CADTH

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

Triheptanoin (Dojolvi)

Indication: as a source of calories and fatty acids for the treatment of adult and pediatric patients with LC-FAOD

Recommendation: Do Not Reimburse

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

CADTH

TRIHEPTANOIN (DOJOLVI — Ultragenyx Canada Inc.)

Therapeutic Area: Long-chain fatty acid oxidation disorders

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that triheptanoin should not be reimbursed as a source of calories and fatty acids for the treatment of adult and pediatric patients with LC-FAOD.

Rationale for the Recommendation

CDEC reviewed available evidence from three studies: one open-label, single-arm, phase II study (Study CL201, N = 29); one ongoing, open-label, long-term extension study (Study CL 202, N = 75); and one double-blind, randomized controlled study (Gillingham et al., N =16). There were no pre-specified primary and secondary endpoints 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 (hospitalizations, emergency department/acute care visits or emergency interventions for rhabdomyolysis, hypoglycemia or cardiomyopathy). These results were mostly driven by the hospitalization component. In Study CL202, only patients who were rolled over from CL201 showed overall notable improvement in the annualized rate of major clinical events (difference in mean of 0.80 events per year). Studies CL201 and CL 202 contained several key limitations and biases, which make the reported results highly uncertain. These limitations, compounded with the heterogenous nature of the disease progression, are likely to bias the reported results in favour of triheptanoin. The double-blind RCT (N = 16) conducted by Gillingham et al. (2017) was powered only for the outcome of total energy expenditure. This study failed to show superiority of triheptanoin compared to trioctanion, an even-carbon medium-chain triglyceride, in total energy expenditure after 4-months of treatment.

Patients identified the need for a treatment 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; reduced hospitalizations; and improved quality of life. At this time, there is no evidence showing superiority of triheptanoin over other sources of medium chain triglycerides (MCT) for clinically relevant endpoints of mortality, morbidity (e.g., clinical events, or hospitalization), or HRQoL. The available evidence does not adequately address the question of whether triheptanoin improves relevant outcomes and unmet needs for patients with LC-FAOD compared to standard of care. Due to the significant risk of bias, potential confounding factors, and statistical uncertainty, it cannot be stated with confidence whether any benefit observed in the trials is attributable to triheptanoin treatment.

Discussion Points

- LC-FAODs are rare disorders with potential life-threatening complications. Current therapy consists of dietary optimization and even-chain MCT products.
- Clinical experts anticipate that, in clinical practice, triheptanoin would be primarily used for more severe cases of LC-FAODs, or as second-line therapy after even-chain MCT products. The clinical experts consulted on this review emphasized the unmet need in previously undiagnosed patients who present with acute, life-threatening cardiovascular or metabolic decompensation. They noted that use as a first-line treatment may be considered in select patients presenting with such life-threatening symptoms of LC-FAODs, which are most often seen, but not limited to, infants. The clinical experts consulted on the review indicated that there is a body of anecdotal evidence to suggest that triheptanoin can be useful in certain patients. Due to limitations described with the reviewed evidence and the nature of the study design employed, CDEC was unable to identify which patients may benefit the most from this treatment.
- CDEC considered that the majority of patients (≥ 90%) enrolled in the studies received prior treatment with a MCT formulation. As such, there is no evidence to support the use of triheptanoin as a first-line treatment for most patients with LC-FAODs.
- CDEC noted that none of the studies measured the effect of triheptanoin on survival. In addition, the HrQoL data were associated with high uncertainty due to the limitations and biases described in the Background – Critical Appraisal section. These were noted as important outcomes in the patient group input.

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 a medium-chain triglyceride 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 one open-label, single-arm Phase II study; one ongoing, open-label, extension study; and one double-blind randomized controlled trial.
- Patients' perspectives gathered by one patient group, MitoAction.
- Input from public drug plans that participate in the CADTH review process.
- Five clinical specialists with expertise diagnosing and treating patients with LC-FAOD.
- Input from one clinician group, the Canadian Association of Centers for the Management of Hereditary Metabolic Disorders (Association Canadienne des Centres de Treatment Pour Les Maladies Metaboliques Hereditaire).
- A review of the pharmacoeconomic model and report submitted by the sponsor

Stakeholder Perspectives

Patient Input

One patient group, MitoAction (Massachusetts, USA), 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, 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.

Ideal outcomes for the patient community include increased energy levels which leads to more physical activity, improved cognitive functioning, decreased stress on organ systems and reduced hospitalizations. This provides for an enhanced quality of life and independence for patients. MitoAction notes with proper treatment and disease management, the hope is 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 positive response and 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, in general, triheptanoin would 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 response is seen, triheptanoin treatment would be expected to continue upon hospital discharge.

According to the clinical experts, it is appropriate for a patient who starts triheptanoin to receive an adequate trial and be evaluated annually for improvement or maintenance of effect, though initial evaluations may be more frequent (e.g., every 3 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, quality of life, etc.). For example, in infants presenting with catastrophic events, survival would be a relevant outcome, and follow-up will be performed frequently. In stable older children and adults, follow-up may be performed every 6-12 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 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 currently, 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 medium-chain triglyceride.

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 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 CoA dehydrogenase (LCHAD) and mitochondrial trifunctional protein deficiencies are at risk of developing retinopathy and peripheral neuropathy. They added that neither MCT supplementations nor triheptanoin treat these symptoms.

Drug program input

Input was obtained from the jurisdictions participating in CADTH reimbursement reviews. The following were identified as key factors that could impact the implementation of recommendations:

- Availability of tests to diagnose LC-FAOD.
- Place in therapy of triheptanoin.
- Eligibility criteria for treatment with triheptanoin.
- Assessment criteria for measuring therapeutic response.

The clinical experts consulted by CADTH provided responses that can be found in the Drug Program Input section.

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 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. Patients must have had severe LC-FAOD with confirmed diagnosis of CPT II, VLCAD, LCHAD or 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 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 CACT deficiency. The study consists of three cohorts: 1) patients who had previously participated in CL201 (CL201 Rollover cohort, N = 24), 2) patients who failed conventional therapy and continued to exhibit clinical manifestations of LC-FAOD (Triheptanoin-Naïve cohort, N = 20), and 3) patients who participated in other programs to access triheptanoin, such as investigator-sponsored trials (ISTs) or compassionate use (IST/Other cohort, N = 31). All three 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 CL202. Data presented in this report reflect an interim analysis with a cutoff date of June 1, 2018; the mean duration of treatment was 25.92 months overall. The mean duration for each treatment cohort was as follows: 23.01 months for the CL201 Rollover (excludes CL201 study duration), 15.68 months for Triheptanoin-naive, and 34.77 months for the IST/Other cohorts.

The study by Gillingham et al. (2017, N=32) was a double-blind RCT that investigated whether triheptanoin therapy (an odd-chain fatty acid triglyceride) 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 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 two 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 age of patients in CL201 and CL202 were younger than patients enrolled in the Gillingham et al. (2017) trial. The two sponsor-funded trials enrolled mostly pediatric patients (< 18 years); the mean age was 12.06 years (standard deviation [SD] 13.21) in CL201, and 13.87 years (SD 13.19) in CL202. The mean age in the Gillingham et al. (2017) study was 24.75 years (SD 14.3). The most common LC-FAOD type diagnosed in the patients enrolled in CL201 and 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 CL202), the majority of patients enrolled in all three studies had received prior treatment with a MCT formulation, and all were being treated with dietary measures. In CL201 and CL202, approximately 65% of patients were receiving carnitine supplementation. Prior to enrolment, patients in the CL201 study had received approximately 17% of DCI as medium chain fat from MCTs.

In study CL201, patients were on average 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 to 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, though on average, most patients consumed over 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 endpoints; rather, the study grouped endpoints as key or supportive. Numerous key endpoints were measured for several disease areas; the following clinical outcomes, relevant to this review, were assessed: major clinical events (MCEs; hospitalizations, emergency room/acute care visits, or emergency interventions for rhabdomyolysis, hypoglycemia, or cardiomyopathy), exercise intolerance (12-minute walk test, cycle ergometry), functional disability and cognitive development (SF-10, SF-12), and cardiac function (echocardiogram [echo]).

The primary endpoint in study CL202 was the annualized LC-FAOD major events rate inclusive of rhabdomyolysis, hypoglycemia, and cardiomyopathy events. Annualized duration of total MCEs was considered a secondary efficacy endpoint, 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 (TEE), cardiac function (as measured by echo), 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 endpoints and parameters which were deemed to show favourable changes for triheptanoin according to the trial reports/publications have been included in this summary. In addition, none of the results discussed below were adjusted for multiplicity, as such, designating differences as ‘statistically significant’ have been avoided. Of note, none of the three 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

Major clinical events were not measured as part of the efficacy analyses in the Gillingham et al. (2017) study. Major clinical events were defined in both CL201 and CL202 as rhabdomyolysis, hypoglycemia, or cardiac disease events caused by LC-FAOD, or an intercurrent illness complicated by LC-FAOD, resulting in any hospitalization, emergency room (ER)/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 as well as separately for major rhabdomyolysis events, hypoglycemia events, and events due to decompensation of cardiomyopathy. Of note, the majority of MCEs reported in both CL201 and 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 his or her own control. In study CL201, medical history from 18 months (78 weeks) prior to study entry was collected to establish a pre-triheptanoin comparison, and was compared to 78 weeks of triheptanoin treatment. In study CL202, historical medical data was collected for patients in the CL-201 Rollover and Triheptanoin-Naïve cohorts. Statistical comparisons were made between data collected from 18 months prior to triheptanoin treatment and the first 36 months (CL201 Rollover cohort, inclusive of treatment received during CL201) or 18 months (Triheptanoin-Naïve cohort) of study treatment. No statistical comparisons were made for the IST/Other cohort in CL202 due to lack of pre-triheptanoin data.

In study CL201, a reduction in annualized event rates and event days were seen across all three 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 endpoint, 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 endpoints), a reduction was generally seen with triheptanoin treatment across all comparisons, but none were notably significant. In the Triheptanoin-Naïve cohort of 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 two relevant subgroups, identified in the CADTH systematic review protocol, were analyzed in both CL201 and 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 CL202. For subgroup analyses based on LC-FAOD diagnosis subtype, results across all diagnosis groups in CL201 were consistent with those seen with the overall population, except for patients with TFP deficiency. For this one subtype, a reduction in annualized event rate, but not in annualized event duration, was seen. Similarly, for both CL201 Rollover and Triheptanoin-Naïve cohorts of study CL202, consistent results 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 CL201 and 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 two 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 three 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, where the mean annualized event days appeared to increase with treatment, though median days decreased. This may be due to the highly skewed distribution of annualized event days observed in this cohort. In the Triheptanoin-Naïve cohort of study CL202, a heavily skewed distribution was observed which limited the interpretability of results. None of the changes observed in hospitalizations were significant.

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

Emergency Department Use

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

Health-Related Quality of Life

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 standard deviation 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/cohort.

In 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%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 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 three cohorts.

In the CL201 Rollover cohort of CL202, SF-10 PHS scores appeared to decline over the 18 months of treatment during CL202; however, scores remained above baseline taken prior to starting triheptanoin in CL201. The SF-10 PSS scores remained generally stable from baseline through CL202; these scores were similar to the population norm. For SF-12v2, PCS scores during 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-Naïve cohort, the baseline mean PHS scores for SF-10 was lower than the population norm, indicating impairment. Scores appeared to improve over time and was 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 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 12-minute walk test (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 confidence intervals (CIs), reducing the certainty of the results. The only notable improvement in the 12MWT parameters was in the energy expenditure index (EEI) from baseline to Week 18, though baseline EEI was already within the normal range as identified in the study (0.14 to 0.89 beats/m).

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 two treatment groups was in maximum heart rate (HR), where the mean difference in change from baseline was 6.98 beats per minute (95% CI, 0.34 to 13.63), in favour of triheptanoin. No difference between the two treatment groups was seen for VO2 or peak double product (a marker of cardiac workload measured by multiplying systolic blood pressure by heart rate); systolic blood pressure remained constant 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 two treatment groups was seen in test results.

Cardiac Function Parameters

Cardiac function was measured using echocardiography in all three included studies. In study CL201, echo was performed on all patients at baseline and 35 patients at Week 24. At baseline, mean left ventricular ejection fraction (LVEF) was within the normal rage 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 echo parameters. In all three cohorts, the mean LVEF at baseline was also within the normal range.

In the Gillingham et al. (2017) study, echocardiogram was assessed in 21 patients (n=10 triheptanoin, n=11 trioctanoin). After 4 months of treatment, a difference between the two 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 two 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. Of note, all except for one patient had normal cardiac function at baseline; the majority of the observed changes occurred within the normal range.

Harms Results

All or almost all (98.7%) of patients enrolled in studies CL201 and CL202, respectively, reported at least one treatment-emergent adverse event (TEAE). Although the total number of patients who experienced at least one TEAE was not reported in the Gillingham et al. (2017) study, it appears that the majority of patients did experience one or more TEAEs; similar frequency of various AEs were generally seen between the triheptanoin and trioctanoin treatment groups. Of note, complications of the underlying LC-FAOD (e.g., rhabdomyolysis) were also captured as an AE in all three 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, GI-related (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 MCEs that were also reported as a SAE. In study CL202, the proportion of patients who experienced at

least 1 SAE during the study were similar across the three 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. Across the three studies, 2 deaths were reported, 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 three studies. According to growth measures collected throughout the study, no clinically significant changes in Z-scores for weight were seen (in pediatric patients for CL201 and CL202), and in the Gillingham et al. (2017) study, no difference was noted between the two 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 CL202 interim data and is unable to provide critical appraisal of the updated analysis. The additional results are included in Appendix 5 of the CADTH Reimbursement Report; these results have not been assessed by CADTH.

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 under the *Clinical Evidence – Results; Critical Appraisal* section of this 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, where each patient served as his/her 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 two 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 (≥ 90%) in studies CL201 and the CL201 Rollover and Triheptanoin-Naïve cohorts of 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 due to low enrolment numbers in study CL202, and these patients were excluded from the CL201 and Gillingham et al. (2017) trials. 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 the Hutterite communities, but data on the efficacy of triheptanoin in these groups are lacking.[11,12] 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 three trials, the sample size of each study and treatment group/cohort were small. As a result, differences in one or two 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 three trials employed a hierarchical testing procedure or strategy to control for the overall type I error rate; no adjustments 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 which 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 (MID) has not been identified in the LC-FAOD population for SF-10 or SF-12, nor have these test been validated in patients with LC-FAOD. 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 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 studies CL202 (except for the CL201 Rollover cohort) and Gillingham et al. (2017), 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 as 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 randomized controlled trial (RCT) by Gillingham et al. (2017) did not include endpoints which were deemed as important by clinicians and patient groups, including survival, clinical events, symptoms such as fatigue, or HRQoL. Thus, the relative efficacy of triheptanoin compared to 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

Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis 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 (SoC) consisting of over-the-counter medium chain triglyceride (MCT) oil
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (97 years)
Key data source	• 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 major clinical events (MCEs) including rhabdomyolysis, hypoglycemia, cardiomyopathy; frequency and severity of gastroenteritis adverse events; and SF-10 and SF-12 scores. • Costs of major clinical events and gastroenteritis were derived from OCCI and CIHI; disutilities were derived from published literature.
Key limitations	• 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 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 CL201 and may not reflect the utility of a patient who has failed triheptanoin. • 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 CL201, a 78-week trial, and does not consider other potential benefits with triheptanoin involving energy expenditure. • The model fails to adequately consider patients who do not respond to triheptanoin. Discontinuation of triheptanoin was based on the observed discontinuation in CL201, in which 4 patients discontinued due to AEs, not on account of a non-response to treatment. Examination of the individual patient responses reveals that about half of patients did not respond to triheptanoin based on their rates/duration of MCEs, a fact not accounted for in the model.

Component	Description
	• 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.
CADTH reanalysis results	• CADTH made one change for the revised base case that involved deriving utility values solely from the SF-12 measure. In the paper 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. • In the CADTH base case, the ICER for triheptanoin is $1,347,825 per QALY compared with SoC; 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. • 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 having 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.

CIHI = Canadian Institute for Health Information; ICER = incremental cost-effectiveness ratio; inc. = incremental; 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; SoC = standard of care; 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 three-year total of $150,522,015. CADTH found the budget impact to be sensitive to the prevalence of LC-FAODs.

Canadian Drug Expert Committee (CDEC) Information

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.

Meeting Date: August 18, 2021

Regrets

Two of expert committee members did not attend.

Conflicts of Interest

None