CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

Sodium phenylbutyrate and ursodoxicoltaurine (Albrioza)

(Amylyx Canada)

Indication: For the treatment of patients with amyotrophic lateral sclerosis (ALS)

July 8, 2022

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0711-000
Brand name (generic)	Albrioza (sodium phenylbutyrate and ursodoxicoltaurine)
Indication(s)	For the treatment of patients with amyotrophic lateral sclerosis (ALS)
Organization	The Canadian ALS Research Network (CALS)
Contact information[a]	Name: Dr. Geneviève Matte Neurologist, Centre Hospitalier de l'Université de Montréal Assistant Professor, Université de Montréal [redacted]

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

Members of the CALS Network are generally in agreement with the committee's reimbursement recommendation for sodium phenylbutyrate and ursodoxicoltaurine (PB-TURSO) and largely support the evidence-based reasoning for aligning the initiation criteria with the patient selection criteria in the CENTAUR study.

An important revision to initiation criterion 1.1. (have a diagnosis of definite ALS) is needed to clarify that a definite diagnosis does not have to be made using the revised El Escorial criteria. Simply deleting the "Implementation Guidance" column would be sufficient. As mentioned in our initial submission, anyone with a diagnosis of ALS according to Gold Coast criteria, confirmed by an ALS specialist could be considered for treatment with this drug. The clinical expert and CDEC both agreed that there is no physiological or pharmacological reason to predict that patients at other levels of the El Escorial diagnostic criteria (i.e., "probable" or "possible") would not respond to the treatment. We feel that a broader criterion for the diagnosis of ALS would be practical and reasonable.

We support the committee's position on pricing and would have expected the cost of PB-TURSO to be similar to IV edaravone.

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 Is our opinion that the initial input provided to CADTH by the CALS Network was considered by the committee when drafting the recommendation.

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

While the reasons for the recommendation are clearly stated, there are some cases where the recommendation does not fully align with the opinions of the clinical expert consulted by CADTH and CDEC. For example, both the clinical expert and CDEC agreed that "there is no physiological or pharmacological reason to predict that patients at other levels of the El Escorial diagnostic criteria (i.e., "probable" or "possible") would not respond to the treatment". However, the initiation criterion 1.1. requires a definite diagnosis of ALS. The revision suggested in Q1 above should rectify this misalignment.

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

The implementation issues have been clearly articulated and adequately addressed. Having said that, one concern is the difference in reimbursement criteria for alternative therapies (edaravone and riluzole). As the clinical expert consulted by CADTH stated (and the CDEC agreed with), "it is expected that PB-TURSO would be offered as add-on therapy in addition to riluzole and/or edaravone". Yet the initiation criteria for the various therapies do not align. There is no rationale for first-, second- or third-line treatments in ALS and these differences in reimbursement criteria could unintentionally lead to drug sequencing. Nevertheless, we understand the decision to align the reimbursement criteria for PB-TURSO with the patient population studied in the CENTAUR trial.

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

Please see responses to Q1, Q3 and Q4.

[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.
- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.
- For conflict of interest declarations:
  - Please 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.
  - Please note that declarations are required for each clinician that contributed to the input.
  - If your clinician group provided input at the outset of the review, only conflict of interest declarations that are new or require updating need to be reported in this form. For all others, please list the clinicians who provided input are unchanged
  - Please add more tables as needed (copy and paste).
  - All new and updated declarations must be included in a single document.

A. Assistance with Providing the Feedback		
2. Did you receive help from outside your clinician group to complete this submission?	No	☒
	Yes	☐
N/A		
3. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	☒
	Yes	☐
N/A		
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: • Dr. Agessandro Abrahao Junior • Dr. Ahmad (Amer) Alavian Ghavanini • Dr. Angela Genge • Dr. Ari Breiner • Dr. Christen Shoesmith • Dr. Colleen O'Connell • Dr. Collin Luk • Dr. Gordon Jewett • Dr. Ian Grant • Dr. Lorne Zinman • Dr. Nicolas Dupré • Dr. Sandrine Larue • Dr. Sylvie Gosselin		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	*Dr. Theodore Mobach*
Position	*Neurologist, ALS clinic director, University of Calgary*
Date	*04-07-2022*
☒	**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**
Amylyx	☐	☒	☐	☐
Mitsubishi Tanabe	☒	☐	☐	☐
Biogen	☐	☐	☒	☐

New or Updated Declaration for Clinician 2	
Name	*Dr. Geneviève Matte, MDCM, FRCPC, CSCN Diplomate (EMG)*
Position	*Neurologist (Centre Hospitalier de l'Université de Montréal), Assistant Professor (Université de Montréal)*
Date	*07-07-2022*
☒	**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**
Amylyx Pharmaceuticals	☒	☐	☐	☐
Mitsubishi-Tanabe Pharma Canada	☐	☐	☒	☐

New or Updated Declaration for Clinician 3	
Name	*Dr. Sean Taylor*
Position	*Attending neurologist NSHA Dalhousie University*
Date	*07-07-2022*
☒	**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**
Bayer Pharmaceuticals	☒	☐	☐	☐

New or Updated Declaration for Clinician 4	
Name	*Dr. Daniel Fok*
Position	*Neurologist (Kelowna General Hospital), Clinical Assistant Professor, University of British Columba – Southern Medical Program*
Date	*07-07-2022*
☒	**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**
Amylyx	☒	☐	☐	☐
Sanofi Genzyme	☒	☐	☐	☐

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0711
Name of the drug and Indication(s)	Sodium phenylbutyrate and ursodoxicoltaurine (Albrioza) Indication: For the treatment of patients with amyotrophic lateral sclerosis (ALS)
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	☐
	No requested revisions	X

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

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
Please provide high-level details regarding the information that requires clarification. You can provide specific comments in the draft recommendation found in the next section. Additional implementation questions can be raised here.

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.

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0711-000
Brand name (generic)	ALBRIOZA (sodium phenylbutyrate and ursodoxicoltaurine)
Indication(s)	For the treatment of patients with amyotrophic lateral sclerosis (ALS)
Organization	ALS Society of Canada
Contact information [a]	Name: Lauren Poplak Title: Manager, Stakeholder Relations [redacted] [redacted]

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

The ALS Society of Canada agrees with the committee's draft recommendation to reimburse sodium phenylbutyrate and ursodoxicoltaurine (PB-TURSO) with conditions. However, we are very concerned that the following initiation criteria may result in inequitable access for people living with ALS.

1.1. Have a diagnosis of definite ALS
1.2. Have had ALS symptoms for 18 months or less

Equitable access to innovative therapies is a critical issue for people and families affected by ALS across Canada. We recommend the following editorial revisions to initiation criterion 1.1. and 1.2. in order to align them with the realities of the diagnosis and treatment of ALS.

1.1 Have a diagnosis of definite ALS, *as determined by a Canadian ALS clinician, using any medically accepted diagnosis criteria.*
1.2 Have had ALS symptoms for 18 months or less, *with flexibility by a Canadian ALS clinician to prescribe where the time to diagnosis exceeds 18 months.*

Our rationale for the suggested wording changes to 1.1 and 1.2 are as follows:

It is important to clarify that a definite diagnosis does not have to be made using the revised El Escorial criteria. ALS clinicians should be able to use any medically accepted diagnosis criteria to confirm the diagnosis. Canadians living with ALS should not need to wait until their progression reaches a specific state before being allowed access to a therapy.

- People living with ALS measure time by loss – **loss of function and loss of life.** No person should lose their life while waiting to access a proven therapy. Given how quickly ALS can progress, requiring a specific level of progression before enabling access to a therapy **does not align with the right to health and life of Canadians.**
- In our initial submission, most **patients taking PB-TURSO** (80%) and **caregivers** (89%) of people on the treatment would recommend that it be made accessible to people living with ALS.

- As one patient stated, ***"I would like to see everyone in the ALS community get it,"*** while another shared that **"*many patients before us have died because time 'ran out' for them. You must understand that delaying the availability of potential drugs can be a death sentence for us."***
- The input from the clinical expert consulted by CADTH noted that **all patients diagnosed with ALS would be suitable for treatment with PB-TURSO**. Furthermore, the clinical expert suggested that **patients who are most suitable for treatment be decided based on clinician judgement** rather than functional rating scores or pulmonary function tests.
- Lastly, the clinical expert stated **there is no physiological or pharmacological reason to predict that patients at other levels of the El Escorial diagnostic criteria (i.e., "probable" or "possible") would not respond to the treatment** – a point that the CDEC agreed with.

With no confirmed biomarkers, and given the heterogeneity of ALS, current methods for diagnosing ALS involve ruling out other diseases that share similar symptoms – timelines for which can differ depending on the province you live in and how readily available appropriate medical testing is. Time-to-diagnosis criterion does not reflect the real-world experience of ALS and should not become a barrier to access.

- Four provinces within Canada have a time-to-diagnosis **that is longer than 18 months**, representing a large population of where people affected by ALS live[1].
- Given the heterogeneity of the disease, people living with ALS have shared that often symptoms – especially those early in the diagnosis process – may not have been attributed to ALS, but rather other health issues. As a result, it took **years before a diagnosis of ALS was confirmed despite having early symptoms**.
- Many people affected by ALS have **expressed great concern over criterion 1.2**. The anticipated impact is that an 18-month timeframe will **deny access to the majority of people affected by ALS.**
- A diagnosis of ALS and the realities of living with the disease already have a profound and pervasive effect on the lives of those who are struck by this devastating disease. People living with ALS should not lose access to a new therapy **because the province they live in has inequitable access to resources needed to confirm a diagnosis in less than 18 months**.

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	☒

In our opinion, two of the initiation criteria in particular (1.1. and 1.2.) do not address the urgency or impact of the disease we communicated, and therefore the recommendation does not demonstrate that the committee considered the entirety of our patient group input submission.

Clarity of the draft recommendation

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

The reasons for the recommendation are clearly stated, but as noted above, contradict to some extent the advice provided by the clinical expert consulted by CADTH and agreed upon by the CDEC.

[1] Hodgkinson, V. L., Lounsberry, J., Mirian, A., Genge, A., Benstead, T., Briemberg, H., Grant, I., Hader, W., Johnston, W. S., Kalra, S., Linassi, G., Massie, R., Melanson, M., O'Connell, C., Schellenberg, K., Shoesmi h, C., Taylor, S., Worley, S., Zinman, L., & Korngut, L. (2018). Provincial Differences in the Diagnosis and Care of Amyotrophic Lateral Sclerosis. The Canadian journal of neurological sciences. Le journal canadien des sciences neurologiques, 45(6), 652–659. https://doi.org/10.1017/cjn 2018.311

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

While they have been clearly articulated, the following implementation issues have not been adequately addressed in the recommendation:

- There is no physiological or pharmacological reason to predict that patients at other levels of the El Escorial diagnostic criteria (i.e., "probable" or "possible") would not respond to the treatment – yet the initiation criterion is limited to patients with a diagnosis of definite ALS.
- According to the clinical expert consulted by CADTH, it is expected that PB-TURSO would be offered as add-on therapy in addition to riluzole and/or edaravone – yet the initiation criteria for the various therapies do not align. These differences in reimbursement criteria could lead to people living with ALS being unable to access a treatment regiment that best meets their needs.

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

The reimbursement conditions are clearly stated and the rationale for the conditions are provided in the recommendation. However, as noted above, the initiation criteria 1.1. and 1.2. do not reflect the reality of people living with ALS and should be modified as suggested.

[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	*Lauren Poplak*
Position	*Manager, Stakeholder Relations*
Date	*05 – 07 - 2022*
☒	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	☐
N/A		
2. Did you receive help from outside your patient group to collect or analyze any information used in your feedback?	No	☒
	Yes	☐
N/A.		

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 Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information			
CADTH project number	SR0711		
Brand name (generic)	Albrioza (sodium phenylbutyrate and ursodoxicoltaurine)		
Indication(s)	For the treatment of patients with amyotrophic lateral sclerosis (ALS).		
Organization	ALS Action Canada		
Contact information[a]	Name: Bre Hamilton, Executive Director and Cali Orsulak, BscPharm, BCPS, CDE, Clinical Trials and Therapeutics Lead		
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.

ALS Action Canada concurs with the Committee's draft recommendation to reimburse Albrioza with conditions, however, we do not believe that the initiation criteria (namely 1.1 and 1.2) reflect the realities of diagnosis and clinical treatment of ALS in Canada, and will inevitably result in inequitable access for people living with ALS.

Given that Albrioza is the first and only Health Canada-approved drug therapy that has shown in clinical trials to significantly decrease the progression of ALS and increase patient survival, and that other potentially more promising drugs under trial are considered emerging drugs of interest by CADTH, it is crucial that CADTH's recommendation ensures equitable access by all people living with ALS, including those whose time since symptom onset exceeds 18 months.

In practical terms, 18-month since symptom onset initiation criteria means that 75% of Canadians currently living with ALS will not be able to access Albrioza, however much they may still benefit from it—indeed, as many of our members well past 18 months since symptom onset have done while accessing Albrioza through the SAP program.

The draft recommendation as it stands does not align with the pragmatic reality of diagnosis and clinical experience of living with ALS, most critically because the current time from symptom onset to diagnosis is overly long, variable throughout Canada, and worse for rural patients than urban ones.

The average mean time to diagnosis is 22.6 months in BC; 23.5 months in Ontario; 27 months in Saskatchewan; and 18.1 months in Alberta; 15.1 months in Nova Scotia; 15.2 months in Quebec; and 23.5 months in New Brunswick.

This means that by the time most Canadians are diagnosed with ALS, they would not qualify to access Albrioza. Time-to-diagnosis can't be a barrier to accessing this therapy.

The arbitrary nature of the "three body parts impacted" criteria is also not pragmatic or equitable. Surely the CDEC did not intend for these patients to wait to see if their ALS progresses to 3 body regions to become eligible. ALS diagnosed at 17 months or 18 months or 19 months is not a categorically different form of ALS such that these people should be treated differently. The difference of a month could mean that a person has categorically less or no access to Albrioza.

Currently there are no validated biomarkers for any ALS therapy, diagnosis, or progression.

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?

We don't believe the current wording of the initiation criteria 1.1 and 1.2 reflect the urgency people with ALS need to access this therapy or the clinical reality of diagnosis and treatment as communicated in our patient group submission.

We ask that CADTH reconsider the following regarding its draft recommendation by:

- **Making editorial revisions to its recommendation to improve equity and access,** and not unduly delay access by Canadians to Albrioza through the minor and major revisions process;
- **Addressing the inequity of access, clinically pragmatic, and ethical dilemmas presented by the recommended Initiation Criteria by expanding access to people diagnosed later than 18 months after symptom onset,** who are just as likely to benefit from the drug as those within the 18-month clinical trial parameter, which the draft recommendation mirrors on this criterion as well as others;
- **Ensuring that at least 75% of all people currently living with or who will be diagnosed with ALS in future have access to Albrioza.** We understand that the term "relatively rapidly progressing" was part of the clinical trial inclusion criteria simply because there are no biomarkers to predict progression. However, these criteria are relatively crude at selecting rapidity of progression in everyday clinical practice. We can only guess that CDEC, by aligning tightly to the clinical trial inclusion criteria, were intending to restrict eligibility to those that are relatively rapidly progressing. Population data shows that the median survival is 20-36 months from symptom onset (we doubt anyone would argue that 20-36 months is rapidly progressing) and only 5-10% survive for more than 10 years—thus, any criteria should allow at least 75% of Canadians with ALS be eligible, even upwards to 90%, depending on the definition of "relatively rapidly progressing."
- **Including Gold Coast criteria as an option in addition to El Escorial to confirm that a patient "definitely" has ALS.** We will also be suggesting to each province that it consider its individual time-to-diagnosis and health system when it comes to diagnostic cutoff times, so as to not exclude people who are otherwise relatively rapidly progressing without suggesting a secific cutoff, since any cutoff is arbitrary.

Clarity of the draft recommendation

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

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

The recommendations are clearly stated, but there are inconsistencies within it that contradict the clinical expert consulted.

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

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

While the implementation issues are clearly articulated, the pragmatic reality of ALS means the following issues need to be addressed/changed:

- Limiting the initation criteria to those with "definite" ALS excludes patients with probable or possible ALS or who may be diagnosed with ALS later than 18 months after symptom onset when there is no reason that they too might benefit from Albrioza.
- The initiation criteria for Albrioza, riluzole, and edavarone are all different, and given that the latter two drugs have no meaningful impact on patient survival or quality of life, designating Albrioza as a secondary therapy means many people living with ALS will likely be unable to access the better therapy when they need it.

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

The conditions and their rationale are clearly stated but as we noted the initiation criteria 1.1 and 1.2 do not reflect the clinical or diagnostic reality of living with ALS in this country and will lead to inequitable and even possible no access to Albrioza by the patients currently accessing Albrioza under the SAP program, much less others who will be diagnosed in future.

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

Appendix 1. Conflict of Interest Declarations for Patient Groups

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- 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	*Bre Hamilton and Cali Orsulak*
Position	*Executive Director and Clinical Trials and Therapeutics Lead*
Date	*06-07-2022*
☒	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	x
	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.

We have not received any financial support from any companies or organizations at any time. All our funding to date is from individual donors.

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	☐	☐	☐	☐

AN ASSESSMENT OF DRAFT CADTH CRITERIA FOR REIMBURSEMENT OF ALBRIOZA (AMX0035) FOR AMYOTROPHIC LATERAL SCLEROSIS (ALS) UNDER PROVINCIAL DRUG BENEFIT PROGRAMS

Originally submitted to the Canadian Agency for Drugs and Technology in Health, 26 May, 2022; Revised 25 June, 2022, based on review of CADTH draft recommendations for ALBRIOZA.

Prepared by:

Dr. Andrew C. Darke* Applied Clinical Decisions, Stouffville, ON.

[redacted]

SUMMARY

The primary objective of this analysis was to assess criteria proposed by the Canadian Agency for Drugs and Technology in Health (CADTH) for coverage of ALBRIOZA (AMX0035) for Amyotrophic Lateral Sclerosis (ALS) under provincial drug benefit programs.

The criteria proposed by CADTH for reimbursement of ALBRIOZA include restriction to patients whose time since symptom onset does not exceed 18 months.

As demonstrated in this analysis, this restriction is both scientifically invalid and clinically unacceptable to ALS patients for the following reasons:

1. It results from an invalid conflation of the ALS clinical trial paradigm with that for routine clinical treatment.
2. It fails to account for the heterogeneity of the disease and the imprecision that exists in establishing its duration in a particular patient.
3. It is based on the erroneous concept that disease duration (however defined) is, in itself, sufficient to define an individual patient's functional state.
4. It fails to recognize that time since symptom onset (however defined), does not predict the capacity of an individual to respond to effective treatments that slow disease progression.
5. It will result in inequity of access among patients with ALS.
6. It conflicts with the Health Canada approved Indication for ALBRIOZA which places no such limitation on its use in the treatment of ALS patients.
7. It is not consistent with the Expert Opinion received by CDEC indicating a lack of mechanistic rationale for such a limitation.

A. THE ALS CLINICAL TRIAL PARADIGM TRAP – CONFLATION WITH THE PRINCIPLES OF ROUTINE CLINICAL TREATMENT

Approval to market a new drug in Canada requires demonstration of its safety and efficacy to the satisfaction of Health Canada. This is achieved through the conduct of double blind randomized controlled clinical trials, often involving comparison between the new drug and placebo.

It is reasonable that in designing such clinical trials, consideration should be given to the most expeditious (time taken to complete the clinical trial) and efficient (least use of resources) ways in which the trials can be conducted to achieve a scientifically valid conclusion of efficacy and safety.

Among the factors that can affect both expeditiousness and efficiency of clinical development programs are: the number of patients required to establish efficacy and safety with statistical validity; the duration of the clinical trials; and the anticipated magnitude of therapeutic effect of the new drug relative to that of the comparison treatment (e.g. placebo).

These considerations are of particular significance in the development of drugs for life threatening rare diseases for which no adequate treatment is currently available, such as ALS. Assessment of therapeutic effect of drugs for ALS invariably includes assessment of the patients' functional capability and mortality. To ensure that a clinical trial will be capable of leading to a valid conclusion of efficacy as expeditiously and efficiently as possible, trials of new drugs for ALS often select patients who have both adequate functional capability but can also be expected to reach the trial endpoints (measurable decrease in functional ability or increase in mortality) over a manageable time frame, such as 6 months.

For practical purposes this means enrolling patients who have not had the disease for very long (e.g. 2 years or less) but whose functional ability can be expected to measurably worsen within a manageable clinical trial duration. These are patients who represent the "classical" presentation of ALS rather than the subtypes with slower disease progression. This approach to patient selection is a recognized and scientifically justifiable methodology for achieving trial endpoints expeditiously and efficiently and is known as a population enrichment strategy.

However as discussed in the following sections, there are major problems when this clinical trial design strategy becomes conflated with the realities of routine clinical practice and is the basis for formulating reimbursement criteria under provincial drug benefit programs. This has resulted in exclusion of patients with more slowly progressing ALS from access to effective treatment,

B. THE HETEROGENEITY OF ALS – IMPRECISION IN DEFINING DISEASE DURATION

The functional disability and life expectancy of patients with ALS varies greatly. While the median duration from ALS onset to death is approximately 2-3 years, approximately 50% of people diagnosed with ALS live at least three or more years after diagnosis, about 25% live five years or more and up to 10% live more than 10 years.

Not only does the inherent rate at which the disease is progressing in a given patient vary considerably but the time of diagnosis also depends on other factors such as patients' own level of awareness of their upper and lower motor neurone signs, their willingness to seek medical follow-up of them and variable access to physicians with the expertise to evaluate possible symptoms and signs of ALS and make a valid diagnosis.

Therefore, the time interval between patients' awareness of signs that can be associated with the onset of ALS and a conclusive diagnosis by a specialist, supported by appropriate neurophysiological test results, can be several years, as demonstrated in the study by Hodgkinson et al (Can J Neurol Sci. 2018; 45: 652-659). In this study there was substantial inter-provincial variability and in Ontario, for example, the median interval between symptom onset and an ALS diagnosis was 23.5 months.

With CADTH's recommended 18 month restriction on time since symptom onset and a median delay in diagnosis of 2 years, it can be expected that approximately 2/3 of ALS patients will be ineligible for treatment with ALBRIOZA under provincial drug benefit programs.

Paradoxically, CDEC agreed with its Clinical Expert that early intervention is important to prevent motor neurone death and yet has proposed that patients with slowly progressing motor neurone death,with longer intervals from symptom onset to diagnosis, but with adequate remaining functional capability, should be blocked from access to this new drug.

Therefore the inherent variability in time to diagnosis means that reimbursement criteria based on

disease duration are inappropriate since they are necessarily dependent on a standardized and precise determination of time since symptom onset, which is not tenable because it depends on which of several possible benchmarks are used.

Possible benchmarks for disease onset could, for example be: patients' retrospective self-observations of signs that were only subsequently assessed as suggesting motor neurone dysfunction; patients' reports of current symptoms or signs to a primary care provider; referral to a community neurologist; referral to an ALS clinic; clinical confirmation of upper motor neurone dysfunction; clinical confirmation of lower motor neurone dysfunction; neurophysiological confirmation of lower motor neurone dysfunction; or final diagnosis of ALS.

In the absence of a standardized clinical definition of disease onset, from among the many possible such benchmarks, there will be significant inter-patient variability in estimates of disease duration which render such estimates as invalid for reimbursement decisions.

C. INVALIDITY OF DISEASE DURATION AS A PREDICTOR OF DRUG RESPONSE

In addition to the inequity in drug access that results from use of time since symptom onset as a reimbursement criterion, the heterogeneity of the time course of functional decline across the ALS patient population means that disease duration (however defined) cannot in itself define an individual patient's functional state, nor can it predict the capacity of that individual to respond to treatments that are effective in slowing progression of the disease.

Therefore, inclusion of disease duration as a criterion for drug reimbursement under Provincial Drug Benefit Programs, as proposed by CADTH for ALBRIOZA is inherently flawed.

While clinical trials may, for the practical reasons discussed in the previous section, exclude patients who have lived with ALS for more than 18 months, application of this 18 month criterion to provincial drug access decisions is based on the following incorrect assumptions:

1. It is based on the premise that it is reasonable to withhold funding for ALS patients with very limited ability to benefit from treatment AND that disease duration (however defined) can be used as a surrogate for extent of disease progression which is IN TURN predictive of a poor response to drugs that slow disease progression.
2. This entire premise is clearly invalid - patients with slowly progressing ALS, even of several years' duration, may well have adequate functional capacity to allow for meaningful functional improvement, or slowing of disease progression, in response to an effective treatment. It is a separate question as to whether patients with very limited functional capacity – whether of long or short duration – have the capacity to benefit from treatment.
3. It presumes that there is a neurophysiological basis for postulating that the underlying mechanisms of motor neurone death differ between the ALS subtypes with classical vs slow disease progression and that the response of those mechanisms to drugs that slow motor neurone death, differs between these subtypes. There is no current basis for this presumption and until there is sufficient evidence for such mechanistic differences there is no basis for restricting these drugs to patients with recent disease onset.
4. It conflicts with the opinion of the Clinical Expert consulted by CDEC, that there was no physiological or pharmacological reason to differentiate between patients with respect to the criteria used for inclusion in the ALBRIOZA pivotal trial.
5. It conflicts with the conclusions of the Health Canada review of the New Drug Submission for ALBRIOZA. The labelling approved in the Notice of Compliance with Conditions (NOC/c) for ALBRIOZA imposes no restrictions on its use for the effective and safe treatment of ALS

patients, with respect to their time of diagnosis or symptom onset.

D. INEQUITY OF DRUG ACCESS AMONG ALS PATIENTS – A CONSEQUENCE OF INVALID REIMBURSEMENT CRITERIA

Prior to the approval of ALBRIOZA, only two drugs were available in Canada for treatment of ALS. Rilutek was marketed in Canada in 2000 and may extend survival and/or time to tracheostomy in some patients with ALS. However, its benefit is limited since it is known to extend life expectancy by only an average of 3 months so additional treatments have been urgently needed for almost two decades. Moreover, it is not available under Provincial Drug Benefit Programs for patients whose disease duration is more than a specified number of years.

Radicava was marketed in Canada in 2019 and is indicated to slow the loss of function in patients with ALS. However, patient access to Radicava requires *inter alia* a diagnosis of ALS within the past 2 years plus a defined level of function for performing activities of daily living and adequate respiratory function. The combination of these criteria fails to reflect the reality of the ALS patient population which is characterized by a wide range of disease progression rates and functional capacities and therefore precludes many patients with more slowly progressing ALS from accessing treatment that will prolong life and reduce the decline in functional ability. As an example, as referenced above, the median time interval between symptom onset and an ALS diagnosis in Ontario is 23.5 months. It is therefore evident that at least 50% of Ontario patients living with ALS will be restricted from access to Radicava.

When access to drugs is limited, physicians caring for patients with ALS may feel obliged to seek creative methods of ensuring their patients have access to new drugs, as a way of dealing with a "lifeboat ethics" dilemma (Breiner et al 2020). In the case of Radicava, prior to its acceptance under provincial drug benefit plans, these practices included: setting up a lottery system for determining which patients received the drug from the limited supply made available by the manufacturer; differential interpretations of the criteria by which the drug was to be made available from the manufacturer; or even efforts to persuade patients to wait to receive the drug until it became available under provincial plans (Breiner, Zinman and Bourque. CMAJ 2020 March 23;192:E319-20).

It is not unreasonable to suppose that similar creative considerations will apply to future ALS drugs that become available under provincial drug benefit programs if they are subject to restrictive, imprecise and invalid criteria such as disease duration. This will lead to inequity of access to provincially funded drugs depending on individual physicians' definition of disease onset and duration. particularly when they are treating patients with slow progression, good functional ability and adequate capacity to respond to a new effective treatment.

E. CONCLUSIONS

1. The criteria proposed by CADTH for reimbursement of ALBRIOZA, under Provincial Drug Benefit Programs, based on time since symptom onset, are scientifically and clinically invalid and will result in inequity of access by patients in Canada

2. Time since onset of disease has no role in reimbursement decisions for ALBRIOZA or other ALS drugs since it is inherently imprecise, does not correlate with functional ability across the various ALS subtypes, and does not predict individual capacity to respond to treatment.

3. Since Health Canada has approved ALBRIOZA for the treatment of ALS without restrictions regarding disease duration, CADTH must base its recommendations for reimbursement of ALBRIOZA

only on functional criteria that have been conclusively established to determine absolute incapacity of individual patients to benefit from the drug.

***Andrew C Darke PhD**

Applied Clinical Decisions

[redacted]

***Biography:**

30 year career with three companies in the Canadian pharmaceutical industry, including executive responsibilities for Clinical Research, Biostatistics, Regulatory Affairs, Provincial Formulary Reimbursement, Pharmacovigilance and Drug Information.

Confirmed diagnosis of ALS in 2021

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0711
Brand name (generic)	ALBRIOZA (sodium phenylbutyrate and ursodoxicoltaurine)
Indication(s)	For the treatment of patients with amyotrophic lateral sclerosis (ALS)
Organization	Amylyx Canada
Contact information[a]	[redacted]

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

The sponsor agrees with the CDEC recommendation to reimburse ALBRIOZA with conditions and thus is **not** requesting a 'Major' or 'Minor' revision reconsideration. Furthermore, the sponsor can understand why CDEC would recommend initiation criteria aligned with the CENTAUR clinical trial inclusion criteria from a strict evidentiary perspective.

However, the sponsor disagrees that the CENTAUR clinical trial inclusion criteria can be directly transposed into clinical practice Initiation Criteria without creating significant equity, inclusivity, and pragmatic implementation issues that CDEC may not have fully contemplated. As such 'Editorial' revisions (**not** a 'Major' or 'Minor' revision reconsideration) are requested. The specific Initiation Criteria that are problematic are:

Patients:

1.1 have a diagnosis of definite ALS

1.2 have had ALS symptoms for 18 months or less

As outlined by the CADTH consulted Clinical Expert, there is a legitimate rationale for why these two criteria were used from a clinical trial design perspective to define and select a *relatively homogeneous* population of patients who would progress *relatively rapidly*, so that less time would be required to demonstrate a change in rate of progression. However, these two criteria are ***not absolute*** for selecting a relatively rapidly progressing ALS population and are intended for only clinical trial purposes in the absence of objective biomarkers that can reliably predict the rapidity of progression. Furthermore, the Clinical Expert stated, ***and CDEC agreed,*** that there is no physiological or pharmacological reason to predict that patients at other levels of the El Escorial diagnostic criteria would not respond to the treatment.

Population-based studies demonstrate that the median survival is only 24-50 months from symptom onset (i.e., relatively rapidly progressing), and only about 10% of ALS patients survive for 10 years or more (i.e., relatively slower progressing).[1] Thus, if the intent of the Initiation Criteria is to align to the goals of the CENTAUR trial inclusion criteria to identify those who are relatively rapidly progressing, then the Initiation Criteria should allow for at least 50% and up to 90% of the ALS population to be eligible for treatment reimbursement.

Thus, the sponsor requests the 'Editorial' revisions outlined in section 5 below to Initiation Criteria 1.1 and 1.2 to address the issues of equity, inclusivity, and pragmatic implementation, while maintaining the intent of the reimbursement conditions to identify ALS patients who are relatively rapidly progressing.

Expert committee consideration of the stakeholder input		
	Yes	☒

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

Yes—In Table 2, CDEC carefully deliberated and ultimately agreed with the Clinical Expert (as well as ALS clinicians, and patient advocacy groups) on the following key principles:

1) There is no physiological or pharmacological reason to predict that patients at other levels of the El Escorial diagnostic criteria would not respond to the treatment
2) Early intervention is important to prevent motor neuron death towards the goals of slowing progression of ALS and preserving muscle function
3) There are no available treatments that have a proven ability to stop disease progression. Those that are available only modestly slow disease progression. Patients should not have to demonstrate treatment failure before being able to access another therapy.

No—The Initiation Criteria do not reflect CDEC's agreement with the above statements that are aligned across stakeholders, thus creating significant equity issues that may not have been fully contemplated by CDEC. Specifically,

- A patient who is 'fortunate' enough (only in terms of early recognition of symptoms, and health system efficiency to be referred quickly to an ALS specialist) to have a confirmed diagnosis of ALS within 18 months of symptom onset but has less than 3 body regions impacted by their ALS would be ineligible for ALBRIOZA based on the Initiation Criteria, and they would have to wait to see if further progression to a third body region occurs to become eligible. This could be further complicated in that by waiting for a third body region to be impacted to qualify for criterion 1.1, a patient may become ineligible based on criterion 1.2 for the 18-month cut off from symptom onset. Such unintended consequences run counter to all 3 principles above, especially as it relates to early intervention to prevent further motor neuron and functional deterioration, and not forcing a patient to demonstrate further progression or failure before being able to initiate ALBRIOZA.
- A patient may meet the arbitrary cut offs for ALBRIOZA but not for other ALS therapies and vice versa, creating inequities of access to the available therapies, even though their ALS may not be categorically different, especially as it relates to its rapidity of progression. ALS diagnosed at 18 months from symptom onset is likely not categorically different from ALS diagnosed at 19 months from symptom onset, yet a patient will have categorically different access to therapies based on a mere 1-month difference in time to diagnosis.

As it relates to criterion 1.2 'patients have had symptoms for 18 month or less at diagnosis', CDEC considered the opinion of one Clinical Expert over more robust evidence from a published Canadian registry study[2] which demonstrated that British Columbia, Saskatchewan, Ontario, and New Brunswick would not meet this 18-month cut off based on these provinces' mean time to diagnosis. This cut off would lead to inequity of access to ALBRIOZA across provinces, an outcome that CADTH should not unintentionally exacerbate. This one Clinical Expert may well have a practice where most patients are diagnosed within 18 months of symptom onset, however his/her singular opinion should not be reflected as the pan-provincial reality. Furthermore, CADTH evidentiary standards would rank a robust registry study as a higher level of evidence than a singular expert opinion.

Clarity of the draft recommendation

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

Yes—CDEC has provided a clear rationale for why it has rendered a positive recommendation with conditions.

No—It is not clear in the recommendation as to whether and how CDEC deliberated on the principles of equity, inclusiveness, and the consideration of pragmatic implementation when transposing the CENTAUR clinical trial criteria to Initiation Criteria 1.1 and 1.2, applied to everyday clinical practice. Interestingly, CDEC modified Initiation Criteria 1.3 from the CENTAUR inclusion criteria of SVC to FVC, and in doing so, recognized the pragmatic realities that, while SVC may be appropriate for

clinical trials, it is not routinely used in clinical practice, and that FVC has equivalency to SVC as it relates to identifying a population with a certain level of pulmonary function. The editorial revisions requested for Initiation Criteria 1.1 and 1.2 in section 5 below, follow that same pragmatic intent that CDEC has applied to 1.3.

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

Yes—The implementation issues have been clearly stated in the left column of Table 2.
No—As highlighted above, while CDEC has agreed with the Clinical Expert and stakeholders on many of the key considerations for implementation, the Initiation Criteria do not adequately address these considerations, and they run counter to the key CDEC agreed upon principles of early initiation to preserve motor neurons and function, and not waiting for failure or progression before granting access.
While the intent of using of El Escorial 'definite' and an 18-month cut off from symptom onset to diagnosis was for clinical trial purposes *only*, to select a relatively rapidly progressing population, directly transposing these criteria to clinical practice to define a rigid and absolute population for eligibility omits many patients who would otherwise be considered as relatively rapidly progressing. Furthermore, as communicated by CALS input and the Clinical Expert, in clinical practice El Escorial categorization is not routinely conducted nor is it updated for a given patient to mark when they become 'definite' if not initially diagnosed as such—in clinical practice, there is no further clinical utility to continue updating a patient's El Escorial categorization once a diagnosis of ALS is confirmed. Other tools, such as the ALSFRS-R have greater clinical utility for measuring progression over time when compared to El Escorial criteria, and tools such as the Gold Coast Criteria may be more appropriate for diagnostic certainty in clinical practice.

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

The sponsor requests that the following 'Editorial' clarifications (*in italics*) be made to the reimbursement conditions for the Initiation Criteria to ensure equity, inclusivity, and pragmatic implementation, while maintaining CDEC's intent to identify a relatively rapidly progressing population for initiation:
Patients:
1.1 have a diagnosis of definite ALS *using the revised El Escorial Criteria or Gold Coast Criteria*.
1.2 have had ALS symptoms for 18 months or less. *However, the application of this cut off should reasonably accommodate the provincial variation in time to diagnosis such that patients who are otherwise relatively rapidly progressing would not be deemed ineligible.*
The Gold Coast Criteria simplify and remove diagnostic categories to unify the diagnosis of ALS, creating a clinically applicable system that better reflects the certainty of diagnosis. Gold Coast Criteria are more practical and have higher sensitivity while maintaining specificity compared to El Escorial Criteria.[3] People with upper motor neuron (UMN) only signs are removed from Gold Coast classification, thus delineating ALS from a group that may have slower progression.
Clarifying that an arbitrary and strict 18-month cut off should not be enforced, and reasonable accommodation be given to account for the pan-provincial variability in time to diagnosis allows for more equitable and inclusive access across provinces for patients with ALS who are otherwise relatively rapidly progressing.
Clarification should also be made to recognize that more equitable, inclusive, and pragmatic Initiation Criteria may lead to a greater budget impact for jurisdictions. As such, the sponsor should address the cost impact of these criteria clarifications in negotiations with the pCPA.

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

[1] Longinetti E, Fang F. Epidemiology of amyotrophic lateral sclerosis: an update of recent literature. Curr Opin Neurol. 2019;32(5):771-776. doi:10.1097/WCO.0000000000000730.

[2] Hodgkinson VL, Lounsberry J, Mirian A, et al. Provincial Differences in the Diagnosis and Care of Amyotrophic Lateral Sclerosis. Can J Neurol Sci. 2018;45(6):652-659. doi:10.1017/cjn.2018.311.

[3] Jewett G, Khayambashi S, Frost GS, et al. Gold Coast criteria expand clinical trial eligibility in amyotrophic lateral sclerosis [published online ahead of print, 2022 Jun 8]. Muscle Nerve. 2022;10.1002/mus.27660. doi:10.1002/mus.27660.