Canadian Journal of Health Technologies

CADTH

January 2023 Volume 3 Issue 1

CADTH Reimbursement Recommendation

Edaravone Oral Suspension (Radicava)

Indication: For the treatment of patients with amyotrophic lateral sclerosis

Sponsor: Mitsubishi Tanabe Pharma Canada, Inc.

Final recommendation: Reimburse with conditions

CADTH

ISSN: 2563-6596

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

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

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

Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Radicava Oral Suspension?

CADTH recommends that Radicava should be reimbursed by public drug plans for the treatment of patients with amyotrophic lateral sclerosis (ALS), if certain conditions are met.

Which Patients Are Eligible for Coverage?

Radicava oral suspension should only be covered to treat patients with ALS provided that it is covered for a similar patient population and in a similar way to the IV formulation of Radicava for the treatment of adult patients with ALS.

What Are the Conditions for Reimbursement?

Radicava oral suspension should only be reimbursed if prescribed in a similar manner as the IV formulation of Radicava is prescribed, and that the cost of Radicava oral suspension does not exceed the drug program cost of IV formulation of Radicava.

Why Did CADTH Make This Recommendation?

- Evidence from 1 randomized clinical trial suggested that Radicava oral suspension showed comparable bioavailability to the IV formulation of Radicava in healthy individuals. Where bioavailability is a measurement of the rate and extent to which a therapeutically active chemical is absorbed from a drug product into the systemic circulation and becomes available at the site of action. Given the comparable bioavailability, Radicava oral suspension might slow the decline in physical function in patients with ALS, as was demonstrated with the IV formulation of Radicava.
- Side effects associated with Radicava oral suspension treatment are manageable.
- Based on CADTH's assessment of the health economic evidence, the annual per patient drug costs with Radicava oral suspension and the IV formulation of Radicava were the same at public list prices. CDEC determined that there was no evidence to justify a greater cost for Radicava oral suspension compared with the IV formulation of Radicava.
- Based on public list prices, Radicava oral suspension is estimated to cost the public drug plans approximately $38 million over the next 3 years.

Additional Information

What Is ALS?

ALS is a rare and incurable disease in which the nerve cells that control muscles break down and die. Patients have muscle weakness, twitching, and tightness leading to difficulties with walking, breathing, swallowing, and speaking. Patients eventually require breathing and/or mobility support and 80% survive fewer than 5 years after symptom onset. There are approximately 3,000 people in Canada living with ALS and about 1,000 patients die from ALS each year.

Unmet Needs in ALS

There is a need for treatments that slow ALS progression, help patients maintain independence, and improve survival.

How Much Does Radicava Oral Suspension Cost?

Treatment with Radicava oral suspension is expected to cost approximately $123,280 in the first year, and $119,600 in subsequent years, per patient.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that edaravone oral suspension be reimbursed for the treatment of patients with ALS only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One single-dose, randomized, open-label study MT-1186-J03 (N = 42) that evaluated the bioequivalence of oral suspension and IV formulation of edaravone in healthy individuals suggested that oral edaravone showed comparable bioavailability to its IV formulation. Since IV edaravone was found to slow the rate of decline in motor function in ALS patients, comparable bioavailability would suggest that the same conclusion applies to oral edaravone. One open-label, single-group study MT-1186-A01 (N = 185) that evaluated the longer-term safety and tolerability of oral edaravone in patients with ALS suggested that the harms profile of oral edaravone may be considered acceptable, and no major safety signal was identified.

At the sponsor submitted price for oral edaravone and publicly listed price for IV edaravone, the annual per patient drug cost of oral edaravone is equivalent to that of IV edaravone and the 2 formulations showed comparable bioavailability. There was no clinical evidence to suggest oral edaravone should cost more than IV edaravone.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation, renewal, discontinuation, and prescribing		
1. List in a similar manner to the IV formulation of edaravone for initiation, renewal, discontinuation, and prescribing.	CDEC considered it appropriate to align the reimbursement conditions for oral edaravone with current Canadian public drug plan reimbursement criteria for IV edaravone.	Based on input from the clinical expert, both edaravone-naive and experienced patients would benefit from the oral formulation of edaravone. Oral edaravone may be administered at home and not in a special setting, but patients should still be under the care of a specialist with experience with ALS.
Pricing		
2. Oral edaravone should be negotiated so that it does not exceed the drug program cost of IV edaravone.	Using publicly available prices, the annual per patient drug cost of oral edaravone is equal to that of IV edaravone.	—
Feasibility of adoption		
3. The feasibility of adoption of oral edaravone must be addressed.	At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption (given the difference between the sponsor's estimate and CADTH's estimate)	—

Reimbursement condition	Reason	Implementation guidance
	and to ensure the reimbursement of oral edaravone does not lead to an increase in drug program budgets.	

ALS = amyotrophic lateral sclerosis.

Discussion Points

- Input received from patients and clinicians emphasized the fact that an oral version of edaravone would be easier for patients to access than the IV formulation, reducing the risk of exposure to unnecessary infusion-associated adverse events and decreasing the burden related to the IV administration both to the health-care system and ALS patients themselves; however, neither comparative efficacy nor safety evidence was identified, leaving uncertainty on the clinical value of oral edaravone.
- CDEC discussed that there is no available evidence on the use of oral edaravone in combination with other drugs for the treatment of ALS.
- CDEC discussed that there is a need for more convenient drug administration and that IV administration is part of that burden and a barrier to access to therapy for some patients. However, there is no evidence available that compares outcomes like patient preference, treatment adherence, or caregiver burden between oral edaravone and IV therapies.
- CDEC discussed that the oral formulation of edaravone may lead to increased use (uptake) than observed for the existing IV formulation. This could increase the budget impact associated with oral edaravone, greater than suggested by CADTH, and would need to be considered within the feasibility of adoption.

Background

ALS is a progressive neuromuscular disorder that is characterized by the degeneration of upper and lower motor neurons. Symptoms of ALS are typically first noticed when limb weakness occurs, though the first symptoms can also be bulbar and involve difficulty in speaking or swallowing. Over time, patients lose function in additional regions, such as the other limbs and respiratory muscles. Progressive muscle weakness and eventual respiratory failure lead to death. ALS is a clinically heterogeneous disease in terms of presentation and rate of progression. There is no definitive test for diagnosing ALS and there can be a long duration from symptom onset to diagnosis. The etiology of the disease is unknown; however, genetics have been implicated in familial clusters. In a Canadian systematic review published in 2009, estimates of age-adjusted annual incidence of ALS ranged from 2.0 to 2.4 per 100,000 persons.

There is no cure for ALS. Health Canada–approved treatments for ALS include riluzole, sodium phenylbutyrate and ursodoxicoltaurine, and edaravone. Riluzole is an oral medication that has been shown to extend tracheostomy-free survival by 2 to 3 months in patients with ALS. Sodium phenylbutyrate and ursodoxicoltaurine is an oral medication that has been

shown to slow decline in physical function in patients with a diagnosis of definite ALS who were within 18 months of symptom onset. Edaravone, a free radical scavenger thought to prevent oxidative damage to vascular endothelial cells and nerve cells, is currently available as an intravenously administered drug, which was found to slow the rate of decline in motor function in some patients with ALS.

Oral edaravone has been approved by Health Canada for the treatment of patients with ALS. The Health Canada recommended dose of oral edaravone is 105 mg (5 mL) taken orally or via a feeding tube (percutaneous endoscopic gastrostomy or nasogastric tube). The recommended treatment regimen starts with an initial treatment cycle of daily dosing for 14 days followed by a 14-day drug-free period. Subsequent treatment cycles involve daily dosing for 10 days out of 14-day periods, followed by 14-day drug-free periods. Oral edaravone should be taken in the morning after fasting overnight for at least 8 hours and waiting at least 1 hour before eating or drinking anything except water. For patients who are unable to fast overnight, the required fasting interval can be shortened depending on the type of meal. Patients treated with 60 mg of edaravone injection may be switched to 105 mg (5 mL) edaravone oral suspension using the same dosing frequency. Upon switching to edaravone oral suspension, patients should follow edaravone oral suspension dosing recommendations with regard to food consumption.

Sources of Information Used by the Committee

To make their recommendation, CDEC considered the following information:

- a review of 2 clinical studies
- patients' perspectives gathered by 1 patient group (the ALS Society of Canada)
- input from public drug plans that participate in the CADTH review process
- one clinical specialist with expertise diagnosing and treating patients with ALS
- input from 1 clinician group (The Canadian ALS [CALS] Research Network)
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

One patient advocacy group, the ALS Society of Canada, submitted the patient input for this review. The submission was based on online survey that collected input from 629 patients and caregivers from Ontario and Quebec and telephone interviews with 7 patients who had experience with oral edaravone.

Respondents indicated that the most severe of ALS symptoms include difficulties with mobility (including walking and standing), gripping and holding things, muscle cramping and twitching, and fatigue caused by muscle exhaustion. These symptoms were also among the most important to control for people living with ALS, in addition to difficulties breathing, speaking, and swallowing. Patients indicated that their social life, travel/hobbies

and family life suffered the most. In addition, caregivers of patients with ALS highlighted a negative impact on emotional and psychological wellbeing, including pervasive feelings of overwhelming grief and struggles with mental health, including stress, anxiety, helplessness, and hopelessness. The loss of independence was mentioned as touching all aspects of patients' lives and dramatically impacting caregivers, as patients eventually need help performing all daily tasks. Patients and caregivers reported treatment experience with riluzole and IV edaravone. Slowing disease progression, maintaining ability to participate in daily activities and increasing survival were identified as the most important benefits from therapy. Access to riluzole and IV edaravone treatments was a problem for some patients. Particular difficulties reported with edaravone were mostly related to the IV administration, including concerns with potential complications, having to schedule activities of daily living around their infusion schedule, needing to have a port catheter implanted and the mode administration adding to the overall burden of care.

Clinician Input

Input From the Clinical Expert Consulted by CADTH

The clinical expert consulted by CADTH for the purpose of the review indicated that there is currently no ideal treatment that prevents disease progression. At the time of this review, the only Health Canada–approved disease-modifying treatments for ALS are riluzole and IV edaravone, both showing modest benefits in slowing disease progression. The expert indicated that patients would usually be prescribed riluzole for its clinical benefits and the fact that it is easily administered and well tolerated. Patients meeting the criteria for reimbursement would then be offered IV edaravone as an add-on therapy.

The mainstay of care for ALS patients consists of symptom management and quality-of-life optimization. The clinical expert highlighted that patients should be diagnosed and followed by an ALS specialist as part of a multidisciplinary care team. The clinical expert noted that current standard of care involves following the patient at regular intervals and monitoring their physical, functional, emotional, and quality-of-life parameters. Medications are titrated appropriate to a patient's condition and also their goals of care, in a palliative-focused approach.

According to the clinical expert, patients with the greatest need are those patients with preservation of the ability to complete at least 1 of their own activities of daily life. 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.

According to the clinical expert, the uptake of IV edaravone has been so far low, considering that the IV formulation is invasive and comes with a time-consuming administration schedule. The clinical expert considered that the oral formulation will be a well-received alternative, as many patients choose not to embark on the currently available IV formulation because of the caveats and excessive requirements and constraints related to IV infusion.

Clinician Group Input

One clinician group, the Canadian ALS Research Network (CALS), has provided input, which was in line with the views from the input provided by the clinical experts consulted by CADTH.

CALS acknowledged the need for ALS disease-modifying treatment options aiming at slowing disease progression, as well as the role of oral edaravone in clinical practice due to increased accessibility.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a CADTH recommendation for oral edaravone:

- relevant comparators
- considerations for initiation of therapy
- considerations for prescribing of therapy
- care provision issues.

The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions from the Drug Programs

Implementation issues	Response
Relevant comparators	
Would the submitted trials be sufficient to state similar efficacy/effectiveness between the oral and IV versions of edaravone?	The clinical expert considers that the submitted trials would be sufficient to show comparable bioavailability, and that there is no reason to think that the efficacy profiles of the 2 versions would differ. CDEC noted that there is no direct or indirect evidence available, and that it will be assumed that similar efficacy between the oral and IV versions of edaravone will be achieved if the 2 drugs are considered bioavailable.
Considerations for initiation of therapy	
The sponsor is requesting a recommendation for ALS patients with the same criteria as IV edaravone. • Consider stating in the criteria something similar to "reimburse in a similar manner as IV edaravone." Would CDEC consider updating the previous recommendation for IV edaravone with recommendation of this new formulation? Or would the oral formulation and the data presented be considered for a new recommendation?	CDEC recommended that oral edaravone be reimbursed in a similar manner to IV edaravone. CDEC also noted that there is no evidence presented that support oral edaravone be recommended for any other populations.
Considerations for prescribing of therapy	
Similar concerns related to accessing clinical specialists and/or special settings to IV edaravone	According to the clinical expert, ALS should be managed by a specialist and multidisciplinary team. It is the clinical expert's opinion that there is sufficient access to ALS specialists across the country and that there is no need to expand to family doctors. The clinical expert considers that delaying introduction of treatment with edaravone is unlikely to significantly affect patients' trajectory. The clinical expert expects an easier access for patients to

Implementation issues	Response
	the oral version of edaravone. Access to IV administration and semi-permanent catheter insertion is an issue depending on where someone lives, which is why having an oral option makes it a lot easier for patients to receive appropriate treatment. CDEC recommended that oral edaravone be prescribed by specialists in the management of ALS but no longer requires a specialized setting for administration.
The prescribing criteria with IV edaravone was: The patient must be under the care of a specialist with experience in the diagnosis and management of ALS. Consider alignment of prescribing criteria with IV edaravone especially given the trials submitted?	According to the clinical expert, ALS should be managed by a specialist and multidisciplinary team. It is the clinical expert's opinion that there is sufficient access to ALS specialists across the country and that there is no need to expand to family doctors. The clinical expert considers that delaying introduction of treatment with edaravone is unlikely to significantly affect patients' trajectory. The clinical expert also noted that the initial prescription and subsequent renewals should happen through specialty clinics. Ongoing management of patients is optimal when performed by a specialized multidisciplinary team rather than through a family doctor. CDEC recommended that prescribing criteria for oral edaravone should be aligned with IV edaravone.
Care provision issues	
An option for new patients (treatment-naive). A possible option for patients on IV edaravone to switch to PO edaravone (treatment-experienced) Initial treatment cycle: There is a Starter Kit that contains 2 35 mL (105 mg/5 mL) bottles which provide daily dosing for 14 days followed by a 14-day drug free period. Subsequent treatment cycle: Daily dosing for 10 days out of 14-day periods, followed by 14-day, drug free periods (1 bottle: 50 mL, 105 mg/5 mL). Noted: Discard 15 days after opening bottle or if unopened, 30 days from date of shipment indicated on the carton pharmacy label. The administration schedule for edaravone is complex. For IV use, patients would undergo 134 infusions in the first year and 130 infusions in subsequent years in a dedicated administration clinic or hospital. The oral formulation, administered via mouth or feeding tube, would target the same patient population, e.g.? at home. Same Sponsor as IV, therefore, the transition to PO may be seamless for patients currently on IV. How would patients access this product, e.g., specialty pharmacy, hospital pharmacy?	The clinical expert indicated to CDEC that an oral version of edaravone would be a lot easier to access than its IV formulation, likely resulting in a displacement of the IV formulation. The clinical expert expects that both edaravone-naive and experienced patients would be prescribed treatment with the oral version of the product, therefore expanding the number of patients using the medication. The clinical expert indicated to CDEC that the oral formulation might be accessed is a similar manner to the IV formulation i.e., through a specialty pharmacy. The sponsor indicated that oral edaravone will be supplied via an exclusive distribution network through Innomar specialty pharmacies. It will be delivered either at the patient pharmacy of choice or through mail-order location of choice for each patient and through the same patient support program as IV edaravone.

ALS = amyotrophic lateral sclerosis.

Clinical Evidence

Description of Studies

To inform on the use of oral edaravone compared to its IV formulation, 2 manufacturer-sponsored studies were included in this review. The single-dose, randomized, open-label study MT-1186-J03 (N = 42) evaluated the bioequivalence of oral suspension and IV formulation of edaravone in healthy Japanese individuals. The study assessed drug concentration (in plasma and urine) of unchanged edaravone, sulphate conjugate, and glucuronide conjugate, as well as various pharmacokinetic parameters, including the area under the plasma concentration-time curve (AUC) and the maximum plasma concentration after administration (C_{max}) with the bioequivalence limit (0.80 to 1.25). Oral edaravone was administered as an oral suspension at a dosage of 105 mg for a single dose.

The multicenter, open-label, single-group study MT-1186-A01 (N = 185) evaluated the longer-term safety and tolerability of oral edaravone in patients with ALS living and functioning independently with first symptom of ALS occurring within the previous 3 years and who had a baseline forced vital capacity (FVC) of at least 70%. At the time of the review, results are available at 24 weeks. Patients received edaravone as a 105 mg oral suspension administered in accordance with the Health Canada–approved regimen. The concomitant use of riluzole was permitted throughout the study.

Efficacy Results

According to the sponsor's conclusions, Study MT-1186-J03 showed that oral suspension edaravone 105 mg was bioequivalent to an IV formulation of edaravone 60 mg in healthy Japanese volunteers. In this analysis, oral edaravone had equivalent $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$ of unchanged edaravone compared to the IV formulation, as both geometric mean ratio and 90% confidence interval (CI) were within the range of 0.80 to 1.25. As for C_{max}, the geometric mean ratio and its lower limit of the 90% CI were also within the prespecified limits, while the upper limit of the 90% CI exceeded 1.25.

Harms Results

One patient in each treatment group reported an adverse event (AE) of mild intensity in the single-dose bioequivalence study MT-1186-J03, which were not judged to be reasonably related to the investigational products by the investigator. There were no serious adverse events (SAEs), no withdrawals due to AEs (WDAEs), and no AEs of special interest reported in the study.

Results from the single-group safety study MT-1186-A01 in patients with ALS were reported for the 24-week interim analysis. A total of 79% of patients experienced at least 1 AE; however, discontinuation due to adverse events was low (6%), suggesting the harm profile might be considered acceptable. SAEs were reported by 11% of patients; the most frequently reported were likely related to the disease: ALS (n = 5), dyspnea (n = 3), and respiratory failure (n = 3). Six patients died over the 24-week study period; causes of death were respiratory failure (n = 3), pneumonia (n = 1), suicide (n = 1) and ALS (n = 1). Among AEs of special interest, 8 patients reported cardiac disorders. All cardiac events arose from ECG findings, with the exception of 1 patient with cardiac failure, so the sponsor considered that they did not reveal a signal of concern.

Critical Appraisal

The most significant limitation associated with the included trials is the study designs. The bioequivalence design in healthy participants and the open-label uncontrolled study are not sufficient designs to evaluate the comparative clinical value added for the drug in the target population for reimbursement. The key assumption of the submission is that given IV edaravone has been approved by Health Canada and recommended for reimbursement by CADTH, establishing bioequivalence is sufficient for establishing clinical value of oral edaravone. However, the 2 formulations (solution for injection and oral suspension) cannot be considered bioequivalent since it involves 2 different dosage forms. Whether they can be considered to display comparable bioavailability of edaravone upon administration is to be assessed by Health Canada during formal review. While there is merit and supporting precedence to the assumption of comparable bioavailability, there remains a degree of uncertainty as to the true treatment effects of oral edaravone given the bioequivalence study design (i.e., single administration, assessing pharmacokinetic [PK] parameters with estimates falling within a range of acceptable values to establish equivalence) and lack of comparative evidence between the PO and IV formulations on clinical outcomes.

The single-dose bioequivalence study MT-1186-J03 does not inform on the efficacy of a Health Canada–approved dosage regimen of oral edaravone in ALS patients on outcomes that are relevant to patients living with the disease. The fact that study MT-1186-A01 was an open-label, uncontrolled trial subjects the study to a high risk of bias and limits the conclusions that can be drawn from the findings. The lack of comparative data for the outcomes of motor function, mobility, muscle pain and fatigue, as well as difficulty breathing and speaking, which were identified by ALS patients as the most important symptoms to control according to the patient input received, is an important gap in the evidence.

Economic Evidence

Cost and Cost-Effectiveness

At the submitted price of $9,200 per 1,050 mg/50 mL bottle or $12,880 per package of 2 of the 735 mg/35 mL bottles, the annual drug cost per patient of treatment with oral edaravone is $123,280 in the first year and $119,600 per subsequent year, which is equivalent to the drug acquisition cost of IV edaravone at publicly available prices. CADTH conducted a reanalysis of the sponsor-submitted cost comparison, considering that costs associated with IV administration and IV-related adverse events differ in the first and subsequent years of therapy. In this analysis, where some of the IV administration costs were assumed to be borne by the sponsor's patient support program (PSP), oral edaravone was associated with an average cost savings of $1,649 per patient compared to IV edaravone in the first year of therapy, and $1,105 per patient in subsequent years of therapy to the public health-care payer.

The cost comparison assumes clinical similarity between the oral and IV formulations of edaravone, based on the sponsor's submitted single-dose bioequivalence study and an uncontrolled, open-label safety study. CADTH was unable to account for uncertainties in neither the comparative clinical effectiveness and safety between edaravone products, nor the confidential pricing and stipulations that may have been negotiated for IV edaravone.

Budget Impact

CADTH identified the following key limitations with the sponsor's budget impact analysis: The use of the sponsor's internal data precludes external validation; the Non-Insured Health Benefits (NIHB) and Ontario Drug Benefit (ODB) populations were inappropriately calculated; the increased uptake of edaravone due to the oral formulation may be underestimated; the proportion of patients on edaravone receiving the oral formulation may be underestimated. CADTH's reanalyses included correcting the NIHB and ODB client eligibility, increasing the uptake of edaravone, and increasing the proportion of patients on edaravone using the oral formulation. These reanalyses suggest that the reimbursement of oral edaravone for the treatment of ALS from a drug plan payer's perspective would be associated with a budgetary increase of $6,266,202 in year 1, $12,861,092 in year 2, and $19,582,815 in year 3, for a 3-year incremental budget impact of $38,710,109. The 3-year incremental budget impact of reimbursing oral edaravone from a health-care payer perspective would be $38,359,198. These estimates are substantially different from those estimated in the sponsor's base case.

CDEC Information

Members of the Committee

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

Meeting date: July 28, 2022

Regrets: Two expert committee members did not attend

Conflicts of interest: None