CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

Edaravone Oral Suspension (Radicava)

(Mitsubishi Tanabe Pharma Canada, Inc.)

Indication: Amyotrophic lateral sclerosis (ALS)

December 8, 2022

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0727-000
Brand name (generic)	Radicava (edaravone)
Indication(s)	Amyotrophic lateral sclerosis
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 Telephone: [redacted] Email: [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 oral edaravone and largely support the evidence-based reasoning for aligning the initiation criteria with that for the IV formulation of edaravone.

However, we feel an important revision to initiation criterion 2.1. (has scores of at least two points on each item of the ALS Functional Rating Scale – Revised (ALSFRS-R)) is needed. Edaravone mitigates ALS disease progression as a whole, though ALS itself is a disease that can affect different regions of the body at different rates. Hence for some patients their disease will be selectively advanced in one domain but very much spared in others.

It would be difficult to justify physiologically why these patients would not benefit from edaravone any differently than those in whom the disease has affected equally across multiple domains. Hence, it is our expert opinion that the ALSFRS-R sub score criteria be removed.

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	☐

Yes, we believe the reasons for the recommendation are clearly stated.

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 (e.g., riluzole, Albrioza). 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 oral edaravone with that for the IV formulation.

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 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. Marvin Chum • Dr. Amanda Fiander • Dr. Christen Shoesmith • Dr. Amer Ghavanini • Dr. Gordon Jewett • Dr. Colleen O'Connell		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	Genevieve Matte, MDCM, FRCPC, CSCN Diplomate (EMG)
Position	Neurologist (Centre Hospitalier de l'Université de Montréal), Assistant Professor (Université de Montréal)
Date	07-12-2022

☒	**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 2

Name	Rami Massie
Position	Associate Professor, Department of Neurology and Neurosurgery
Date	07-12-2022
☒	**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
Mitsubishi Pharma	☒	☐	☐	☐
Akcea	☒	☐	☐	☐
Kye pharmaceuticals	☒	☐	☐	☐
Alnylam Pharmaceuticals	☒	☐	☐	☐
Pfizer	☒	☐	☐	☐
Amylyx	☒	☐	☐	☐

CADTH

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0727-000
Brand name (generic)	Radicava (edaravone)
Indication(s)	For the treatment of patients with amyotrophic lateral sclerosis (ALS)
Organization	The ALS Society of Canada
Contact information	Name: Lauren Poplak Title: Senior manager, Advocacy & Stakeholder Relations Email: [redacted] Phone: [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 edaravone oral suspension and understands the rationale for aligning the reimbursement conditions for oral edaravone with current Canadian public drug plan reimbursement criteria for IV edaravone.

However, we are concerned the initiation criteria for IV edaravone may no longer reflect the reality of care and treatment of ALS in Canada, especially the use of the ALS Functional Rating Scale – Revised (ALSFRS-R) as a measure.

ALS is a heterogeneous disease, meaning the disease varies from person to person, including where symptoms first appear in the body, age of onset and rate of disease progression. It can affect different areas of the body at different rates, meaning that someone with ALS may have significant paralysis in one body part while maintaining function in another.

As our understanding of ALS has evolved, so has the clinical approach to diagnosis, treatment and care. As such, the ALS community, including clinicians, has been vocal about the ALSFRS-R not being an ideal way to measure disease progression due to the heterogeneity of the disease.

Equitable access to innovative therapies is a critical issue for people and families affected by ALS across Canada. Therefore, we ask that CADTH consider an editorial change to update the edaravone oral suspension initiation criteria to remove any sub-score criteria.

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 committee considered the initial input provided to CADTH by the ALS Society of Canada when drafting the recommendation.

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

Yes, we believe the reasons for the recommendation are clearly stated.

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.		
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		

[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	*Senior Manager, Advocacy and Stakeholder Relations*
Date	*08-12-2022*
☒	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	☐
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

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0727
Brand name (generic)	Radicava (edaravone oral suspension)
Indication(s)	For the treatment of patients with amyotrophic lateral sclerosis (ALS)
Organization	Mitsubishi Tanabe Pharma Canada, Inc. (MTP-CA)
Contact information[a]	[redacted]

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

The sponsor is in agreement with the CDEC recommendation to reimburse Radicava Oral Suspension with conditions, as well as with the clinician and the Canadian ALS Research Network (CALS) input (p. 6, draft recommendation), which states that *"based on the clinical expert's experience, it would not be appropriate to recommend that patients try and fail other treatments before initiating oral edaravone. Requiring the patient to demonstrate failure before introduction of another treatment would subject them to irreversible progression that would otherwise have been slowed had other therapies been given concurrently, and would not be reflective of current evidence."*

It is in the spirit of the above that the sponsor kindly requests "Editorial" revisions (not a "Major" or "Minor" revision reconsideration) that the recommended initiation and renewal criteria for Radicava Oral Suspension align with that of Albrioza (Project Number: SR0711-000) and that patient's rate of decline based on ALS Functional Rating Scale – Revised (ALSFRS-R) scores be removed for consistency and consideration for seamless drug plan implementation in ALS. CDEC provides the following rationale in the Albrioza (PB-TURSO) final recommendation (p. 10, Albrioza CADTH reimbursement recommendation, August 2022): "*The clinical expert explained that clinicians are unlikely to have an accurate reading of a patient's rate of decline based on ALSFRS-R scores before treatment and on treatment to compare on an individual patient level. CDEC agreed with the clinical expert and did not consider it practical to require assessment of treatment response based on ALSFRS-R scores."* It is the sponsor's understanding that CDEC hereby recognized the inherent problems with the applicability of clinical trial design strategies to the realities of routine clinical practice for this life-threatening disease that has no cure in formulating the criteria for Albrioza for the public drug plans under its jurisdiction and thinks it appropriate that the same acknowledgement applies to Radicava Oral Suspension.

Further, the sponsor would like CDEC to note parallels between the clinical trial designs for PBTURSO and Radicava Oral Suspension. In the PB-TURSO phase II, double-blind (DB), placebocontrolled study (CENTAUR) (p. 12, Albrioza CADTH reimbursement recommendation, 2022) "*the primary efficacy end point was ALSFRS-R total score*". As outlined in the Radicava IV CADTH

recommendation (Project Number: SR0573, p. 6) "*The primary outcome in studies 16, 17, and 19 was change in mean ALSFRS-R total score from baseline to the end of treatment*."

The sponsor therefore kindly requests "Editorial" revisions (not a "Major'' or "Minor'' revision reconsideration) so that the final recommended criteria for Radicava Oral Suspension be exempt of the following text in strikethrough within the initiation and renewal criteria (See Radicava IV CADTH recommendation, Project Number: SR0573, p. 1 for the complete criteria) for consistency and consideration for seamless drug plan implementation in ALS:

Initiation Criteria: ~~2.1. has scores of at least two points on each item of the ALS Functional Rating Scale – Revised (ALSFRS-R)~~

Renewal Criteria: 1.1. patient becomes non-ambulatory ~~(ALSFRS-R score ≤ 1 for item 8)~~ AND is unable to cut food and feed themselves without assistance, irrespective of whether a gastrostomy is in place ~~(ALSFRS-R score < 1 for item 5a or 5b);~~ or

The sponsor believes that a holistic consideration of the ALSFRS-R scores may not have been considered by CDEC as the review periods for Radicava Oral Suspension and PB-TURSO were overlapped; hence the need for this request for "Editorial'' revisions (not a "Major'' or "Minor'' revision reconsideration): (PB-TURSO Project Number: SR0711-000: 09-12-21 to 08-08-22 (final recommendation posted)) & (SR0727 Radicava Oral Suspension: 25-03-22 & ongoing).

As per the Albrioza CADTH reimbursement recommendation (p. 10, Albrioza CADTH reimbursement recommendation, 2022), *"that clinicians are unlikely to have an accurate reading of a patient's rate of decline based on ALSFRS-R scores before treatment and on treatment to compare on an individual patient level"*, the sponsor is of the view that if the misalignment persists in the criteria with regards to the ALSFRS-R scores between these treatments that it will result in inequity of access among patients with ALS, confusion at the clinic level, hence delay in treatment initiation (due to additional testing requirements), to the detriment of Radicava patients. It also conflicts with the Health Canada approved indication for Radicava (IV and Oral Suspension) which places no such limitation on its use in the treatment of ALS patients. Further, it would show inconsistency on the part of CDEC to recommend the use of one ALS treatment in clinical practice while denying it to another when the primary outcomes in their respective clinical trials are the same without clear rationale.

In conclusion, the sponsor thanks CDEC for recognizing the inherent problems with the applicability of clinical trial design strategies to the realities of routine clinical practice and for the "Editorial" revisions (not a "Major'' or "Minor'' revision reconsideration) of removing the ALSFRS-R scores requirements from the initiation and renewal criteria when formulating the final criteria for Radicava Oral Suspension for CADTH-participating drug plans. We also recognize these criteria are currently in place for Radicava IV, which was reviewed a number of years ago. Given the shift, we will look to engage CADTH-participating public drug programs on this issue in the future.

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	☒

As outlined in response to Q #1 above, the sponsor agrees with the clinician and the CALS input (p. 6), which states that "*based on the clinical expert's experience, it would not be appropriate to recommend that patients try and fail other treatments before initiating Radicava Oral Suspension. Requiring the patient to demonstrate failure before introduction of another treatment would subject them to irreversible progression that would otherwise have been slowed had other therapies been given concurrently, and would not be reflective of current evidence*."

However, for consistency and consideration for seamless drug plan implementation in ALS, and as per the above rationale provided to response to Q #1, the sponsor kindly requests "Editorial" revisions (not a "Major'' or "Minor'' revision reconsideration) so that the ALSFRS-R scores requirements be removed from the final recommended initiation and renewal criteria for Radicava Oral Suspension to avoid inequity of access among patients with ALS and a delay in treatment initiation due to additional testing requirements, to the detriment of Radicava patients.

Clarity of the draft recommendation

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

While the sponsor agrees that the reasons for the recommendation are clearly stated, it fails to recognize that the treatment paradigm in ALS has evolved, as described above in responses to Q #1 & Q #2, hence the need for the "Editorial" revisions (not a "Major'' or "Minor'' revision reconsideration) request that the ALSFRS-R scores requirements be removed from the initial and renewal criteria for Radicava Oral Suspension.

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

The sponsor recognizes that overall, the committee has provided clear guidance for implementation.

However, the sponsor believes that "Editorial" revisions (not a "Major'' or "Minor'' revision reconsideration) are required in order to avoid additional burden on patients and the healthcare system (i.e., treating physicians, public drug plans, etc.). The sponsor suggests that provisions be added stipulating that patients already receiving Radicava IV treatment with adequate treatment response should be able to switch to Radicava Oral Suspension without the need for meeting initiation criteria again AND that if they are within a funded period prior to renewal, they should be eligible to switch seamlessly from the IV to the oral formulation without delay (i.e., without the need for reassessment of eligibility) or the reverse (allowing seamless switching from the oral to the IV formulation without delay).

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

Overall, the sponsor acknowledges that the rationale provided in the reimbursement conditions and associated reasons are clearly stated but is requesting "Editorial" revisions (not a "Major'' or "Minor'' revision reconsideration) as per responses to Q #1, Q #2, Q #3 & Q #4 to help ALS patients obtain equitable access to Radicava Oral Suspension at time of initiation and renewal, and to allow them to transition seamlessly between Radicava IV and Radicava Oral Suspension at their discretion when approved for coverage.

As noted above, the Health Canada approved indication for Radicava (IV and Oral Suspension) places no such limitation on its use in the treatment of ALS patients. Further, not removing the ALSFRS-R scores requirements for Radicava Oral Suspension may show inconsistency on the part of CDEC by indicating a lack of rationale for such usage in the clinical practice for one ALS treatment (PB-TURSO) but denying it to another (Radicava Oral Suspension) when the primary outcomes in their respective clinical trials are the same.

The sponsor therefore thanks CDEC in advance for implementing these “Editorial” revisions (not a “Major’’ or “Minor’’ revision reconsideration) for consistency and consideration for seamless drug plan implementation in ALS and to avoid inequity of access among patients facing such a debilitating and life-threatening disease as well as to avoid creating delays in treatment initiation due to additional testing requirements, all to the detriment of Radicava patients.

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