

## CADTH Reimbursement Recommendation

# Triheptanoïn (Dojolvi)

**Indication:** 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)

**Sponsor:** Ultragenyx Canada Inc.

**Final recommendation:** Reimburse with conditions

**ISSN:** 2563-6596

**Disclaimer:** The information in this document is intended to help Canadian health care decision-makers, health care professionals, health systems leaders, and policy-makers make well-informed decisions and thereby improve the quality of health care services. While patients and others may access this document, the document is made available for informational purposes only and no representations or warranties are made with respect to its fitness for any particular purpose. The information in this document should not be used as a substitute for professional medical advice or as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision-making process. The Canadian Agency for Drugs and Technologies in Health (CADTH) does not endorse any information, drugs, therapies, treatments, products, processes, or services.

While care has been taken to ensure that the information prepared by CADTH in this document is accurate, complete, and up-to-date as at the applicable date the material was first published by CADTH, CADTH does not make any guarantees to that effect. CADTH does not guarantee and is not responsible for the quality, currency, propriety, accuracy, or reasonableness of any statements, information, or conclusions contained in any third-party materials used in preparing this document. The views and opinions of third parties published in this document do not necessarily state or reflect those of CADTH.

CADTH is not responsible for any errors, omissions, injury, loss, or damage arising from or relating to the use (or misuse) of any information, statements, or conclusions contained in or implied by the contents of this document or any of the source materials.

This document may contain links to third-party websites. CADTH does not have control over the content of such sites. Use of third-party sites is governed by the third-party website owners' own terms and conditions set out for such sites. CADTH does not make any guarantee with respect to any information contained on such third-party sites and CADTH is not responsible for any injury, loss, or damage suffered as a result of using such third-party sites. CADTH has no responsibility for the collection, use, and disclosure of personal information by third-party sites.

Subject to the aforementioned limitations, the views expressed herein are those of CADTH and do not necessarily represent the views of Canada's federal, provincial, or territorial governments or any third-party supplier of information.

This document is prepared and intended for use in the context of the Canadian health care system. The use of this document outside of Canada is done so at the user's own risk.

This disclaimer and any questions or matters of any nature arising from or relating to the content or use (or misuse) of this document will be governed by and interpreted in accordance with the laws of the Province of Ontario and the laws of Canada applicable therein, and all proceedings shall be subject to the exclusive jurisdiction of the courts of the Province of Ontario, Canada.

The copyright and other intellectual property rights in this document are owned by CADTH and its licensors. These rights are protected by the Canadian *Copyright Act* and other national and international laws and agreements. Users are permitted to make copies of this document for non-commercial purposes only, provided it is not modified when reproduced and appropriate credit is given to CADTH and its licensors.

**Redactions:** Confidential information in this document may be redacted at the request of the sponsor in accordance with the *CADTH Drug Reimbursement Review Confidentiality Guidelines*.

**About CADTH:** CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

**Funding:** CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

## What Is the CADTH Reimbursement Recommendation for Dojolvi?

CADTH recommends that Dojolvi should be reimbursed by public drug plans as a source of calories and fatty acids for the treatment of adult and pediatric patients with a long-chain fatty acid oxidation disorders (LC-FAOD) if certain conditions are met.

## Which Patients Are Eligible for Coverage?

Dojolvi should only be covered to treat patients with and without a confirmed LC-FAOD diagnosis if they present with acute life-threatening symptoms that are consistent with those of LC-FAOD. Dojolvi should only be covered in patients who need a different treatment than over-the-counter even-chain medium-chain triglyceride (MCT) oil.

## What Are the Conditions for Reimbursement?

Dojolvi should only be reimbursed if prescribed by clinicians experienced in the management of LC-FAOD and if the price of Dojolvi is reduced. Reimbursement of Dojolvi should be renewed every 12 months if individual patient treatment goals are being met.

## Why Did CADTH Make This Recommendation?

- Evidence from 3 studies suggests that Dojolvi 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.
- 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.
- Based on public list prices, Dojolvi is not considered cost-effective at a willingness to pay of \$50,000 per quality-adjusted life-year (QALY) for the indicated population relative to standard of care, which consists of over-the-counter MCT oil. A price reduction is therefore required. Economic evidence suggests that a 96% price reduction is needed to ensure Dojolvi is cost-effective at a \$50,000 per QALY threshold.
- Based on public list prices, the 3-year budget impact is \$150,522,015.

## Additional Information

### What Are Long-Chain Fatty Acid Oxidation Disorders?

LC-FAOD are a group of rare genetic disorders in which patients cannot breakdown certain types of fat to make energy. Patients can show many symptoms, including tiredness, irritability, noticeably enlarged liver, irregular heartbeat, cardiac failure, poor muscle tone, and periodic severe muscle pain caused by muscle breakdown. In Canada, it is estimated that 10 to 15 babies are born with this disease every year. Some patients can present with life-threatening events.

### Unmet Needs in Long-Chain Fatty Acid Oxidation Disorders

There is a need for treatments that increase energy levels in patients and improve their ability to engage in usual activities of daily life, maintain muscle tone, decrease stress on organ systems, reduce hospitalizations, and improve quality of life.

### How Much Does Dojolvi Cost?

Treatment with Dojolvi is expected to cost approximately \$118,678 to \$466,971 per patient per year at the recommended dose of 35% of a patient's daily caloric intake.

## Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that triheptanoin should be reimbursed as a source of calories and fatty acids for the treatment of adult and pediatric patients with an acute life-threatening long-chain fatty acid oxidation disorders (LC-FAOD) only if the conditions listed in Table 1 are met.

## Rationale for the Recommendation

Evidence from 3 studies in patients with LC-FAOD (1 open-label, single-arm, phase II study [Study CL201, N = 29]; 1 ongoing, open-label, long-term extension study [Study CL202, N = 75]; and 1 double-blind, randomized controlled study [Gillingham et al., N = 32]) demonstrated that treatment with triheptanoin leads to reductions in some of the measured end points. There were no pre-specified primary and secondary end points in Study CL201, and none of the studies adjusted for multiple comparisons. Patients enrolled in Study CL201 demonstrated a reduction in the mean annualized event rate (difference in mean of 0.81 events per year) and duration (difference in mean of 3 days) of major clinical events (MCEs) such as hospitalizations, emergency department (ED) or acute care visits, or emergency interventions for rhabdomyolysis, hypoglycemia, or cardiomyopathy. Most patients who rolled over from Study CL201 into Study CL202 (N = 24) continued to demonstrate improvements in the annualized event rate (difference in mean of 0.80 events per year MCEs), the primary end point of CL202. Improvement in the annualized rate and duration of MCEs was not demonstrated in all patients. The study by Gillingham et al. (2017) compared triheptanoin with trioctanoin, a conventional even-chain medium-chain triglyceride (MCT), in patients with a confirmed diagnosis of LC-FAOD who had at least 1 episode of rhabdomyolysis and were on a stable diet that included MCT. Some benefit with triheptanoin over trioctanoin was seen in exercise tolerance and cardiac parameters (i.e., left ventricular ejection fraction and left ventricular mass on echocardiography), although the clinical relevance of these findings was unclear. Patients identified as having the greatest need for a new treatment were those with acute life-threatening cardiovascular or metabolic decompensation who require alternative therapy to conventional even-chain MCT. Despite the heterogenous nature of the disease presentation and progress, triheptanoin may meet the needs of this specific patient population in whom there are no other treatment options.

Using the sponsor-submitted price for triheptanoin of \$6,365.00 per 500 mL bottle, 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. A reduction in price of at least 96% is required for triheptanoin to be considered cost-effective at a \$50,000 per QALY threshold.

**Table 1: Reimbursement Conditions and Reasons**

| Reimbursement condition   | Reason  |
|---|---|
| <b>Initiation</b>   |   |
| <p>1. Treatment with triheptanoin should be initiated in either of the following:</p> <p>1.1. patients with a confirmed diagnosis of LC-FAOD and acute life-threatening events who require alternative therapy to conventional even-chain MCT supplementation</p> <p>1.2. patients without a confirmed diagnosis of LC-FAOD presenting with acute life-threatening events consistent with LC-FAOD who require alternative therapy to conventional even-chain MCT supplementation.</p> | <p>All reviewed studies suggest that treatment with triheptanoin may be associated with a clinical benefit only in patients with a confirmed LC-FAOD diagnosis.</p> <p>The clinical experts suggested that triheptanoin should be considered as a treatment option in select patients presenting with acute life-threatening symptoms consistent with LC-FAOD.</p>  |
| <b>Renewal</b>  |   |
| <p>2. Continued benefit of triheptanoin and whether it meets the patient’s treatment goals should be reviewed every 12 months.</p>  | <p>According to the clinical experts, the heterogeneity of disease presentation requires treatment goals to be individualized to each patient.</p> <p>Assessment of response must be individualized based on the patient’s history. In general, a treatment period of 12 months would allow adequate length of time for patients to demonstrate improvement or maintenance of benefit in various presenting symptoms.</p> |
| <b>Prescribing</b>  |   |
| <p>3. Triheptanoin should only be prescribed by clinicians experienced in the management of LC-FAOD.</p>  | <p>Accurate diagnosis of patients with LC-FAOD is important to ensure that triheptanoin is prescribed to appropriate patients.</p>  |
| <b>Pricing</b>  |   |
| <p>4. A reduction in price.</p>   | <p>The ICER for triheptanoin is \$1,347,825 per QALY when compared with standard of care.</p> <p>A price reduction of 96% would be required for triheptanoin to be able to achieve an ICER of \$50,000 per QALY compared with standard of care.</p>   |

ICER = incremental cost-effectiveness ratio; LC-FAOD = long-chain fatty acid oxidation disorders; MCT = medium-chain triglyceride.

## Implementation Guidance

Issues that may impact the drug plan’s ability to implement a recommendation as identified by CDEC and the drug plans are summarized in Table 2.

**Table 2: Implementation Guidance From CDEC**

| Condition no. in Table 1 | Implementation considerations and guidance   |
|--------------------------|--|
| 1                        | Diagnosis of LC-FAOD should be made by a specialist in metabolic diseases and include all aspects of clinical, biochemical, or molecular diagnosis. Initiation of therapy should be reviewed by a panel of metabolic disease specialists, with allowance for retrospective review due to the urgent need for initiation of therapy. In patients without a confirmed diagnosis, efforts should be made to establish a diagnosis of LC-FAOD in a timely manner.  |
| 1                        | <p>An acute life-threatening event in a patient with a LC-FAOD may be the presenting feature or it may occur in a known patient who was either previously asymptomatic or previously managed successfully with traditional treatment and then decompensates. A life-threatening event can include:</p> <ul style="list-style-type: none"> <li>• a catastrophic presentation with acute or recurrent rhabdomyolysis with severe pain, compartment syndrome, acute renal failure requiring hospitalization and life-saving interventions including dialysis, treatment of hyperkalemia, and surgical treatment of compartment syndrome</li> <li>• severe hypoglycemia, recurrent or acute, with or without seizures</li> <li>• cardiomyopathy with or without arrhythmia.</li> </ul> |
| 2                        | Continued benefit of triheptanoin and whether it meets the patient’s treatment goals should be adjudicated by a panel of metabolic disease specialists.  |

CDEC = CADTH Canadian Drug Expert Committee; LC-FAOD = long-chain fatty acid oxidation disorders.

## Discussion Points

- CDEC considered that 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.
- CDEC considered the significant unmet need in patients who present with acute life-threatening cardiovascular or metabolic decompensation (who are usually but not always infants) who require alternative therapy to conventional even-chain MCT supplementation, as well as the lack of treatment options beyond optimized dietary measures and conventional even-chain MCT supplementation.
- CDEC heard from clinical experts that treatment of patients with LC-FAOD has historically been guided by case studies and case series in which improvements in chronic cardiomyopathy, rhabdomyolysis, and muscle weakness with triheptanoin treatment were reported.
- Initiation of therapy should be reviewed by a panel of metabolic disease specialists because LC-FAODs are largely heterogeneous in terms of disease presentation, progression, and treatment goals. Considering the uncertainty in the evidence, it is not currently possible to identify in advance patients who may definitively benefit from triheptanoin.
- CDEC noted that conclusions could not be drawn about the effects of triheptanoin on survival and health-related quality of life (HRQoL), which are important to patients with LC-FAOD. None of the studies measured the effect of triheptanoin on survival 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.

## Background

Triheptanoin has a Health Canada indication as a source of calories and fatty acids for the treatment of adult and pediatric patients with LC-FAOD. Triheptanoin is an MCT consisting of 3 odd-chain 7-carbon-length fatty acids (heptanoates). It 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.

## Sources of Information Used by the Committee

To make their recommendation, the committee considered the following information:

- a review of 1 open-label, single-arm phase II study; 1 ongoing, open-label, extension study; and 1 double-blind randomized controlled trial (RCT)
- patients' perspectives gathered by 1 patient group: MitoAction
- input from public drug plans and cancer agencies that participate in the CADTH review process
- five clinical specialists with expertise diagnosing and treating patients with LC-FAOD
- input from 1 clinician group: the Canadian Association of Centres for the Management of Hereditary Metabolic Disorders (Association Canadienne des Centres de Traitement Pour Les Maladies Metaboliques Hereditaire), also known as the Garrod Association
- a review of the pharmacoeconomic model and report submitted by the sponsor.

## Stakeholder Perspectives

### Patient Input

One patient group, MitoAction (Massachusetts, US), responded to the call for patient input for this CADTH Reimbursement Review. Input was not received from any Canadian patient group. MitoAction has engaged with the patient community through weekly support calls, Facebook groups, and Mito411 Support line, and have received direct feedback from the patient community in the US about their experience with triheptanoin.

The patient group emphasized that the energy depletion for patients with LC-FAOD can be debilitating, and patients often cannot participate in normal day-to-day activities. Patients must manage their energy exertion throughout the day, so a simple task can physically overwhelm an individual with LC-FAOD. Limitations to activity can lead to depression, isolation, and other mental health issues, which are very common in patients with a rare disease. Manifestations of LC-FAOD can also lead to hospitalization and organ damage. The MitoAction submission also notes that before the approval of Dojolvi there have been no therapies available specifically indicated for LC-FAOD; rather, patients have had to rely on over-the-counter MCT oils and symptomatic treatments. Some patients continue to experience debilitating fatigue and other symptoms of LC-FAOD despite the availability of MCT oils, pointing to a significant unmet need.

The description of the patient experience makes it clear that they would value a therapy that provided an increased level of energy that enhanced their ability to engage in the normal activities of life, avoided loss of muscle tone, decreased stress on organ systems, and reduced hospitalizations. These factors would lead patients to hope for an improved quality of life. MitoAction notes that with proper treatment and disease management it is hoped that patients with LC-FAOD can lead full and meaningful lives despite their diagnosis.

## Clinician Input

### Input From Clinical Experts Consulted by CADTH

The clinical experts consulted by CADTH stated that current treatments may help some patients, but there are patients who still experience recurrence of symptoms despite optimized therapy. There is a need for more effective treatment for patients with ongoing symptomatic LC-FAOD, particularly those with severe forms of the disease. Supplementation with even-chain MCT has effectively led to a positive response and a reduction of complications in some patients. However, tolerability is an issue (i.e., gastrointestinal [GI] adverse effects) which in turn affects adherence to the treatment regimen.

The experts indicated that triheptanoin would typically be reserved for more severe cases of LC-FAOD or as second-line therapy after even-chain MCT products. For most patients, the clinical experts anticipate triheptanoin to be used when there is inadequate response to optimized dietary measures and conventional even-chain MCT supplementation. Triheptanoin may be used as first-line therapy in select patients (usually neonates or infants) presenting with acute, life-threatening cardiovascular or metabolic decompensation; if a response is seen, triheptanoin treatment would be expected to continue upon hospital discharge.

According to the clinical experts, in general, it is appropriate for a patient who starts triheptanoin to receive an adequate trial and be evaluated annually for improvement or maintenance of effect, although initial evaluations may be more frequent (e.g., every 3 months or 6 months). The clinical experts emphasized that assessing response to treatment should be individualized. Depending on the age of the patient, type of LC-FAOD, presenting symptoms, and clinical severity, the goals of treatment vary (e.g., address rate of progression of left ventricular dysfunction, frequency of events such as rhabdomyolysis or hospitalization, length of hospital admissions, recurrent episodes of metabolic decompensation, exercise intolerance, muscle pain with exertion, and quality of life). For example, in infants presenting with catastrophic events, survival would be a relevant outcome, and follow-up would be performed frequently. In stable older children and adults, follow-up might be performed every 6 months to 12 months. The clinical experts stated that the decision to discontinue treatment is according to individualized parameters that are based on the patient's medical history. If parameters used to measure response in the patient return to pre-treatment levels or there is a failure to maintain gains, then triheptanoin treatment should be discontinued at the annual assessment. Treatment should also be discontinued if unacceptable side effects develop.

## Clinician Group Input

This section was prepared by CADTH staff based on the input provided by clinician groups.

One group clinician input was received from the Garrod Association Guideline Committee on the reimbursement review on triheptanoin. The clinician group noted that the current treatment available for the management of patients with LC-FAOD mainly includes medical

nutrition therapy. The group commented that this typically includes the restriction of long-chain fatty acids and supplementation with MCT.

The clinician group noted that patients with severe LC-FAOD have the greatest unmet need versus patients with milder LC-FOADs. The group added that this is because patients with severe LC-FOAD can present with symptoms regardless of good compliance to standard treatment. The Garrod Association Guideline Committee noted that the drug under review will replace and not complement MCT supplements. They recommended that the 2 supplementations (triheptanoin and MCT) should not be given together due to a theoretical concern that MCT oil and triheptanoin compete for enzyme activity. The Garrod Association Guideline Committee noted that patients with moderate-to-severe LC-FAOD are likely to respond to the treatment under review and thus would be best suited for treatment.

The group commented that triheptanoin should be used as first- or second-line treatment based on the clinical judgment of the treating physician in this group. The clinician group added that mild, asymptomatic patients with LC-FAOD who are diagnosed via newborn screening programs would be least suited for treatment with the drug under review. In addition, the clinician group noted that patients diagnosed with long-chain 3-hydroxyacyl-coenzyme A dehydrogenase (LCHAD) and mitochondrial trifunctional protein deficiencies are at risk of developing retinopathy and peripheral neuropathy. They added that neither MCT supplementation nor triheptanoin treat these symptoms.

## Drug Program Input

**Table 3: Responses to Questions From the Drug Programs**

| Implementation issues   | Clinical expert response   |
|---|--|
| <b>Relevant comparators</b>   |  |
| Is MCT supplementation a relevant comparator in this population? Is there a preferred formulation or composition of MCT oil in the treatment of LC-FAOD (e.g., C8, C10, C12)? | MCT supplementation is a relevant comparator in this population because it is used as part of the treatment regimen in Canadian patients with LC-FAOD. There is no preferred formulation or composition, and the choice is guided by the funding guidelines of the jurisdiction.   |
| <b>Considerations for initiation of therapy</b>   |  |
| Are the tests used to help diagnose LC-FAOD available in all Canadian jurisdictions?  | <p>Following ascertainment of a baby with a positive newborn screen (available throughout Canada), confirmatory biochemical testing, including acylcarnitine profile and urine organic acids, is also widely available in Canada. Molecular testing is available via provincial newborn screening programs or diagnostic genomic laboratories (in or out of the province). Jurisdictions that perform newborn screening using tandem mass spectrometry and acylcarnitine analysis would have the ability to identify LC-FAOD disorders; however, all results may not always be reported.</p> <p>Most patients are diagnosed with LC-FAOD via newborn screening programs in Canada. There may be undiagnosed adults, born before the implementation of newborn screening, who present with symptoms and are diagnosed clinically with late-onset disease.</p> |

| Implementation issues   | Clinical expert response  |
|---|---|
| <p>How should “severe” disease be defined?<br/>Would patients with mild or moderate LC-FAOD be treated with triheptanoin?</p>   | <p>The phenotypes are not classified as moderate or severe but rather by organ system involvement (e.g., cardiomyopathy, rhabdomyolysis, retinopathy, neuropathy). Every patient is unique in terms of their presentation; within each organ system, it can be classified as mild, moderate, or severe. Thus, in LC-FAOD disorders, broad classifications are useful but only as a general guide.</p> <p>In general, earlier presentation (i.e., younger age group) is more severe in terms of extent of organ system involvement. However, later-onset presentations can still be very severe or life-threatening. Differentiation between mild disease variants and classical disease is often possible via biochemical and/or genetic testing.</p> <p>The mildest cases of LC-FAOD do not require specific dietary therapy; asymptomatic adult patients are unlikely to require chronic interventions including MCTs such as triheptanoin. Moderate-to-severe cases of LC-FAOD require dietary modifications and supplementation with MCT or triheptanoin.</p> <p>Pre-symptomatic patients with biochemical markers (acylcarnitine profile, enzyme activity), molecular results, or cardiac function evaluation (echocardiography, electrocardiogram) suggestive of more significant disease are currently treated with diet and MCT supplementation. Triheptanoin would likely be used as second-line treatment in most patients.</p> |
| <p>Would patients &lt; 6 months old be treated with triheptanoin?<br/>The Health Canada indication does not include any age restrictions, but it is noted that Study CL201 included patients ≥ 6 months (median age was 5 years [range = 0.9 years to 59 years]).</p>   | <p>The general treatment principles for all age groups of patients with LC-FAOD disorders are similar. In neonates or infants, MCT supplementation with formula feeds may be given as first-line treatment. Although the CL201 and CL202 studies only included patients older than 6 months of age, triheptanoin is still expected to be prescribed to younger patients with severe forms of LC-FAOD who are not adequately treated with other available measures. Additionally, infants with catastrophic symptomatic presentation of LC-FAOD are expected to be treated immediately with all available treatment, including triheptanoin. After discharge, these infants are expected to continue on triheptanoin therapy, without requiring a trial of even-chain MCT.</p>   |
| <p>If patients should be managed on a stable treatment regimen (including diet), as per inclusion criteria for Study CL201, before being eligible for triheptanoin, how should “stable treatment regimen” be defined (e.g., what prior therapies should be included and the duration of the trial of treatment)?<br/>Can a patient’s diet potentially impact outcomes of treatment with MCT oils or triheptanoin?</p> | <p>Because patients have varying clinical presentations, treatment is individualized based on the type of LC-FAOD, organ system involved, and frequency of events that occur. As such, the type and duration of prior therapies differ with each individual, and there is no standardized protocol in this patient population. Common treatments include dietary measures, avoidance of fasting, MCT products, and carnitine in some patients.</p> <p>Dietary measures should be optimized before initiating even-chain MCT supplementation or triheptanoin.</p>  |
| <p>Would even-chain MCT oil be prescribed before triheptanoin?<br/>When should triheptanoin be used first-line and why?</p>   | <p>Even-chain MCT products are expected to continue being used in the chronic treatment of LC-FAOD. Triheptanoin will likely be used in patients who do not respond to even-chain MCT products or in young patients presenting with acute crisis of new-onset LC-FAOD.</p>  |

| Implementation issues   | Clinical expert response   |
|---|--|
| <b>Considerations for continuation or renewal of therapy</b>  |  |
| How should response to triheptanoin be defined? What outcome measure(s) should be used and when should response be assessed? Would the outcome measure(s) be different based on the age of the patient? | Response to triheptanoin would be assessed in the same manner as response to other treatments for LC-FAOD. Measures of response should be tailored to the patient and will depend on the presenting organ system involvement and clinical status. Ideally, measures should be based on those which can objectively quantify clinical improvement such as change in frequency and length of hospitalization. Formal exercise tolerance tests may also provide indication of a patient's response to treatment. Subjective parameters, such as residual pain and activities of daily living, may also be considered. In infants with catastrophic presentation, survival is an important measure as are frequency of hospitalization and emergency department visits; in children, long-term growth and development would also be monitored. |
| <b>Generalizability</b>   |  |
| Are there any specific types of LC-FAOD that may not benefit from treatment with triheptanoin?  | The general treatment principles and approach for the different types of LC-FAOD disorders are similar. Although Study CL201 and the study by Gillingham et al. (2017) did not include patients with carnitine-acylcarnitine translocase or carnitine palmitoyl transferase – type 1 deficiency, triheptanoin is still expected to be prescribed to patients with severe forms of these types of deficiencies that are not adequately treated with other available measures.   |
| Is there any evidence to support the use of triheptanoin for the treatment of medical conditions beyond LC-FAOD, including other inborn errors of metabolism (e.g., GLUT1 deficiency)?                  | There is currently insufficient evidence to support the use of triheptanoin in the treatment of medical conditions beyond the current indication, including patients with other inborn errors of metabolism.   |

LC-FAOD = long-chain fatty acid oxidation disorder; MCT = medium-chain triglyceride.

## Clinical Evidence

### Pivotal Studies and Protocol-Selected Studies

#### Description of Studies

A total of 3 sponsor-submitted studies were included in this report. Aside from these sponsor-submitted pivotal studies, none of the other identified citations met the inclusion criteria for the CADTH systematic review. Two of the studies (CL201 and CL202) were funded by the sponsor, whereas the third study (Gillingham et al. [2017]) was conducted by an independent investigator.

Study CL201 (N = 29) was a multicentre, 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. Patients must have had severe LC-FAOD with confirmed diagnosis of carnitine palmitoyl transferase – type 2 (CPT II), very long-chain acyl-coenzyme A dehydrogenase (VLCAD), LCHAD or trifunctional protein (TFP) deficiency, and had been on stable treatment (including dietary measures). At the baseline visit, any prior MCT was discontinued and treatment with triheptanoin was initiated (i.e., added to standard therapy). The target dose of triheptanoin

was 25% to 35% of daily caloric intake (DCI) or maximum tolerated dose, and treatment was continued up to 78 weeks (18 months).

Study 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 had a confirmed diagnosis of CPT I, CPT II, VLCAD, LCHAD, TFP, or carnitine-acylcarnitine translocase (CACT) deficiency. The study consists of 3 cohorts: patients who had previously participated in Study CL201 (CL201 rollover cohort, N = 24), patients who failed conventional therapy and continued to exhibit clinical manifestations of LC-FAOD (triheptanoin-naïve cohort, N = 20), and patients who participated in other programs to access triheptanoin, such as investigator-sponsored trials (ISTs) or compassionate use (IST/other cohort, N = 31). All 3 were single-arm cohorts; none included a parallel comparator group. The target dose of triheptanoin was 25% to 35% of DCI, and treatment was continued up to 5 years (60 months) while enrolled in Study CL202. Data presented in this report reflect an interim analysis with a cut-off date of June 1, 2018; the mean duration of treatment was 25.92 months. The mean duration for each treatment cohort was 23.01 months for the Study CL201 rollover cohort (excludes Study CL201 study duration), 15.68 months for the triheptanoin-naïve cohort, and 34.77 months for the IST/other cohort.

In a double-blind RCT, Gillingham et al. (2017, N = 32) investigated whether triheptanoin therapy (an odd-chain fatty acid triglyceride) has a therapeutic advantage over conventional treatment for LA-FAODs. Before study enrolment, patients must have had at least 1 episode of rhabdomyolysis and have been on a stable diet that included 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 DCI. Randomization occurred separately at 2 investigative sites and was stratified according to diagnosis (CPT II, VLCAD, or TFP/LCHAD). Baseline assessments were completed at enrolment and patients were admitted to the research centre for 4 days for outcome measurements. Upon discharge, patients continued treatment with assigned diet and MCT supplementation for 4 months. At the end of 4 months, baseline assessments were repeated.

At baseline, the average ages of patients in Study CL201 and Study CL202 were younger than that of patients enrolled in the Gillingham et al. (2017) trial. The 2 sponsor-funded trials enrolled mostly pediatric patients (< 18 years); the mean age was 12.06 (standard deviation [SD] = 13.21) years in Study CL201, and 13.87 (SD = 13.19) years in Study CL202. The mean age in the Gillingham et al. (2017) study was 24.75 (SD = 14.3) years. The most common LC-FAOD type diagnosed in the patients enrolled in Study CL201 and Study CL202 were VLCAD and LCHAD deficiencies. In the Gillingham et al. (2017) study, a similar number of patients were diagnosed with VLCAD, LCHAD/TFP, or CPT II deficiencies. According to available data (i.e., excluding the IST/other cohort of Study CL202), the majority of patients enrolled in all 3 studies had received prior treatment with a MCT formulation, and all were being treated with dietary measures. In Study CL201 and Study CL202, approximately 65% of patients were receiving carnitine supplementation. Before enrolment, patients in the CL201 study had received approximately 17% of DCI as medium-chain fat from MCTs.

In Study CL201, patients were prescribed a mean triheptanoin dose 31.20% DCI (SD = 8.88%). The mean dose of triheptanoin that was consumed was 27.5% (SD = 4.58%) of DCI. During the study, there was a 10% DCI increase (from average 17.4% to 27.5%) in the amount of medium-chain fat consumed compared with the pre-triheptanoin period. In Study CL202, the mean dose of triheptanoin prescribed was 26.95% of DCI (SD = 7.48%); the mean triheptanoin

dose (% DCI) actually consumed was not reported, although on average, most patients consumed more than 90% of their prescribed dose. In the Gillingham et al. (2017) study, patients consumed 16.62% (SD = 2.66%) and 14.83% (SD = 3.40%) of DCI from triheptanoin and trioctanoin, respectively.

The CL201 study did not explicitly identify primary and secondary efficacy end points; rather, the study grouped end points as key or supportive. Numerous key end points were measured for several disease areas; the following clinical outcomes, relevant to this review, were assessed: MCEs (hospitalizations, ED or acute care visits, and emergency interventions for rhabdomyolysis, hypoglycemia, or cardiomyopathy), exercise intolerance (12-minute walk test [12MWT], cycle ergometry), functional disability and cognitive development (SF-10, SF-12), and cardiac function (echocardiogram).

The primary end point in Study CL202 was the annualized LC-FAOD MCE rate inclusive of rhabdomyolysis, hypoglycemia, and cardiomyopathy events. Annualized duration of total MCEs was considered a secondary efficacy end point, as were the annualized event rate and annualized event days (also referred to as annualized duration rate) of each of the MCEs separately (i.e., rhabdomyolysis, hypoglycemia, and cardiomyopathy).

The primary outcomes in the Gillingham et al. (2017) study included changes in total energy expenditure, cardiac function (as measured by echocardiogram), exercise tolerance (measured by treadmill ergometry), and phosphocreatine recovery following acute exercise.

## Efficacy Results

Results for efficacy outcomes identified in the review protocol are reported; only the efficacy end points and parameters which were deemed to show favourable changes for triheptanoin according to the trial reports and publications have been included in this summary. In addition, none of the results discussed subsequently were adjusted for multiplicity; as such, designating differences as “statistically significant” has been avoided. Of note, none of the 3 studies evaluated the following efficacy outcomes that were identified in the CADTH review protocol: survival, symptom relief, reduction in concomitant medications, or productivity.

## Major Clinical Events

MCEs were not measured as part of the efficacy analyses in the Gillingham et al. (2017) study. MCEs were defined in both Study CL201 and Study CL202 as rhabdomyolysis, hypoglycemia, or cardiac disease events caused by LC-FAOD or an intercurrent illness complicated by LC-FAOD resulting in any hospitalization, ED or acute care visit, or emergency intervention (any unscheduled administration of therapeutics at home or in the clinic). These measures were presented as annualized event rate and event days (also called duration rate) as an aggregate and separately for major rhabdomyolysis events, hypoglycemia events, and events due to decompensation of cardiomyopathy. Of note, the majority of MCEs reported in both Study CL201 and Study CL202 were due to rhabdomyolysis events.

Due to the heterogeneity of clinical manifestations with LC-FAOD, both studies used a retrospective control to compare MCEs before and during triheptanoin treatment. Retrospective data collection was intended to provide a within-subject comparison for MCEs; thus, each patient acted as their own control. In Study CL201, a medical history from 18 months (78 weeks) before study entry was collected to establish a pre-triheptanoin comparison that was compared with 78 weeks of triheptanoin treatment. In Study CL202, historical medical data were collected for patients in the CL-201 rollover and triheptanoin-

naive cohorts. Statistical comparisons were made between data collected from 18 months before triheptanoin treatment and the first 36 months (CL201 rollover cohort, inclusive of treatment received during CL201) or 18 months (triheptanoin-naive cohort) of study treatment. No statistical comparisons were made for the IST/other cohort in Study CL202 due to lack of pre-triheptanoin data.

In Study CL201, reduced annualized event rates and event days were seen across all 3 clinical manifestations with triheptanoin treatment but was most favourable for the aggregate measure including all event types. For total MCEs, including all event subtypes, the difference in the mean annualized event rate was 0.81 events per year and the difference in mean annualized event days was 2.997 in favour of triheptanoin.

In the CL201 rollover cohort of Study CL202, the most notable improvement with triheptanoin was in the annualized event rate of total MCEs. For this primary efficacy end point, the difference in the mean annualized event rate of total MCEs, including all event subtypes, was 0.80 events per year in favour of triheptanoin treatment. For the remaining annualized event rates and event days (secondary efficacy end points), a reduction was generally seen with triheptanoin treatment across all comparisons, but none were notably significant. In the triheptanoin-naive cohort of Study CL202, a heavily skewed distribution was observed which limited the interpretation of results; none of the changes observed in MCEs were significant.

To evaluate the effect of triheptanoin on MCEs in different subgroups, several ad hoc analyses were performed. The following 2 relevant subgroups, identified in the CADTH systematic review protocol, were analyzed in both Study CL201 and Study CL202: age at triheptanoin initiation (< 6 years, ≥ 6 to < 18 years, and ≥ 18 years) and LC-FAOD diagnosis subtype (LCHAD, VLCAD, CPT II, and TFP deficiency). For subgroup analyses based on age at treatment initiation, results across different age groups in CL201 were generally consistent with those seen with the overall population. Inconsistent and variable results were observed in Study CL202. For subgroup analyses based on LC-FAOD diagnosis subtype, results across all diagnosis groups in Study CL201 were consistent with those seen with the overall population, except for patients with TFP deficiency. For this 1 subtype, a reduction in annualized event rate, but not annualized event duration, was seen. Similarly, for both the CL201 rollover and triheptanoin-naive cohorts of Study CL202, results consistent with the overall population were seen with all subtypes except for TFP deficiency. The analyses and interpretability of subgroup data are limited by the small sample sizes of individual subgroups and skewed data seen in CL202.

## Hospitalizations

Hospitalizations were captured as part of the MCEs in Study CL201 and Study CL202. Across both studies, most MCEs that occurred before and during triheptanoin treatment were hospitalizations due to rhabdomyolysis. Although few events due to cardiomyopathy occurred during the 2 trials, almost all led to hospitalization due to the serious nature of the event.

In Study CL201, a reduction in annualized hospitalization rates and hospitalization days were seen across all 3 clinical manifestations with triheptanoin treatment but was most favourable for the aggregate measure including all event types. For hospitalizations due to total MCEs, including all event subtypes, the difference in the mean annualized event rate was 0.74 hospitalizations per year, and the difference in mean annualized event days was 2.92 in favour of triheptanoin.

In the CL201 rollover cohort of Study CL202, the most notable improvement with triheptanoin treatment was in the annualized hospitalization rate of total MCEs. The difference in the mean annualized hospitalization rate of total MCEs, including all event subtypes, was 0.67 events per year in favour of triheptanoin treatment. For the remaining annualized hospitalization rates and hospitalization days due to specific event subtypes, a reduction was generally seen with triheptanoin treatment across all comparisons, but none were notably significant. The exception was hospitalization for major rhabdomyolysis events, in which the mean annualized event days appeared to increase with treatment, although median days decreased. This may be due to the highly skewed distribution of annualized event days observed in this cohort. In the triheptanoin-naive cohort of Study CL202, a heavily skewed distribution was observed that limited the interpretability of the results. None of the changes observed in hospitalizations were significant.

In the study by Gillingham et al. (2017), 7 hospitalizations for acute rhabdomyolysis were reported in each treatment group. There was no difference in length of hospital stay.

### Emergency Department Usage

ED usage was not measured as part of the efficacy analyses in the Gillingham et al. (2017) study. ED visits were captured as part of the MCEs in Study CL201 and Study CL202. Overall, very few ED visits occurred before and during triheptanoin treatment, and all ED visits were due to rhabdomyolysis. In Study CL201, there was no meaningful difference in annualized ED visit rates between the pre-triheptanoin and triheptanoin treatment period. In Study CL202, no statistical analyses were performed to compare ED visits before and during treatment with triheptanoin. Numerically, an increase in ED visits during triheptanoin treatment was seen in the CL201 rollover cohort, whereas a decrease was seen in the triheptanoin-naive cohort. However, the small number of events and lack of statistical testing preclude drawing any definitive conclusions.

### Health-Related Quality of Life

HRQoL was not measured in the Gillingham et al. (2017) study. In studies CL201 and CL202, changes in HRQoL were measured using Medical Outcomes Study 10-Item Short Form (SF-10) in children 5 to 17 years of age, and Medical Outcomes Study 12-Item Short Form version 2 (SF-12v2) in adults 18 years and older. For both assessments, a score of 50 constituted the normalized base score, and each factor of 10 represented 1 SD above or below the mean. Overall, the population included in the assessments of HRQoL was much smaller than the number of patients enrolled in each study or cohort.

In Study CL201, the main statistical comparison in HRQoL was the change from baseline at week 24. For pediatric patients (SF-10), mean baseline physical summary score (PHS) indicated impairment whereas the psychosocial summary score (PSS) was similar to the general population. At week 24, no notable changes from baseline were observed in PHS (mean change = 2.16; 95% confidence interval [CI], -2.62 to 6.94) or PSS (mean change = 0.82; 95% CI, -4.34 to 5.97) scores. Beyond week 24, the PHS improved over time with treatment across week 48 and week 78; however, scores remained below the population norm. For adults (SF-12v2), the mean baseline physical component summary (PCS) score was lower than the population mean; the mental component summary (MCS) score was slightly below the norm. At week 24, there was notable improvement with treatment in both PCS (mean change = 8.87; 95% CI, 5.67 to 12.08) and MCS (mean change = 9.70; 95% CI, 1.87 to 17.54) scores. This benefit was maintained through week 78 for the PCS score (mean

change = 3.62; 95% CI, 0.25 to 6.99), but not MCS (mean change = 4.42; 95% CI, -8.78 to 17.62). Despite improvement, mean PCS scores remained below the population norm.

In Study CL202, no statistical tests were performed to compare the change in scores over time, thus observations can only be made regarding the general trend in scores with treatment in each of the 3 cohorts.

In the CL201 rollover cohort of Study CL202, SF-10 PHS scores appeared to decline over the 18 months of treatment; however, scores remained above baseline taken before starting triheptanoin in Study CL201. The SF-10 PSS scores remained generally stable from baseline through Study CL202; these scores were similar to the population norm. For SF-12v2, PCS scores during Study CL202 were relatively stable and similar to pre-treatment levels. The MCS scores of SF-12 were also relatively stable through CL202, and mean values remained within the population norm.

In the triheptanoin-naive cohort, the baseline mean PHS scores for SF-10 was lower than the population norm, indicating impairment. Scores appeared to improve over time and were similar to the population average while on treatment. The mean SF-10 PSS scores were similar to the population norm at baseline and remained within this range throughout Study CL202. For SF-12v2, changes in HRQoL were difficult to assess due to the small number of patients in each post-baseline assessment.

In the IST/other cohort, scores for both SF-10 and SF-12v2 remained relatively stable throughout the 18 months of treatment in CL202.

## Physical Function or Exercise Tolerance

Physical function and exercise tolerance were measured using the 12MWT and cycle ergometry in Study CL201, and treadmill ergometry and phosphocreatine recovery in the study by Gillingham et al. (2017). Study CL202 did not assess physical function or exercise tolerance.

In Study CL201, the primary analysis for the 12MWT was assessed at week 18, and 8 patients performed the 12MWT at all key assessment points. Although results showed overall improvement with triheptanoin treatment in the various parameters, most were not significant, and the mean change from baseline was often associated with wide CIs, reducing the certainty of the results. The only notable improvement in the 12MWT parameters was in the energy expenditure index from baseline to week 18, although baseline energy expenditure index was already within the normal range as identified in the study (0.14 beats/minute to 0.89 beats/minute).

In Study CL201, the primary analysis for the cycle ergometry test was assessed at week 24, and 7 patients performed the cycle ergometry test at both baseline and latter assessment. At week 24, an overall improvement from baseline was seen in cycle ergometry workload and duration, though neither were significant.

In the Gillingham et al. (2017) study, all patients completed the treadmill ergometry test to measure exercise tolerance. After 4 months of treatment, the only notable difference seen between the 2 treatment groups was in maximum heart rate, where the mean difference in change from baseline was 6.98 (95% CI, 0.34 to 13.63) beats/minute, in favour of triheptanoin. No difference between the 2 treatment groups was seen for VO<sub>2</sub> or peak double

product (a marker of cardiac workload measured by multiplying systolic blood pressure by heart rate); systolic blood pressure remained consistent throughout the test.

The study by Gillingham et al. (2017) also measured phosphocreatine recovery after repetitive lower leg exercise to evaluate muscle adenosine triphosphate (ATP) synthesis. This exercise protocol was completed by 8 adults in the triheptanoin group and 7 adults in the trioctanoin group. After 4 months of treatment, no difference between the 2 treatment groups was seen in test results.

## Cardiac Function Parameters

Cardiac function was measured using echocardiography in all 3 included studies. In Study CL201, echocardiography was performed on all patients at baseline and on 35 patients at week 24. At baseline, mean left ventricular ejection fraction (LVEF) was within the normal range specified in the study (55% to 70%), and no significant change was observed at week 24. In Study CL202, there were no notable changes overall in the echocardiogram parameters. In all 3 cohorts, the mean LVEF at baseline was also within the normal range.

In the Gillingham et al. (2017) study, echocardiograms of 21 patients (n = 10 triheptanoin, n = 11 trioctanoin) were assessed. After 4 months of treatment, a difference between the 2 treatment groups was seen in change from baseline in mean left ventricular (LV) wall mass as well as mean LVEF. For LV wall mass, the difference in relative change from baseline between the 2 treatment groups was 20% in favour of triheptanoin. For LVEF, the difference between triheptanoin and trioctanoin in change from baseline was 7.4% (95% CI, -0.1% to 15%) in favour of triheptanoin. All but 1 patient had normal cardiac function at baseline; the majority of the observed changes occurred within the normal range.

## Harms Results

All patients enrolled in Study CL201 and almost all (98.7%) patients enrolled in Study CL202 reported at least 1 treatment-emergent adverse event (TEAE). Although the total number of patients who experienced at least 1 TEAE was not reported in the Gillingham et al. (2017) study, it appears that the majority of patients did experience 1 or more TEAEs; similar frequencies of various adverse events (AEs) were generally seen between the triheptanoin and trioctanoin treatment groups. Complications of the underlying LC-FAOD (e.g., rhabdomyolysis) were also captured as an AE in all 3 studies, which likely contributed to the high rates of reported TEAEs. Overall, the reported TEAEs were similar across studies and generally consistent with the known AE profile of triheptanoin or associated with the underlying LC-FAOD. 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 Study CL201 and 76.0% of patients in Study CL202; these numbers included MCEs that were also reported as an SAE. In Study CL202, the proportion of patients who experienced at least 1 SAE during the study was similar across the 3 cohorts. The most common SAEs were related to the underlying LC-FAOD (e.g., rhabdomyolysis) or acute infectious disease, including GI infections. The study by Gillingham et al. (2017) did not categorize TEAEs by severity or seriousness. In Study CL201, 4 patients discontinued triheptanoin treatment due to TEAEs, most of which were GI-related. Treatment was discontinued due to TEAEs in 1 patient in Study CL202 (non-serious rhabdomyolysis), and none in the Gillingham et al. (2017) study. A total of 2 deaths were reported across the 3 studies, both in Study CL201; neither were

considered to be due to triheptanoin. Although weight gain was identified as a notable harm in the CADTH review protocol, this was not reported as an AE in any of the 3 studies. According to growth measures collected throughout the study, no clinically significant changes in z scores for weight were seen (in pediatric patients for Study CL201 and Study CL202), and in the Gillingham et al. (2017) study, no difference was noted between the 2 treatment groups in body composition or weight gain.

## Additional Information

As part of the sponsor's feedback on this CADTH reimbursement review report, CADTH received a summary of updated analysis for certain outcomes in Study CL202 from the sponsor. Due to the brief and selective nature of the provided information, CADTH could not use the summary to update all the relevant Study CL202 interim data and is unable to provide a critical appraisal of the updated analysis.

## Critical Appraisal

A few major limitations and sources of bias are provided below. Further details for each point, as well as a complete list of limitations and sources of bias are available in the main clinical report.

- Studies CL201 and CL202 were single-arm, phase II trials that did not include a parallel treatment comparator. Analyses of MCEs were conducted using a before-after design. The MCEs were evaluated before and after initiation of triheptanoin; therefore, each patient served as their own control using data collected retrospectively from medical records. 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 these 2 trials could be considered supportive, but cannot offer solid evidence of treatment benefits. The comparative efficacy of triheptanoin to even-chain MCTs was only investigated in the Gillingham et al. (2017) trial.
- The effects of triheptanoin as first-line treatment in patients who have not received any form of prior MCT supplementation require further investigation. The majority of patients ( $\geq 90\%$ ) in Study CL201 and the CL201 rollover and triheptanoin-naive cohorts of Study CL202 received prior treatment with MCT formulation. As per inclusion criteria, all patients enrolled into the Gillingham et al. (2017) study had received prior supplementation with MCT.
- Study results cannot be generalized to patients with CACT or CPT I deficiencies because these patients were excluded from the CL201 and Gillingham et al. (2017) trials and the enrolment numbers in Study CL202 were low. Notably, in Canada, the CPT IA P479L variant is prevalent in certain Indigenous communities (e.g., British Columbian First Nations and Inuit populations) and the CPT IA G710E variant is seen in Hutterite communities, but data on the efficacy of triheptanoin in these groups are lacking. However, the clinical experts consulted on this review note that patients with these CPT IA variants typically have mild disease or are asymptomatic and generally do not require active treatment with MCTs.
- In all 3 trials, the sample size of each study and treatment group or cohort were small. As a result, differences in 1 or 2 patients can have a substantial impact on results, leading to a high degree of uncertainty due to imprecise estimates. Nevertheless, due to the rarity of this disease population, such a small sample size is not unusual.
- None of the 3 trials employed a hierarchical testing procedure or strategy to control for the overall type I error rate; no adjustments were made for multiple testing among any of the

outcomes analyzed. Consequently, results should be interpreted with consideration of the potential for inflated type I error.

- The evaluation of patient-reported outcomes (e.g., HRQoL), exercise tests that depended on patient effort, or AEs in studies CL201 and CL202 may have been influenced by the unblinded treatment regimens, resulting in reporting bias. Furthermore, an estimated minimally important difference has not been identified in the LC-FAOD population for SF-10 or SF-12, nor have these tests been validated in patients with LC-FAOD. Although no overall decrement in HRQoL was seen in Study CL201 or Study CL202, it is unclear whether there are any sustained benefits with the new treatment, thus the overall effect of triheptanoin on HRQoL is inconclusive. For these reasons, along with the small sample sizes, the clinical significance of the HRQoL findings is unclear.
- Confounding due to changes in diet and MCT dose cannot be ruled out. For example, in Study CL201, there was an increase of approximately 10% DCI in the dose of MCT when patients transitioned from MCT oil to triheptanoin after study enrolment. For Study CL202 (except for the CL201 rollover cohort) and the Gillingham et al. (2017) study, no baseline dietary treatment information, including dose of prior MCT supplementation, was available.
- The efficacy of triheptanoin on survival, peripheral neuropathy, or retinopathy is unknown because none of the studies measured these important clinical outcomes. As well, the majority of MCEs documented in studies CL201 and CL202 were due to rhabdomyolysis. The small number of events and patients who had cardiomyopathy or experienced hypoglycemia limits the interpretation of efficacy for MCEs other than rhabdomyolysis.
- The RCT by Gillingham et al. (2017) did not include end points that were deemed important by clinicians and patient groups, including survival, clinical events, symptoms such as fatigue, and/or HRQoL. Thus, the relative efficacy of triheptanoin compared with even-chain MCTs (i.e., trioctanoin) for these important outcomes is unknown, and available data do not provide evidence to support the use of triheptanoin over trioctanoin to prevent or reduce clinical events.

## Economic Evidence

**Table 4: Cost and Cost-Effectiveness**

| Component                   | Description   |
|-----------------------------|---|
| Type of economic evaluation | Cost-utility analysis<br>Markov model   |
| Target population           | Patients exhibiting serious clinical manifestations of LC-FAOD despite current management   |
| Treatment                   | Triheptanoin  |
| Submitted price             | Triheptanoin, 500 mL bottle: \$6,365.00   |
| Treatment cost              | The recommended dose is 35% of the patients daily caloric intake, leading to an average daily cost of \$325.14 to \$1,279.37 per patient, or \$118,678 to \$466,971 annually. |
| Comparator                  | Standard of care consisting of over-the-counter MCT oil   |
| Perspective                 | Canadian publicly funded health care payer  |
| Outcomes                    | QALYs, LYs  |

| Component                | Description  |
|--------------------------|--|
| Time horizon             | Lifetime (97 years)  |
| Key data source          | <ul style="list-style-type: none"> <li>• Single-arm phase II study (CL201) of 78 weeks of treatment with triheptanoin in patients with symptomatic LC-FAOD was used to determine: the frequency and severity of MCEs including rhabdomyolysis, hypoglycemia, cardiomyopathy; frequency and severity of gastroenteritis adverse events; and SF-10 and SF-12 scores.</li> <li>• Costs of MCEs and gastroenteritis were derived from OCCI and CIHI; disutilities were derived from published literature.</li> </ul>   |
| Key limitations          | <ul style="list-style-type: none"> <li>• The sponsor calculated EQ-5D utility values by converting, through the use of a published algorithm, the SF-10 and SF-12 scores collected in Study CL201. This conversion of utility scores adds uncertainty to the analysis, specifically when using the SF-10 which was not intended for the algorithm. Furthermore, the CADTH clinical review noted that both scores have not been validated in a population with LC-FAOD. Lastly, the utility measure in the alive (off triheptanoin) health state was collected at baseline in Study CL201 and may not reflect the utility of a patient who has failed triheptanoin.</li> <li>• The model structure does not explicitly model the disease, making it difficult to explore the uncertainty in the clinical benefits of triheptanoin. Clinical effectiveness is captured via the rates of MCEs observed in Study CL201, a 78-week trial, and does not consider other potential benefits with triheptanoin involving energy expenditure.</li> <li>• The model fails to adequately consider patients who do not respond to triheptanoin. Discontinuation of triheptanoin was based on the observed discontinuation in Study CL201, in which 4 patients discontinued due to AEs not non-response to treatment. Examination of the individual patient responses reveals that approximately half of patients did not respond to triheptanoin based on their rates or duration of MCEs, a fact not accounted for in the model.</li> <li>• There is a lack of long-term data on clinical effectiveness for triheptanoin, a treatment that is expected to be used lifelong. The model structure does not allow for the consideration of treatment waning or re-treatment with triheptanoin.</li> </ul> |
| CADTH reanalysis results | <ul style="list-style-type: none"> <li>• CADTH made 1 change to the revised base case that involved deriving utility values solely from the SF-12 measure. In the article cited by the sponsor, the SF-12 alone (not the SF-10) was the only health-related quality of life measure used for mapping to the EQ-5D.</li> <li>• In the CADTH base case, the ICER for triheptanoin is \$1,347,825 per QALY compared with standard of care; the probability of triheptanoin being cost-effective at a WTP threshold of \$50,000 per QALY was 0%. A price reduction of 96% would be required for triheptanoin to be cost-effective at this threshold.</li> <li>• Scenario analyses were performed to assess the other aspects of uncertainty, particularly as they related to health state utilities, treatment discontinuation, triheptanoin dosing, and treatment adherence. The scenario with the largest impact on the ICER involved equating health state utilities to address clinical uncertainty, which led to an ICER of \$16,487,953 per QALY.</li> </ul>   |

CIHI = Canadian Institute for Health Information; ICER = incremental cost-effectiveness ratio; LY = life-year; MCE = major clinical event; MCT = medium-chain triglyceride; OCCI = Ontario Case Costing Initiative; QALY = quality-adjusted life-year; SF-10 = 10-item short form survey; SF-12 = 12-item short form survey; WTP = willingness to pay.

## Budget Impact

CADTH identified the following key limitations with the sponsor's budget impact analysis: the prevalence of LC-FAODs was likely underestimated based on the sponsor's reference and the proportion of adult cases of LC-FAODs was likely underestimated. CADTH reanalysis increased the prevalence of LC-FAODs based on the sponsor's reference. In the CADTH base case, the budget impact is expected to be \$39,226,635 in year 1, \$51,508,521 in year 2, and \$59,816,860 in year 3, with a 3-year total of \$150,522,015. CADTH found the budget impact to be sensitive to the prevalence of LC-FAODs.

## CADTH Canadian Drug Expert Committee Information

### Initial Meeting Date: August 18, 2021

#### Members of the Committee

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Sally Bean, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Allen Lefebvre, Dr. Kerry Mansell, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

**Regrets:** Two expert committee members did not attend.

**Conflicts of interest:** None

### Reconsideration Meeting Date: November 24, 2021

#### Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunskey, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed.

**Regrets:** Three expert committee members did not attend.

**Conflicts of interest:** None