CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

EDARAVONE (RADICAVA — MITSUBISHI TANABE PHARMA CORPORATION)
Indication: For the treatment of amyotrophic lateral sclerosis.

RECOMMENDATION
The CADTH Canadian Drug Expert Committee recommends that edaravone be reimbursed for the treatment of amyotrophic lateral sclerosis (ALS), if the following conditions are met:

Conditions for Reimbursement

Initiation Criteria
1. Patient with a diagnosis of probable ALS or definite ALS
2. Patient who meets all of the following:
   - 2.1. has scores of at least two points on each item of the ALS Functional Rating Scale – Revised (ALSFRS-R)
   - 2.2. has a forced vital capacity greater than or equal to 80% of predicted
   - 2.3. has had ALS symptoms for two years or less
   - 2.4. patient is not currently requiring permanent non-invasive or invasive ventilation.

Administration Criteria
1. Patient must be under the care of a specialist with experience in the diagnosis and management of ALS.

Renewal Criteria
1. Reimbursement of treatment should be discontinued in patients who meet any one of the following 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
   - 1.2. patient requires permanent non-invasive or invasive ventilation.

Pricing Condition
1. Reduction in price.

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Redactions: Confidential information in this document has been redacted at the request of the manufacturer in accordance with the *CADTH Common Drug 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.

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2. Patient who meets all of the following:
   - 2.1. has scores of at least two points on each item of the ALS Functional Rating Scale – Revised (ALSFRS-R)
   - 2.2. has a forced vital capacity (FVC) greater than or equal to 80% of predicted
   - 2.3. has had ALS symptoms for two years or less
   - 2.4. patient is not currently requiring permanent non-invasive or invasive ventilation.

Administration Criteria

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   - 1.2. patient requires permanent non-invasive or invasive ventilation.

Pricing Condition

1. Reduction in price.

Reasons for the Recommendation

1. In one double-blind, parallel-group, randomized controlled trial (RCT) (Study 19; N = 137 patients), edaravone was found to have a statistically significant and potentially clinically important improvement from baseline on motor function, based on the ALSFRS-R total score, as compared with placebo at 24 weeks (least squares mean [LSM] difference of 2.49 [95% confidence interval (CI), 0.99 to 3.98]). Edaravone also slowed the rate of decline in motor function as compared with placebo (–0.88 units per cycle versus –1.35 units per cycle, respectively; LSM difference of 0.47 [95% CI, 0.19 to 0.74]). These findings were supported by improvements with edaravone, as compared with placebo, on the modified Norris Scale total score (motor function) and ALS Assessment Questionnaire-40 (ALSAQ-40) (health-related quality of life). No serious safety signals were identified during the clinical trial. Although more patients in the edaravone group than in the placebo group reported serious adverse events (SAEs), these likely represented worsening of their disease. Patients had to be categorized as definite ALS or probable ALS, have grade 1 or 2 ALS, score at least two points on each item of the ALSFRS-R, have an FVC of at least 80% predicted, and be within two years of ALS symptom onset to be eligible for participation in Study 19.
2. ALS is a life-altering, rare, and seriously debilitating disease, which may progress rapidly. There is no currently available treatment that effectively addresses the underlying neurologic degeneration associated with ALS.
3. The manufacturer-submitted price of edaravone is $1,424 per 60 mg, or $1,424 per patient daily, and $185,182 per patient annually ($190,880 in the first year of treatment). Reanalysis of the manufacturer-provided cost-utility model by the CADTH Common Drug Review (CDR) estimated the incremental cost-utility ratio (ICUR) for edaravone compared with standard of care to be greater than $1.9 million per quality-adjusted life-year (QALY).

Implementation Considerations

- The administration schedule for edaravone is complex and requires that patients receive infusions over 10 to 14 days each month. It is unclear what proportion of patients will receive edaravone infusions at a dedicated administration clinic or hospital (compared with their home), which could create logistical complications for patients eligible for treatment.
- The budget impact of using edaravone may be considerable given the high cost of the drug, even if the price is reduced significantly. Hence, it is important to identify those patients who are most likely to benefit from treatment, and in whom the treatment is considered most cost-effective.

Discussion Points

- CDEC discussed the results of four studies on the efficacy and safety of edaravone for the treatment of ALS. Only Study 19 showed benefit in the primary efficacy outcome for edaravone in a select ALS patient subpopulation.
- CDEC considered clinician expert input that patients who start treatment early in the course of ALS are most likely to benefit from edaravone. Currently, evidence for the benefit of edaravone treatment over placebo, from Study 19, is limited to patients diagnosed with probable or definite ALS and who had ALS symptom onset two years or less before enrollment into the study.

- CDEC heard from clinicians with experience in the diagnosis and management of ALS that patients with this condition require a multidisciplinary health care approach to managing their disease. Patient outcomes are more likely to be improved if patients receive edaravone in combination with coordinated care from other health professionals at centres with health care teams that have experience in managing patients with ALS.

Background

Edaravone has a Health Canada indication for the treatment of ALS. Edaravone is a free radical scavenger. It is available as 30 mg edaravone in a 100 mL isotonic, sterile, aqueous solution and the Health Canada–approved dose is an intravenous infusion of 60 mg administered over a 60-minute period according to the following schedule: an initial treatment cycle with daily doses for 14 days, followed by a 14-day drug-free period; subsequent treatment cycles with daily doses for 10 days out of a 14-day period, followed by 14-day drug-free periods.

Summary of Evidence Considered by CDEC

The committee considered the following information prepared by CDR: a systematic review of RCTs of edaravone and a critique of the manufacturer's pharmacoeconomic evaluation. The committee also considered input from clinical experts with experience in treating patients with ALS, and patient group–submitted information about outcomes and issues important to patients.

Summary of Patient Input

The ALS Society of Canada, in coordination with seven provincial ALS societies, provided input for this submission. Patient perspectives were obtained from a survey of patients and caregivers and two focus groups. The following is a summary of key input from the perspective of the patient group:

- ALS is a degenerative, terminal disease that typically causes death within two to five years of diagnosis. Patients described the disease as "advancing paralysis" that causes a wide range of symptoms that profoundly impact the lives of both the patients and their caregivers. Symptoms can progress rapidly and the burden of medical equipment and resulting home renovations can cause an enormous financial burden.

- There is no cure for ALS and the only disease-modifying treatment available for ALS is the oral agent riluzole, which has a modest benefit in reducing tracheostomy-free survival and has contraindications for patients with hepatic disease or elevated liver enzymes. There was mixed feedback regarding the efficacy of riluzole, with some patients describing an improvement in mood and energy, and others noting no improvement at all. Patients also found the drug to be restrictive and only effective during a certain time period of the disease.
- ALS symptoms may be managed to varying degrees by a range of pharmacologic therapies. These drugs are associated with a wide range of adverse effects. With the use of multiple medications patients also reported experiencing sleepiness, diarrhea, constipation, fatigue, and mood changes, which impacts their ability to function. Additionally, some oral medications can be difficult for patients with ALS to swallow.
- Although multidisciplinary non-pharmacologic care is important for managing symptoms and improving the quality of life of patients with ALS, only approximately half of patient respondents reported having access to a multidisciplinary care clinic. There were difficulties reported in travelling to clinics and delays in accessing equipment and devices, allied health services, and home care, as well as limitations to government-funded programs.
- Aside from a cure for ALS, patients value treatments that would enable them to maintain the ability to perform activities of daily living, give them more time with family and friends, and control symptoms. Treatments that prolong survival would give patients hope, more time with loved ones, delay in loss of function, and delay in needing more invasive treatment.
- Patients and caregivers are hoping for a drug that slows down the progression of ALS. Despite the logistical and financial challenges associated with edaravone treatment, most patients are willing to try the treatment with hopes that it will meet their expectations.
- Of the patients who had experience with edaravone treatment, most agreed that it controlled their ALS symptoms better than any other treatment they used, though some reported not experiencing any benefit with edaravone treatment.

Clinical Trials

The systematic review included four double-blind, parallel-group, placebo-controlled RCTs of patients with ALS.

- Three trials in patients randomized (1:1) to edaravone or placebo:
  - Study MCI186-16 (N = 206; referred to here as “Study 16”; conducted from 2006 to 2008)
  - Study MCI186-18 (N = 25; referred to here as “Study 18”; conducted from 2006 to 2008)
  - Study MCI186-19 (N = 137; referred to here as “Study 19”; conducted from 2011 to 2014).
- Study MCI186-17 (N = 181; referred to here as “Study 17”; conducted from 2007 to 2009) included only patients who had completed Study 16. Patients assigned to edaravone in Study 16 were assigned to either edaravone (edaravone-edaravone group) or placebo (edaravone-placebo group) in Study 17, according to randomization performed at the start of Study 16. Patients who received placebo in Study 16 were assigned to edaravone in Study 17 (placebo-edaravone group).

To be eligible for Study 16, patients had to be categorized as definite ALS, probable ALS, or “probable ALS – laboratory supported” according to the El Escorial revised Airlie House diagnostic criteria, have grade 1 or 2 ALS according to the Japanese ALS severity classification, have an FVC of at least 70% of predicted, and be within three years of ALS onset. The inclusion criteria were the same in Study 18 as for Study 16, except that patients had to have grade 3 ALS according to the Japanese ALS severity classification and an FVC of at least 60% of predicted.

To be eligible for Study 19, patients had to be categorized as definite ALS, or probable ALS, have grade 1 or 2 ALS, have an FVC per cent predicted of at least 80%, be within two years of ALS onset, and score at least two points for each item of the ALSFRS-R. In studies 16, 18, and 19, patients had to have a decrease in ALSFRS-R score of one to four points during the 12-week pre-observation period prior to initiation of treatment.

Patients received either 60 mg of edaravone or placebo diluted in saline and intravenously infused over 60 minutes once a day. In the first treatment cycle in studies 16, 18, and 19, the study treatment was administered daily for 14 consecutive days, followed by a two-week period with no study treatment administration. In subsequent treatment cycles (including the first cycle in Study 17), the study treatment was administered for a total of 10 days within the first 14 days, followed by a two-week treatment-free period. In all

four trials, double-blind study treatment lasted for six treatment cycles or a total of 24 weeks. The concomitant use of riluzole was allowed with no change in dose or administration route during the trials, though riluzole therapy could not be initiated during the trials.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, the committee discussed the following: ALSFRS-R score, occurrence of death or certain disease progression, Modified Norris Scale, ALSAQ-40 score, and FVC per cent predicted. The primary outcome in studies 16, 17, and 19 was change in mean ALSFRS-R total score from baseline to the end of treatment. Study 18 was an exploratory trial with no primary end point.

Efficacy

Studies 16, 17, and 18 showed no statistically significant differences in the change from baseline to the end of treatment in ALSFRS-R total score between the edaravone and placebo groups. In Study 16, the change in ALSFRS-R score was –5.70 (standard error [SE] = 0.85) in the edaravone group and –6.35 (SE = 0.84) in the placebo group. In Study 17, the change in ALSFRS-R score was –4.42 (SE = 0.69) in the edaravone-edaravone group and –5.58 (SE = 0.74) in the edaravone-placebo group. In Study 18, the change in ALSFRS-R score was –6.52 (SE = 1.78) in the edaravone group and –6.00 (SE = 1.83) in the placebo group.

Study 19 showed a statistically significant difference in the change from baseline to the end of treatment in ALSFRS-R total score between the edaravone (–5.01 [SE = 0.064]) and placebo groups (–7.5 [SE = 0.66]), with an LSM difference of 2.49 (95% CI, 0.99 to 3.98) in favour of edaravone. In a secondary analysis using a mixed-effects model, the expert-determined clinically meaningful change of 20% in the slope of decline was exceeded. The slope of decline in the edaravone treated group was –0.88 units per cycle (four-week period) compared with –1.35 units per cycle in the placebo group (LSM difference = 0.47; 95% CI, 0.19 to 0.74). In addition, the Modified Norris Scale and the ALSAQ-40 showed a nominal statistical significance favouring edaravone over placebo in total score, although a minimal clinically important difference was not found for the total score for either instrument.

In all four trials, survival analysis did not show any differences between treatment groups in death or certain disease progression events and there were no differences in pulmonary function assessed through FVC per cent predicted. Outside of Study 19, there were no differences between treatment groups in the ALSAQ-40.

Harms (Safety)

There were no notable differences between treatment groups in adverse events (AEs) in any of the trials. The percentage of patients receiving edaravone versus placebo with at least one AE was 89.2% versus 88.5% in Study 16; 91.7% (edaravone-edaravone group) versus 97.8% (edaravone-placebo group) in Study 17; 92.3% versus 100.0% in Study 18; and 84.1% versus 83.8% in Study 19. The most commonly reported AEs were infections and infestations and gastrointestinal disorders.

The percentage of patients receiving edaravone versus placebo with at least one SAE was 17.6% versus 23.1% in Study 16; 52.1% (edaravone-edaravone group) versus 28.9% (edaravone-placebo group) in Study 17; 23.1% versus 16.7% in Study 18; and 15.9% versus 23.5% in Study 19. The most commonly reported SAEs were dysphagia, musculoskeletal disorder, and respiratory failure.

Notable harms related to the method of administration were not considered serious aside from one SAE of catheter site infection in the placebo-edaravone group of Study 17. AEs related to injection, infusion, or catheter site were each reported in less than 5% of each group in all the trials. Respiratory failure and respiratory-related disorders were the cause of death in the all cases except for one death that was due to cardiac arrest. Similar to Study 17, an extension to Study 19 did not identify any new safety signals when edaravone was administered for up to 48 weeks.

Cost and Cost-Effectiveness

The manufacturer submitted a price of $1,424 per 60 mg of edaravone, which is available as a 30 mg/100 mL solution for infusion. It is intravenously administered as 60 mg infusions over 60 minutes daily for 10 days out of a 14-day period, followed by a 14-day drug-

free period. In the first month of treatment, edaravone is administered for 14 days (rather than 10). The cost of edaravone is $1,424 per patient for each day it is administered or $185,182 per patient annually ($190,880 in the first year of treatment).

The manufacturer submitted a cost-effectiveness analysis based on a Markov state-transition model comparing current standard of care (interdisciplinary supportive care plus riluzole) to edaravone plus current standard of care. In standard of care, 85% of patients were concurrently taking riluzole, the only disease-modifying treatment currently available for ALS. The manufacturer assumed that all patients, at any stage of the disease, were eligible for edaravone therapy and that edaravone slowed disease progression at all stages of the disease. The manufacturer did not assume a direct treatment effect on disease-specific mortality. The analysis was run over a 20-year time horizon using a three-month cycle length. The analysis was conducted from the perspective of the Canadian public health care system. The manufacturer's analysis indicated that edaravone is not cost-effective compared with standard of care, with an ICUR of $1,957,200 per QALY gained.

CADTH identified a several key limitations with the manufacturer's economic model and analysis, which had the potential for a direct impact on the estimates of cost-effectiveness of edaravone:

- The manufacturer considered a cohort of patients with various disease severity levels at treatment initiation, which averaged the cost-effectiveness of treatment with edaravone across different patient groups. Other patient characteristics, such as age of onset, region of onset, gender, and age, were not described for the initial patient cohort, nor how these features affect disease progression.
- The manufacturer did not permit disease progression to non-adjacent states (i.e., progression from Stage 1 to Stages 3 or 4A) in its model, which is inconsistent with the disease natural history. This is a key limitation as the model does not accurately capture the progression of ALS.
- The manufacturer assumed that edaravone is equally effective at reducing the disease progression rate at all stages of the disease. This is inconsistent with the proposed mechanism of action and clinical evidence stratified by disease severity, where available, which suggest greater progression benefit for patients in the earlier stages of ALS. This further highlights the importance of conducting stratified analyses.
- The manufacturer's analysis only included the costs of twelve 28-day treatment cycles per year. However, there are thirteen 28-day cycles per year, underestimating the treatment cost by $14,245 per year.
- The manufacturer assumed little to no costs associated with drug administration. For patients living at home, it proposed that these costs would not be incurred by a public payer but covered by a manufacturer-sponsored patient support program. For patients living in a health care facility, it did not consider the opportunity cost of nursing time to administer the drug. Where any of the administration cost is borne on the public payer, this will increase the ICUR for edaravone.
- The manufacturer assumed substantially higher health care costs by ALS disease stage than reported in the literature. The estimates used by the manufacturer do not appear to reflect the Canadian setting.

CDR reanalysis addressed all of the previously mentioned concerns: changes to the ALS natural history transitions enabling progressive transitions to non-adjacent health states; using a constant hazard rate and hazard rate ratio approach for estimating the clinical effectiveness of edaravone; incorporating the costs of one additional treatment cycle per year; revised costs for administration of edaravone; and, revised costs for non-drug ALS-stage-stratified health care. CDR also explored uncertainty in disease progression and mortality rates to gain insight into how patient heterogeneity may affect the cost-effectiveness of edaravone compared with standard of care. Scenario analyses were also performed to explore the potential impacts of differential treatment effectiveness by disease stage, stopping rules for edaravone after disease progression, and the annual cost of edaravone.

CDR found that the ICUR for edaravone compared with standard of care ranges from $1,441,000 per QALY gained in patients with Stage 1 ALS to $3,152,000 per QALY gained in patients with Stage 3 ALS. A 95% price reduction is required to reduce the ICUR to less than $200,000 per QALY gained in patients with Stage 1 ALS. At price reductions of more than 97%, the ICUR for edaravone remains more than $200,000 per QALY gained for patients treated in other stages. Sensitivity analysis indicated that three factors can substantially lower the incremental cost-effectiveness of edaravone compared with standard of care: substantial price reduction for edaravone, higher level of effectiveness in the early stages of ALS, and hard-stopping rules after progression to King's ALS Stage 2 or 3.

CDEC Members

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Ms. Heather Neville, Mr. Allen Lefebvre, Dr. Rakesh Patel, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

November 21, 2018 Meeting (Initial)

Regrets

Three CDEC members did not attend.

Conflicts of Interest

None

March 20, 2019 Meeting (Reconsideration)

Regrets

None

Conflicts of Interest

None