the Common Drug Review (CDR) of the Canadian Agency for Drugs and Technologies in Health (CADTH) on [January 21, 2022], which included clinical and pharmacoeconomic evidence review material and the recommendations from the Canadian Drug Expert Committee (CDEC). The DBC also considered Patient Input Questionnaire responses from two patients, as well as patient input provided to the CDR, and a Budget Impact Assessment.

Dosage Forms:

Dojolvi is available as an oral liquid containing 100% w/w of triheptanoin as an active ingredient. Each mL of triheptanoin oral liquid provides 8.3 kcal.

Recommendations:

1. The Drug Benefit Council (DBC) recommends not to list triheptanoin (Dojolvi™).

Reasons for the Recommendation:

1. Summary

- Evidence from three studies suggest that triheptanoin may lead to improvements in some aspects of the disease, such as a reduced yearly event rate, improved exercise tolerance, and improvement in some heart measures.

None of the studies measured the effect of triheptanoin on survival, symptom relief, reduction in concomitant medications, or productivity. Study results pertaining to

- health-related quality of life (HRQoL) were associated with high uncertainty due to the high risk of bias, potential confounding factors, and lack of statistical testing.
- CADTH estimated a reduction in price of at least 96% is required for triheptanoin to be considered cost-effective at a $50,000 per QALY threshold.

1. Clinical Efficacy

- The DBC considered the CDEC systematic review, which included three studies: Study CL201, Study CL202, and Gillingham et al. (2017).
- CL201 (N = 29) was a multi-centre, open-label, single-arm Phase II study investigating the efficacy and safety of triheptanoin in adults and children (6 months of age and older) exhibiting serious clinical manifestations of LC-FAOD despite current management. Eligible patients in CL201 must have had severe LC-FAOD with confirmed diagnosis of carnitine palmitoyltransferase (CPT) II, very long-chain acyl coenzyme A dehydrogenase (VLCAD), long-chain 3-hydroxy-acyl-CoA dehydrogenase (LCHAD), or trifunctional protein (TFP) deficiency, and had been on stable treatment, including dietary measures.
- CL202 (N=75) is an ongoing, open-label, extension study investigating the long-term safety and efficacy of triheptanoin in patients older than 6 months of age with LC-FAOD. Eligible patients must have a confirmed diagnosis of CPT I, CPT II, VLCAD, LCHAD, TFP, or carnitine-acylcarnitine translocase (CACT) deficiency.
- Gillingham et al. (2017) (N=32) was a double-blind RCT that investigated whether triheptanoin therapy has a therapeutic advantage over conventional treatment for long-chain fatty acid oxidation disorders. Prior to study enrolment, patients must have had at least one episode of rhabdomyolysis and be on a stable diet that included medium-chain triglyceride (MCT). Adults and children 7 years of age and older with confirmed diagnosis of CPT II, VLCAD, TFP, or LCHAD were randomized 1:1, to a diet containing triheptanoin or trioctanoin (an even-chain fatty acid triglyceride), with both MCTs dosed at 20% of estimated daily caloric intake (DCI).
- Studies CL201 and CL202 were single-arm, phase II trials that did not include a parallel treatment comparator. Due to inherent limitations in the study design (e.g., lack of relevant comparator as a control, no blinding of treatment, potential influence of concurrent therapies, impact of growth and maturation of patients themselves on test performance), results from CL201 and CL202 could be considered supportive, but cannot offer solid evidence of treatment benefits.
- The majority of patients (≥ 90%) enrolled in the studies received prior treatment with MCT formulation. As such, there is no evidence to support the use of triheptanoin as a first-line treatment.
- None of the studies measured the effect of triheptanoin on survival, symptom relief, reduction in concomitant medications, or productivity and study results pertaining to HRQoL were associated with high uncertainty due to the high risk of bias, potential confounding factors, and lack of statistical testing.
- The evaluation of patient-reported outcomes like health-related quality of life (HRQoL), exercise tests which depended on patient effort, or adverse events (AEs) in studies CL201 and CL202 may have been influenced by the unblinded treatment regimens, resulting in reporting bias.

- Though no overall decrement in HRQoL was seen in CL201 or CL202, it is unclear whether there are any sustained benefits with the new treatment and thus, the overall effect of triheptanoin on HRQoL is inconclusive.
- For detailed information on the systematic review of triheptanoin please see the CDEC Final Recommendation at: https://www.cadth.ca/triheptanoin.

1. Safety

- All patients enrolled in CL201 and almost all (98.7%) enrolled in CL202 reported at least 1 treatment-emergent adverse event (TEAE). It appears the majority of patients in Gillingham et al. (2017) experienced 1 or more TEAEs.
- Complications of the underlying LC-FAOD (e.g., rhabdomyolysis) were also captured as an adverse event (AE) in all 3 studies, which likely contributed to the high rates of reported TEAEs. The most commonly reported TEAEs were rhabdomyolysis and GI-related events (e.g., diarrhea, vomiting, GI upset) or infections (e.g., upper respiratory tract infections, viral illnesses).
- Treatment-emergent serious adverse events (SAEs) were reported in 65.5% of patients in CL201 and 76.0% of patients in CL202; these numbers included major clinical events (MCEs) that were also reported as an SAE. The most common SAEs were related to the underlying LC-FAOD (e.g., rhabdomyolysis) or acute infectious disease, including GI infections.
- For detailed information on the safety and tolerability of triheptanoin, please see the CDEC Final Recommendations at the links above.

2. Economic Considerations

- CADTH reported that, at the sponsor submitted price, the incremental cost-effectiveness ratio (ICER) for triheptanoin was $1,347,825 per quality-adjusted life-year (QALY) compared with standard of care.
- At this ICER, triheptanoin is not cost-effective at a $50,000 per QALY willingness to pay (WTP) threshold for adults and children exhibiting serious clinical manifestations of LC-FAOD despite current management. CADTH estimated a reduction in price of at least 96% is required for triheptanoin to be considered cost-effective at a $50,000 per QALY threshold.

3. Of Note

- There are no other treatment options for patients who suffer from a life-threatening episode and need an alternative to over-the-counter MCT oil.
- The DBC considered Patient Input Questionnaire responses from two patients, neither of whom had tried triheptanoin. Patients noted symptoms of the condition such as exercise intolerance, pain, tight throat, and fatigue, brain fog and hoped for a treatment that would offer better efficacy with fewer side effects. One patient noted having tried antidepressants, benzodiazepine, anti-inflammatories, and autoimmune medications, which did not help or offered only minimal benefits with side effects.