Drug Coverage Decision for B.C. PharmaCare

About PharmaCare B.C. PharmaCare is a government-funded drug plan. It helps British Columbians with the cost of eligible prescription drugs and specific medical supplies.

Details of Drug Reviewed

Drug	**edaravone**
Brand Name	Radicava™
Dosage Form(s)	30 mg/100 mL solution for intravenous infusion
Manufacturer	Mitsubishi Tanabe Pharma America, Inc.
Submission Type	**New Submission**
Use Reviewed	For the treatment of amyotrophic lateral sclerosis (ALS).
Common Drug Review (CDR)	Yes, CDR recommended: **to Reimburse with clinical criteria and/or conditions**. Visit the CDR website for more details: https://www.cadth.ca/sites/default/files/cdr/complete/sr0573-radicava-cdec-rec-march-29-2019.pdf
Drug Benefit Council (DBC)	On May 6, 2019 the DBC met and reviewed the drug submission of edaravone for the treatment of ALS. In their review, the DBC considered the following: the final reviews released by the CDR on March 27, 2019, which included clinical and pharmacoeconomic evidence review material and the recommendations from the Canadian Drug Expert Committee (CDEC). The DBC also considered Patient Input Questionnaire responses from 13 patients, six caregivers, and one Patient Group, patient input received by the CDR, Clinical Practice Reviews from one specialist, and an Other Drug Agencies Review Recommendations document from the Canadian Agency for Drugs and Technologies in Health (CADTH). The DBC recommended edaravone (Radicava®) not be listed.
Drug Coverage Decision	**Limited Coverage Benefit.** Access the edaravone criteria at **www.gov.bc.ca/pharmacarespecialauthority**

Date	August 19, 2020
Reason(s)	• Drug coverage is consistent with the CDEC recommendation and coverage in other Canadian provinces. • In a systematic review of four clinical trials evaluating the efficacy and safety of edaravone versus placebo in patients with ALS, edaravone was found in only one trial, which included a select ALS patient subpopulation, to have a statistically significant and potentially clinically important improvement from baseline on motor function and to have slowed the rate of decline. • None of the studies showed a difference between treatment groups in death or certain disease-progression events, nor did any of the included studies show a statistically significant difference in pulmonary function. • ALS is a life-altering, rare, and seriously debilitating disease, which may progress rapidly. ALS is characterized by the degeneration of motor neurons and progressive muscle weakness. ALS typically causes death within two to five years of diagnosis. • Currently, there is no cure for ALS and the only treatment available is the oral agent riluzole. Although characterized as modest, riluzole did show benefits in patients' survival rate. There are no head-to-head trials comparing riluzole to edaravone. • At the submitted price the cost of edaravone is extremely high and is not cost-effective.The CDEC recommended that price of edaravone should be substantially reduced. • BC participated in the pan-Canadian Pharmaceutical Alliance (pCPA) negotiations with the manufacturer and an agreement was reached.
Other Information	None

The Drug Review Process in B.C.

A manufacturer submits a request to the Ministry of Health (Ministry).

An independent group called the Drug Benefit Council (DBC) gives advice to the Ministry. The DBC looks at:

- whether the drug is safe and effective
- advice from a national group called the Common Drug Review (CDR)
- what the drug costs and whether it is a good value for the people of B.C.
- ethical considerations involved with covering or not covering the drug
- input from physicians, patients, caregivers, patient groups and drug submission sponsors

The Ministry makes PharmaCare coverage decisions by taking into account:

- the existing PharmaCare policies, programs and resources
- the evidence-informed advice of the DBC
- the drugs already covered by PharmaCare that are used to treat similar medical conditions
- the overall cost of covering the drug

Visit the The Drug Review Process in B.C. - Overview and Ministry of Health - PharmaCare for more information.

This document is intended for information only.
It does not take the place of advice from a physician or other qualified health care provider.

Drug Benefit Council (DBC) Recommendation and Reasons for Recommendation

FINAL

Edaravone (Radicava®)
Mitsubishi Tanabe Pharma Corporation

Description:

Drug review of edaravone (Radicava®) for the following Health Canada approved indications:

For the treatment of amyotrophic lateral sclerosis (ALS).

In their review, the DBC considered the following: the final reviews completed by the Common Drug Review (CDR) on March 27, 2019, which included clinical and pharmacoeconomic evidence review material and the recommendations from the Canadian Drug Expert Committee (CDEC). The DBC also considered Patient Input Questionnaire responses from 13 patients, six caregivers, and one Patient Group, patient input received by the CDR, Clinical Practice Reviews from one specialist, and an Other Drug Agencies Review Recommendations document from the Canadian Agency for Drugs and Technologies in Health (CADTH).

Dosage Forms:

Radicava® is available as edaravone intravenous solution, 30 mg/100 mL per infusion bag.

Recommendations:

The Drug Benefit Council (DBC) recommends that edaravone (Radicava®) not be listed.

Reasons for the Recommendation:

1. Summary

- In a systematic review of four double-blind, parallel-group, placebo-controlled randomized controlled trials (RCTs) evaluating the efficacy and safety of edaravone versus placebo in patients with ALS, edaravone was found in only one trial to have a statistically significant and potentially clinically important improvement from baseline on motor function and to have slowed the rate of decline in motor function as compared with placebo at 24 weeks.
- None of the RCTs showed a difference between treatment groups in death or certain disease-progression events, nor did any of the included studies show a statistically significant difference in pulmonary function. Only one study showed a result favoring edaravone with regards to muscle strength or quality of life.
- CDR found that edaravone was not a cost-effective treatment for patients with ALS at any stage of the disease.
- The merits of each study were carefully reviewed, and the final recommendation is based on a consideration of the totality of evidence available.

2. Clinical Efficacy

- The DBC considered the CDR systematic review, which included four double-blind, parallel-group, placebo-controlled RCTs evaluating the efficacy and safety of edaravone versus placebo in patients with ALS.
- Three trials randomized patients 1:1 to edaravone or placebo: Study MCI186-16 (subsequently referred to as Study 16), Study MCI186-18 (Study 18), and Study MCI186-19 (Study 19). Study MCI186-17 (Study 17) included only patients who had completed Study 16, with patients assigned to edaravone in Study 16 assigned to either edaravone or placebo, and patients who received placebo in Study 16 assigned to edaravone.
- The primary outcome in studies 16, 17, and 19 was change in mean ALS Functional Rating Scale – Revised (ALSFRS-R) total score from baseline to the end of treatment. Other outcomes discussed were occurrence of death or certain disease progression, Modified Norris Scale (a motor function), ALS Assessment Questionnaire-40 (ALSAQ-40) score (a health-related quality of life outcome), and forced vital capacity (FVC) per cent predicted. Study 18 was an exploratory trial with no primary end point.
- 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 19, 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. Edaravone also slowed the rate of decline in motor function as compared with placebo. These findings were supported by improvements with edaravone, as compared with placebo, on the modified Norris Scale total score (motor function) and ALSAQ-40.
- Only Study 19 showed benefit in the primary efficacy outcome for edaravone in a select ALS patient subpopulation. Other outcomes related to respiratory function, strength, and disease severity classification did not show between-group differences. No statistically significant finding was demonstrated in other studies.
- 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 percent predicted.
- For detailed information on the systematic review of edaravone please see the CDEC Final Recommendation at: https://www.cadth.ca/edaravone.

3. Safety

- No serious safety signals were identified during Study 19 trial. more patients in the edaravone group than in the placebo group reported serious adverse events (SAEs), although these likely represented worsening of their disease.
- For detailed information on the safety and tolerability of edaravone, please see the CDEC Final Recommendations at the links above.

4. Economic Considerations

- The manufacturer-submitted price of edaravone is $1,424 per patient daily, and $185,182 per patient annually ($190,880 in the first year of treatment).
- In agreement with CADTH, at the manufacturer's submitted price, the estimated incremental cost-utility ratio (ICUR) for edaravone compared with standard of care ranges from $1,441,000 in stage 1 ALS to $3,152,000 per quality-adjusted life-year (QALY) gained in patients in stage 3 ALS. A 95 percent price reduction is required to reduce the ICUR to less than $200,000 per QALY gained in patients with stage 1 ALS, while even

at a 97 percent price reduction, the ICUR remains more than $200,000 per QALY for patients treated in other stages.

5. Of Note

- 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. The DBC considered both the unmet need and severity of the disease. These are only two of several factors that are evaluated by the DBC and the final recommendation reflects the totality of the evidence reviewed.

The DBC also received Patient Input Questionnaire responses from 13 patients, six caregivers, and one Patient Group. Several patients reported they had received treatment with edaravone. One patient reported less fatigue, less muscle ache and less spasms and cramping while receiving edaravone but symptoms reverted to baseline after treatment stopped. Patients and caregivers responded that more treatment options are needed for ALS, but several patients also expressed concerns about the cost of the drug in Canada.