CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

triheptanoin (Dojolvi)

Ultragenyx Canada Inc

Indication: Long-chain fatty acid oxidation disorders

September 23, 2021

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0684-000
Brand name (generic)	Dojolvi (Triheptanoin)
Indication(s)	Long-chain fatty acid oxidation disorders
Organization	The Hospital for Sick Children
Contact information[a]	Name: Dr Andreas Schulze

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☐
	No	☒

I am a professor of Pediatrics and Biochemistry at the University of Toronto and a clinician scientist at the Hospital for Sick Children. For 29 years, I am treating patients with LC-FAODs. There has major progress been made since the 90ies of last century; in diagnosis by means of acylcarnitine analysis with tandem mass spectrometry allowing early detection via newborn screening, and in treatment using medium chain triglyceride (MCT) containing nutritional products and formulas. Still, there are significant unmet medical needs for this patient group. They still die with sudden cardiac arrest/arrhythmia, they still may develop hypertrophic cardiomyopathy and/or rhabdomyolysis. They still are at risk for hypoglycemia. And all the above combined with frequent emergency room visits and hospital admissions during infancy and early childhood leads to a large burden of the disease both for the patients and their families but also for the society at large.

Triheptanoin is a new treatment that can change that. I am personally am very disappointed that CADTH concluded to recommend not to reimburse this treatment and that despite of the involvement of my metabolic colleagues and my self in the process.

Here I am listing three major aspects:

1. The mechanism and biological rational of action of Triheptanoin as treatment for LC-FAODs, a triglyceride with three odd-chain fatty acids, has been demonstrated in the laboratory quite convincingly by the late Charles Rowe.

2. The studies performed by Ultragenyx (CL101 and 201), but also the Gillingham study (Gillingham et al 2017), the study from Guffon et al. (Guffon et al 2021) and the observations and arguments from the LC-FAOD consortium (lead author Jerry Vockley) have all been able to demonstrate and rationalize the beneficial effect of Triheptanoin treatment (Vockley et al 2015; Vockley et al 2016; Sklirou et al 2020; Vockley 2020; Vockley et al 2021).

3. Concordance of theoretical medical concept with clinical observation has to be sufficient to grant patients with ultra-rare conditions like LC-FAODs access to crucial new treatments.

If CADTHs recommendation not to reimburse is upheld, our patients in Canada will be deprived from a treatment that patients in the US and Europe have access to. Even if I can understand the intention of CADTH to have the highest levels of evidence, like the one gets from RCT trials, that is not realistic in the orphan drug realm. We have limited impact on how pharmaceutical industry conducts clinical trials. After drugs get approval by FDA and EMA, no pharmaceutical company would set up a

clinical trial only to meet Canadian requirements, and we would not even be able to recruit enough patients. If CADTHs recommendation is upheld our patients are at the losing end.

Gillingham MB, Heitner SB, Martin J, et al (2017) Triheptanoin versus trioctanoin for long-chain fatty acid oxidation disorders: a double blinded, randomized controlled trial. J Inherit Metab Dis 40: 831-843.

Guffon N, Mochel F, Schiff M, De Lonlay P, Douillard C, Vianey-Saban C (2021) Clinical outcomes in a series of 18 patients with long chain fatty acids oxidation disorders treated with triheptanoin for a median duration of 22 months. Mol Genet Metab.

Sklirou E, Alodaib AN, Dobrowolski SF, Mohsen AA, Vockley J (2020) Physiological Perspectives on the Use of Triheptanoin as Anaplerotic Therapy for Long Chain Fatty Acid Oxidation Disorders. Front Genet 11: 598760.

Vockley J (2020) Long-chain fatty acid oxidation disorders and current management strategies. Am J Manag Care 26: S147-S154.

Vockley J, Charrow J, Ganesh J, et al (2016) Triheptanoin treatment in patients with pediatric cardiomyopathy associated with long chain-fatty acid oxidation disorders. Mol Genet Metab 119: 223-231.

Vockley J, Longo N, Madden M, et al (2021) Dietary management and major clinical events in patients with long-chain fatty acid oxidation disorders enrolled in a phase 2 triheptanoin study. Clin Nutr ESPEN 41: 293-298.

Vockley J, Marsden D, McCracken E, et al (2015) Long-term major clinical outcomes in patients with long chain fatty acid oxidation disorders before and after transition to triheptanoin treatment--A retrospective chart review. Mol Genet Metab 116: 53-60.

Expert committee consideration of the stakeholder input

2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☐
	No	☒

If the recommendation of our experts of Inborn Errors of Metabolism for the management of LC-FAODs would have been acknowledged the recommendation would have been Recommend Re-imbursement for specificized groups of patients with LC-FAOD.

Clarity of the draft recommendation

3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐

The reason stated is the lack of studies to allow evidence-based assessment. Although clearly stated that makes the reasoning not better.

4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☐
	No	☒

If not, please provide details regarding the information that requires clarification.

5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☐
If not, please provide details regarding the information that requires clarification.		

[a] CADTH may contact this person if comments require clarification.

Appendix 2. Conflict of Interest Declarations for Clinician Groups

- To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest.
- This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the feedback from patient groups and clinician groups.
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A. Assistance with Providing the Feedback		
1. Did you receive help from outside your clinician group to complete this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your clincian group to collect or analyze any information used in this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
B. Previously Disclosed Conflict of Interest		
3. Were conflict of interest declarations provided in clinician group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section C below.	No	☐
	Yes	☒
If yes, please list the clinicians who contributed input and whose declarations have not changed: • Dr Andreas Schulze		

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0684-000
Brand name (generic)	Dojolvi (Triheptanoin)
Indication(s)	Long-chain fatty acid oxidation disorders
Organization	The Garrod Guidelines Committee
Contact information	Name: Pranesh Chakraborty/ Graeme Nimmo

Stakeholder agreement with the draft recommendation

1. Does the stakeholder agree with the committee's recommendation?	Yes	☐
	No	☒

While we acknowledge that the current body of literature to support Triheptanoin use in LC-FAODs is limited, a recommendation of "do not reimburse" will essentially remove the possibility for clinical biochemical geneticists in Canada to prescribe this medication. This has two main implications:

This treatment will not be available for those who are unable to tolerate the current standard of care (MCT oil) or did not respond optimally to standard treatment. Based on the clinical expertise of some committee members in treating LC-FAODs, Triheptanoin can be lifesaving in those facing severe cardiac complications or life-threatening episodic decompensations as a result of the underlying LC-FAODs.

Given the medication is already approved in a large market (USA), the motivation/incentive for the pharmaceutical company to continue to fund trials or compassionate use of this medication is low/non-existent for a small market like Canada. This means the likelihood of the evidence for the effectiveness of triheptanoin is unlikely to expand further; importantly it also removes the possibility of Canadian investigator-led studies.

We suggest a recommendation to consider conditional reimbursement. For example, setting clear treatment eligibility criteria and a plan for annual monitoring of clinical stability/ improvement for treatment renewal. Consideration can be given to restricting prescribing access to treating physicians subspecialized in inherited metabolic diseases.

Expert committee consideration of the stakeholder input

2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☐
	No	☒

If not, what aspects are missing from the draft recommendation?

On page 4 of the CADTH reimbursement review, it is noted that "clinical experts anticipate that, in clinical practice, triheptanoin would be primarily used for more severe cases of LCFAODs, 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 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 Garrod Guideline Committee submitted our review on April 22, 2021. It is summarized on pages 5-6 of the CADTH reimbursement review. We noted that patients with severe LC-FAOD have the

greatest unmet needs as they can present with symptoms regardless of good compliance to standard treatment and that the drug under review would address some of the unmet needs of these patients.

Hence, the recommendation not to reimburse is against the advice provided by clinical experts and our committee's recommendations.

Clarity of the draft recommendation

3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐

If not, please provide details regarding the information that requires clarification.

4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☐
	No	☒

If not, please provide details regarding the information that requires clarification.

Please see our response above.
As outlined in our previous responses, the recommendations do not address action plans for severe LC-FAOD patients that do not respond or do not respond optimally to treatment with the currently approved therapy (even-chain MCT products).

5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☐

If not, please provide details regarding the information that requires clarification.

Not applicable. The recommendation is not to reimburse.

In January 2021, Health Canada launched a national online engagement to let Canadians — especially patients with rare diseases, their families, and other interested stakeholders — share their views and ideas for a national strategy. This document noted that "because of the small numbers of people with rare diseases, meeting the usual standard of evidence for drug approvals is rarely possible. Many participants said rare-disease drugs need to be assessed differently than drugs for common diseases. People overwhelmingly ranked innovative approaches to approval and coverage as the most important option for building a better evidence base" (https://www.canada.ca/en/health-canada/programs/consultation-national-strategy-high-cost-drugs-rare-diseases-online-engagement/what-we-heard.html#a7).

We strongly urge CADTH to consider conditional reimbursement models for triheptanoin and methods/mechanisms to assess real-world effectiveness in individual patients and generally (Winquist et al. Value in Health. 2012;15(6):982-6. doi: 10.1016/j.jval.2012.06.009). Many of us are lead investigators with the Canadian Inherited Metabolic Diseases Research Network (CIMDRN), a multi-stakeholder network that aims to generate evidence regarding interventions and outcomes for Canadian children with rare inherited metabolic diseases and would be happy to assist in assessing real-world effectiveness of triheptanoin in this patient population.

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	Yes	☐
If yes, please detail the help and who provided it.		
3. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		

B. Previously Disclosed Conflict of Interest		
4. Were conflict of interest declarations provided in clinician group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section C below.	No	☐
	Yes	☒
If yes, please list the clinicians who contributed input and whose declarations have not changed: • Graeme Nimmo • Shailly Jain • Potter, Murray • Andreas Schulze • Sylvia Stockler		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	Michal Inbar Feigenberg
Position	Physician, Division of Clinical and Metabolic Genetics, the Hospital for Sick Children, Toronto, ON

Date	*22-09-2021*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have a direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
I do not have a new payment to disclose. I will participate as a site PI in a clinical study done by Ultagenyx that is related to LC-FAOD. I am in the process of submitting this to our hospital's REB committee.	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 2

Name	Pranesh Chakraborty
Position	Physician and Chief, Division of Metabolics and Newborn Screening, CHEO, Ottawa, ON Medical Director, Newborn Screening Ontario, CHEO, Ottawa, ON
Date	*23-09-2021*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Ultragenyx – I have not received a payment but have agreed to provide them advice in which case I would receive reimbursement	☒	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 3

Name	*Please state full name*
Position	*Please state currently held position*

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	
Brand name (generic)	Triheptanoin (Dojolvi)
Indication(s)	For pediatric patients with LC-FAOD
Organization	Shared Health, Winnipeg
Contact information[a]	Name :Nicole Aylward, RD

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☐
	No	☒
This product is currently being used for the treatment of pediatric patients with severe LC-FAOD, this decision will affect the future care of these pts.		
Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☐
	No	☒
It appears that there was some agreement that triheptanoin is indicated for the treatment of moderate to severe LC-FAOD, however the recommendation does not separate out the severity classes of disease.		
Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☐
	No	☒
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☐
	No	☒
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☒
It would be helpful to look at the disease severity separately. As this is a rare disease, anecdotal evidence should be factored into the decision. It is clear that he patient group has seen some improvement with the use of triheptanoin.		

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A. Assistance with Providing the Feedback		
2. Did you receive help from outside your clinician group to complete this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
3. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		

B. Previously Disclosed Conflict of Interest		
4. Were conflict of interest declarations provided in clinician group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section C below.	No	☒
	Yes	☐
If yes, please list the clinicians who contributed input and whose declarations have not changed: • Clinician 1 • Clinician 2 • *Add additional (as required)*		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	*Nicole Aylward*
Position	*Metabolic Dietitian*
Date	*16/09/2021*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.
Conflict of Interest Declaration	

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 2	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

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Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 3	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

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Add or remove rows as required	☐	☐	☐	☐

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0684-000
Brand name (generic)	**Triheptanoin** (Dojolvi)
Indication(s)	**Long-chain fatty acid oxidation disorders (LC-FAOD)**
Organization	Stollery Children's Hospital University of Alberta Hospital
Contact information[a]	Name: Saadet Andrews [redacted]

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☐
	No	☒
Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.		

Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☐
	No	☒
Triheptanoin will be important treatment in patients who are not responding well to MCT oil. This treatment is to prevent recurrent admissions or metabolic decompensation to improve patient outcomes. MCT is not well tolerated in patients with LC-FAOD. LC-FAOD patients have deficiencies of tricarboxylic acid cycle (TCA) intermediates, which is the major energy production pathway. Triheptanoin provides C7 to TCA to replenish TCA intermediate deficiency.		

Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☐
	No	☒
The recommendation summarizes that small number of patients were included into previous trials. These disorders are very rare and cannot include large number of patients. The current treatment is very challenging and not well tolerated to improve outcomes. One of the most important outcomes is the decreased number of hospital admissions which is a high morbidity for the patients and families.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☐
	No	☒
The CADHT listed few key factors that could impact implementation of recommendations (on page 6, under drug program input) without clear explanation why these could impact implementation. As a clinician treating these patients, there are no issues with the diagnosis and availability of diagnostic tests for LC-FAOD. There must be clear explanation why CADTH list these.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		

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	Yes	☒
If yes, please list the clinicians who contributed input and whose declarations have not changed: • Clinician Saadet Andrews • Clinician 2 • *Add additional (as required)*		

C. New or Updated Conflict of Interest Declarations

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Stakeholder information	
CADTH project number	SR0684-000
Brand name (generic)	Dojolvi (Triheptanoin)
Indication(s)	LC-FAOD treatment
Organization	Stollery Children's Hospital, University of Alberta, Alberta Health Services
Contact information[a]	Name: Dr. Shailly Jain

Stakeholder agreement with the draft recommendation		
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If yes, please list the clinicians who contributed input and whose declarations have not changed: • Clinician 1: Dr. Shailly Jain • Clinician 2 • *Add additional (as required)*		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.
Conflict of Interest Declaration	

CADTH

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0684
Name of the drug and Indication(s)	Triheptanoin (Dojolvi) as a source of calories and fatty acids for the treatment of adult and pediatric patients with LC-FAOD
Organization Providing Feedback	FWG

1. Recommendation revisions Please indicate if the stakeholder requires the expert review committee to reconsider or clarify its recommendation.		
Request for Reconsideration	**Major revisions:** A change in recommendation **category** or patient **population** is requested	☐
	Minor revisions: A change in reimbursement **conditions** is requested	☐
No Request for Reconsideration	**Editorial revisions:** Clarifications in recommendation **text** are requested	X
	No requested revisions	☐

2. Change in recommendation category or conditions Complete this section if major or minor revisions are requested
N/A

3. Clarity of the recommendation Complete this section if editorial revisions are requested for the following elements
a) Recommendation rationale
N/A
b) Reimbursement conditions and related reasons
N/A
c) Implementation guidance
For Discussion Point #2, it is requested that the language be revised and consistent with other negative recommendations where clinical experts suggest a subpopulation where the drug under review may be useful, but there is currently insufficient evidence to recommend funding. The last portion of this discussion point could be revised to: …"CDEC heard from clinical experts that there is potential that triheptanoin can be useful in certain patients; however, 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."

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0684-000
Brand name (generic)	triheptanoin
Indication(s)	Long-chain fatty acid oxidation disorders
Organization	Rare Disease Foundation
Contact information[a]	Name: Millan Patel, Chief Medical Officer

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☐
	No	☒

The recommendation states "There is a lack of long-term data on clinical effectiveness for triheptanoin" when the study CL 201 was an 18 month observation followed by 18 month intervention study. No company can afford to perform multi-decade trials and even in high payoff diseases like breast cancer, the longest trials are 5 years long so this is a factually correct and completely unreasonable statement that essentially condemns all rare disease patients with chronic intermittent presentations to have their needs unmet in perpetuity.

The recommendation states "…results from these two trials could be considered supportive, but cannot offer solid evidence of treatment benefits." This conclusion is correct if one is considering a homogenous disease with continuous readout, such as LDL-cholesterol levels. In this case, a basket of rare diseases with a chronic intermittent course, the committee failed to define what would constitute reasonable evidence. In not doing so, the committee introduces a 'traditionalist' type II error into their analysis. Given this body of evidence for a heterogeneous population in an extremely rare disease, we believe it is reasonable to conclude that this formulation is leading to significant treatment benefits.

We partially agree with the Cost-utility analysis and suggest revision of the draft to reflect approvability once a cost-effective threshold realistic to rare diseases has been met. A WTP threshold of $50,000 per QALY is reasonable for chronic, adult, often lifestyle diseases. We believe it would be appropriate to use a higher threshold for rare diseases of $150,000 to $500,000, depending on the specific disorder in question. Cost-utility analyses should also take a broader societal perspective into account as rare diseases affect whole families and typically result in very high out of pocket costs for caregivers that are not usually captured in standard analyses.

Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☐
	No	☒

Not applicable. We did not provide any input previously.

Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒

	No	☐
If not, please provide details regarding the information that requires clarification.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		

[a] CADTH may contact this person if comments require clarification.

Appendix 1. Conflict of Interest Declarations for Patient Groups

- To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest.
- This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the feedback from patient groups and clinician groups.
- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.

A. Patient Group Information	
Name	*Millan Patel, Rare Disease Foundation*
Position	*Chief Medical Officer*
Date	*14-09-2021*
☒	I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

B. Assistance with Providing Feedback		
1. Did you receive help from outside your patient group to complete your feedback?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your patient group to collect or analyze any information used in your feedback?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		

C. Previously Disclosed Conflict of Interest		
1. Were conflict of interest declarations provided in patient group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section D below.	No	☒
	Yes	☐

D. New or Updated Conflict of Interest Declaration

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Ultragenyx Canada Inc	☒	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0684-000
Brand name (generic)	Triheptanoin (Dojolvi)
Indication(s)	Long-chain fatty acid oxidation disorders
Organization	MitoAction
Contact information[a]	Name: Kira Mann

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☐
	No	☒

Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.

We disagree with the rationale for the CADTH recommendation based upon the finding that "the available evidence does not adequately address the questions of whether triheptanoin improves relevant outcomes and unmet needs for patients with LC-FAOD compared to standard of care." Patient testimony provided by MitoAction would indicate real-world patient experience pointed to significant improvements in factors most important to the patient community, including increased energy, avoided loss of muscle tone, protection of organs such as the liver and heart and decreased hospitalization.

In Canada there are estimated to be 455 individuals living with LC-FAOD and 14 babies born each year. While this number may seem small, for these 455 individuals and the parents of the newborns, having an affordable treatment option that provides improved quality of life and potential to prevent progression of a rare disease is critical. According to the World Health Organization, "catastrophic" health expenditures are those that cannot be afforded unless a household cuts down on basic necessities such as food, clothing, or education. For families living with the burden of a rare disease, having to pay out of pocket for treatments such as Dojolvi would be catastrophic, denying them access to treatment. Not having access to therapies that can reduce hospitalization, potentially reduce the long-term effects of chronic diseases such as LC-FAOD, will put undue strain on families and ultimately on the healthcare system as these patients will need to be treated for more dire complications.

Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☐
	No	☒

Patient testimony provided by MitoAction would indicate real-world patient experience pointed to significant improvements in factors most important to the patient community.

According to Health Canada, *Building a National Strategy for High-Cost Drugs for Rare Diseases: Discussion Paper for Engaging Canadians*, https://www.canada.ca/en/health-canada/programs/consultation-national-strategy-high-cost-drugs-rare-diseases-online-engagement/discussion-paper.html, one of the 3 key issues explored in assessing the need for a national strategy for rare disease drugs is "how to ensure decisions on covering high-cost drugs for rare disease are informed by the best evidence available, when evidence is often limited." Each of

the four recommendations to address this issue incorporated patient feedback of the real-world benefit of a rare disease drug and how it is working for the patient as a key component. While this national strategy is still in the planning phases, what is consistent in the findings and recommendations related to rare disease drugs, is the weight that real-world patient feedback should have in determining coverage. As such, in addition to the previous input provided by MitoAction, I provide additional testimonies from both Canadian and US patients and caregivers, further supporting the positive impacts of Dojolvi:

Michael, CPT2 Patient, Canada
"I am a 44-year-old man who was diagnosed at 12 with CPT2 Def. I was prescribed MCT at the time of my diagnosis. It did not work. Nothing worked until I was in the trail for C7 in 2006. It was a game changer. But I was only able to participate in the trial for 6 months. I have been trying since then to get on it, and after a lengthy 2-year process within Ontario, I finally started on 60ml a day in May of 2021. It is incredibly life changing! There is absolutely no comparison to MCT. Despite having had several periods in my life where I took MCT and felt no benefit, I took MCT for 3 months at the same dosage prior to starting Dojolvi so that we could directly compare. I am now more active than I have ever been in my life, and I have no symptoms. I was still symptomatic with the MCT in the 3 months prior. My apple watch trends, show my active calories are averaging over 1000 cal/day, exercising over 100 minutes/day. I can move more, and for longer than ever. I haven't even figured out my limits yet!"

Jenn, VLCAD Parent, Canada

"I would move heaven and earth to get my daughter what she needed. I don't understand why we would not allow for a treatment that may seem to provide limited benefit now, but can reduce the potential burdens on the healthcare system and families by treating these patients today, before they become critical."

Melissa, LCHAD Parent, Canada

"My daughter's body seems to adapt to MCT oil and it becomes ineffective. Dojolvi out of pocket is unaffordable. She's 2 years old and we've had 2 hospital admissions. When she gets sick, it disrupts our entire family. I feel like by not having access to Dojolvi we are playing Russian Roulette with her life. Cardiomyopathy doesn't always give you warnings and my biggest fear is that in time she's going to develop these life-threatening complications. We should be preventative first and not reactive. We are losing a lot of FAOD kids due to cardiomyopathy. Then we will be asking what we could have done. Well, we know what we could have done."

Fred, CPT2 Patient, US

"Imagine, if you will, not knowing whether you will ever have enough energy to get through the day. Imagine one minute doing whatever it is you are doing and then, the next minute, your location loses electricity and now you are stuck in place. It is nighttime and the room is dark. You can't move, unless you want to risk injuring yourself. You ask yourself, "What can I do?" But you know the answer, "Nothing." So, you stay in place, waiting for the electricity to return, hoping that it won't be too, too long before your body craves food and water and the opportunity to relieve yourself.
Well, that is what it is like, every minute of the day when you are living within the body of a person who has a metabolic defect that affects the body's ability to create energy. You never know when you are going to run out of energy and then your body tells you, "Lights out!" And there you are, struggling. Struggling to complete a task. Struggling to get yourself to a safe place so you can "crash." Struggling to find food in an attempt to get your body to function. Function, just a little bit, so

your body does not revolt and begin the downward spiral into rhabdomyolysis. Function enough so you don't need to go to the hospital. Function enough so you don't damage your kidneys. Function enough so you don't die.

That is what it is like every day without Triheptanoin.

With most other chronic disorders, there are warning signs, or ways to monitor and measure your disorder. Blood tests or machines can give you an idea of what you should be doing or how much of a medicine you need to take to keep symptoms at bay. Not so with fatty acid oxidation disorders. Like an electrical blackout, so occurs the loss of energy with these types of disorders. One minute you are functioning, the next second, you are not.

Since taking Triheptanoin, I have never had a metabolic break down. It works. It gets me through the day. Life is definitely not easy. I live a measured life. Since there is no way of measuring or monitoring my energy needs, I make sure I start my day taking the Triheptanoin. And then, I carefully go through the motion of the day. Figuring out how much activity I am going to do and then making sure I am eating and taking my oil is always weighing on my mind, every minute of every hour of every day.

Triheptanoin keeps me moving and alive."

Ali, VLCAD patient, US

"I was born with VLCADD and was immediately started on MCT oil. This oil is very helpful to many people, however to those like me it was just barely giving me energy. When I was 6 years old, I was switched to C7 oil (Dojolvi). In that same day, I was suddenly able to run around and play like a normal kid. My mom called it magic and I agree with her. I've been drinking C7 oil (Dojolvi) since then and have never looked back. The oil gave me the energy to thrive and succeed as a premed student who will one day help many others who have similar genetic abnormalities. Without the C7 oil (Dojolvi) I probably wouldn't be alive today."

Eileen, Trifunctional Protein Deficiency parent, Tasia VLCAD patient, Ali, VLCAD patient, US – Excerpt from joint statement to FDA, July 25, 2018

"Given the long-term problems associated with FAODs, including continued muscle weakness leading to supportive therapy such as walkers or wheelchairs, loss of vision in some patients, and risk to any patient who may have to undergo surgery with these conditions, only to mention a few, it is imperative that these patients have access to a treatment that may support metabolic health to provide proper energy in their daily lives, and prevent permanent liver and heart damage with often grave outcomes….Our further understanding is that FAOD patients who use UX007 (Dojolvi) can confirm that with continued use of UX007 (Dojolvi), patients often live with decreased hospitalizations, decreased incidence of cardiomyopathy and a better quality of life due to the way this medication sustains the metabolic system in patients like ourselves."

Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐

If not, please provide details regarding the information that requires clarification.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☐
If not, please provide details regarding the information that requires clarification.		

[a] CADTH may contact th s person f comments requ re c ar f cat on.

Appendix 1. Conflict of Interest Declarations for Patient Groups

- To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest.
- This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the feedback from patient groups and clinician groups.
- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.

A. Patient Group Information	
Name	*Kira Mann, MitoAction*
Position	*CEO*
Date	*23-09-2021*
☒	I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

B. Assistance with Providing Feedback		
1. Did you receive help from outside your patient group to complete your feedback?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your patient group to collect or analyze any information used in your feedback?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		

C. Previously Disclosed Conflict of Interest		
1. Were conflict of interest declarations provided in patient group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section D below.	No	☐
	Yes	☒

D. New or Updated Conflict of Interest Declaration

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

triheptanoin (Dojolvi)

Ultragenyx Canada Inc

Indication: Long-chain fatty acid oxidation disorders

January 7, 2022

CADTH

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0684
Name of the drug and Indication(s)	Triheptanoin (Dojolvi) as a source of calories and fatty acids for the treatment of adult and pediatric patients with LC-FAOD
Organization Providing Feedback	FWG

1. Recommendation revisions Please indicate if the stakeholder requires the expert review committee to reconsider or clarify its recommendation.		
Request for Reconsideration	**Major revisions:** A change in recommendation **category** or patient **population** is requested	☐
	Minor revisions: A change in reimbursement **conditions** is requested	☐
No Request for Reconsideration	**Editorial revisions:** Clarifications in recommendation **text** are requested	X
	No requested revisions	☐

2. Change in recommendation category or conditions Complete this section if major or minor revisions are requested
Please identify the specific text from the recommendation and provide a rationale for requesting a change in recommendation.

3. Clarity of the recommendation Complete this section if editorial revisions are requested for the following elements
a) Recommendation rationale
Please provide details regarding the information that requires clarification.
b) Reimbursement conditions and related reasons
Please provide details regarding the information that requires clarification.
c) Implementation guidance
Add a definition if possible of what acute life threatening events is defined as to assist in implementation, in criteria.

Outstanding Implementation Issues

In the event of a positive draft recommendation, drug programs can request further implementation support from CADTH on topics that cannot be addressed in the reimbursement review (e.g., concerning other drugs, without sufficient evidence to support a recommendation, etc.). Note that outstanding implementation questions can also be posed to the expert committee in Feedback section 4c.

Algorithm and implementation questions
1. Please specify sequencing questions or issues that should be addressed by CADTH (oncology only)
1. 2.
2. Please specify other implementation questions or issues that should be addressed by CADTH
1. 2.
Support strategy
3. Do you have any preferences or suggestions on how CADTH should address these issues?
May include implementation advice panel, evidence review, provisional algorithm (oncology), etc.