

Radicava® (Edaravone)

Policy Number: 2024D0062K
Effective Date: May 1, 2024

[➔ Instructions for Use](#)

| Table of Contents | Page |
|---|------|
| Coverage Rationale | 1 |
| Applicable Codes | 2 |
| Background | 2 |
| Benefit Considerations | 2 |
| Clinical Evidence | 2 |
| U.S. Food and Drug Administration | 3 |
| References | 3 |
| Policy History/Revision Information | 4 |
| Instructions for Use | 5 |

| Related Commercial Policy |
|--|
| <ul style="list-style-type: none"> Provider Administered Drugs – Site of Care |
| Community Plan Policy |
| <ul style="list-style-type: none"> Radicava® (Edaravone) |

Coverage Rationale

[➔ See Benefit Considerations](#)

This policy refers to Radicava (edaravone) for administration by intravenous infusion by a healthcare professional. Radicava ORS (edaravone) oral suspension is obtained under the pharmacy benefit.

Radicava (edaravone) is proven and medically necessary for¹ the treatment of amyotrophic lateral sclerosis (ALS) in patients who meet all of the following criteria:

- For **initial therapy**, all of the following:
 - Submission of medical records (e.g., chart notes, previous medical history, diagnostic testing including: imaging, nerve conduction studies, laboratory values) to support¹⁴ the diagnosis of “definite” or “probable” ALS per the El Escorial/revised Airlie House diagnostic criteria, and prescribed by, or in consultation with, a neurologist with expertise in the diagnosis of ALS; **and**
 - Submission of the most recent [ALS Functional Rating Scale-Revised \(ALSFRS-R\) score](#) confirming that the patient has scores ≥ 2 in **all** items of the ALSFRS-R criteria at the start of treatment¹³; **and**
 - Submission of medical records (e.g., chart notes, laboratory values) confirming that the patient has a % forced vital capacity (%FVC) $\geq 80\%$ at the start of treatment¹³; **and**
 - Radicava dosing for ALS is in accordance with the United States Food and Drug Administration approved labeling; **and**
 - Provider attestation that the patient or caregiver is not competent or is physically unable to administer Radicava ORS oral suspension either orally or via feeding tube; **and**
 - Initial authorization will be for no more than 12 months.
- For **continuation of therapy**, all of the following:
 - Diagnosis of “definite” or “probable” ALS per the El Escorial/revised Airlie House diagnostic criteria, and prescribed by, or in consultation with, a neurologist with expertise in the diagnosis of ALS; **and**
 - Patient is currently receiving Radicava therapy; **and**
 - Patient is **not** dependent on invasive ventilation or tracheostomy; **and**
 - Radicava dosing for ALS is in accordance with the United States Food and Drug Administration approved labeling; **and**
 - Provider attestation that the patient or caregiver is not competent or is physically unable to administer Radicava ORS oral suspension either orally or via feeding tube; **and**
 - Authorization will be for no more than 12 months.

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

| HCPCS Code | Description |
|------------|----------------------------|
| J1301 | Injection, edaravone, 1 mg |

| Diagnosis Code | Description |
|----------------|-------------------------------|
| G12.21 | Amyotrophic lateral sclerosis |

Background

Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, is a rapidly progressive, invariably fatal neurological disease that attacks neurons responsible for controlling voluntary muscles. The disease belongs to a group of disorders known as motor neuron diseases, which are characterized by the gradual degeneration and death of motor neurons. Eventually, all muscles under voluntary control are affected. Individuals lose their strength and the ability to move their arms, legs, and body. When muscles in the diaphragm and chest wall fail, individuals lose the ability to breathe without ventilatory support. Individuals with ALS usually survive for only 3 to 5 years from the onset of symptoms. However, about 10 percent of those with ALS survive for 10 or more years.⁸

The mechanism by which Radicava (edaravone) exerts its therapeutic effect in patients with ALS is unknown.¹ It has been characterized as a free radical scavenger, which is thought to block radicals that mediate both neuronal and vascular damage.⁹⁻¹⁰

Benefit Considerations

Some Certificates of Coverage allow for coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The member specific benefit plan document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances when certain conditions are met. Where such mandates apply, they supersede language in the benefit document or in the medical or drug policy. Benefit coverage for an otherwise unproven service for the treatment of serious rare diseases may occur when certain conditions are met. Refer to the Policy and Procedure addressing the treatment of serious rare diseases.

Clinical Evidence

The efficacy and safety of edaravone for amyotrophic lateral sclerosis (ALS) was examined in a double-blind, parallel-group, placebo-controlled, phase III trial.¹⁰ The 36-week confirmatory trial consisted of a 12-week pre-observation period followed by a 24-week treatment period. The eligible patient population included those who were diagnosed with ALS as defined as "definite ALS," "probable ALS" or "probable-laboratory-supported ALS" based on the revised El Escorial World Federation of Neurology criteria, also known as Airlie House criteria. With their baseline disease state, patients also must have been able to eat a meal, excrete, or move with oneself alone, and did not need assistance in everyday life. Patients must have begun the trial within 3 years after onset of ALS and have a FVC of at least 70%. Patients who complained of dyspnea and had deterioration of respiratory function, among other criteria were excluded from the study. Patients aged 20 to 75 were randomized to receive either placebo (saline, n = 104), or edaravone (n = 102) 60mg intravenously per day. A single treatment cycle consisted of 14 days of study drug administration period followed by a 14-day observation period. Study drugs were administered every day for 14 days in the administration period of the first cycle, and for 10 out of 14 days in the administration periods of cycles 2 to 6. The end of the administration period in each cycle was followed by a 14-day observation period. Primary efficacy endpoint was the change in ALSFRS-R score. Secondary endpoints were: changes of FVC, grip strength (left/right mean), pinch strength

(left/right mean), Modified Norris Scale score, ALSAQ-40 (ALS Assessment Questionnaire), and time to death or a specified state of disease progression (incapable of independent ambulation, loss of function in upper limbs, tracheotomy, artificial respirator with intubation, or tube feeding). Changes in ALSFRS-R during the 24-week treatment were -6.35 ± 0.84 in the placebo group ($n = 99$) and -5.70 ± 0.85 in the edaravone group ($n = 100$), with a difference of 0.65 ± 0.78 ($p = 0.411$). The results with primary outcome, the inter-group difference in the change of the ALSFRS-R at the end of treatment, was not statistically significant. Of all of the secondary outcomes, edaravone only showed statistically significant benefit over placebo in pinch strength (-1.03 ± 0.15 placebo vs. -0.83 ± 0.15 edaravone; difference of 0.20 ± 0.14 ; $p = 0.165$). There were no significant differences in the safety profile reported between the two experimental groups. The authors admit that this study failed to demonstrate efficacy of edaravone to delay the progression of ALS.¹⁰

For post-hoc analysis, two subpopulations were identified in which edaravone might be efficacious, the efficacy-expected subpopulation (EESP), and the definite/probable EESP 2 years (dpEESP2y) subpopulation. The EESP group was defined by scores of ≥ 2 points on all 12 items of the ALSFRS-R and a %FVC $\geq 80\%$ at baseline. The dpEESP2y group, in addition to EESP criteria, had definite or probable ALS diagnosed by El Escorial revised criteria, and disease duration of ≤ 2 years. The primary endpoint for the efficacy analysis was the change in the ALSFRS-R score during a 24-week treatment period. Secondary endpoints included %FVC, Modified Norris Scale score, and ALS Assessment Questionnaire (ALSAQ-40) score. The full analysis set (FAS) included 205 patients (104 patients in the placebo group and 101 patients in the edaravone group). The EESP group included 104 patients (50 patients in the placebo group and 54 patients in the edaravone group). The dpEESP2y group included 72 patients (32 patients in the placebo group and 40 patients in the edaravone group). Results showed intergroup differences of the least-squares mean change in the ALSFRS-R score were 0.65 ($p = 0.4108$) in the FAS, 2.2 ($p = 0.036$) in EESP, and 3.01 ($p = 0.027$) in the dpEESP2y. The analysis showed a significant intergroup difference in both the EESP and dpEESP2y, with larger differences for dpEESP2y than for the EESP group. Similar differences were also seen for secondary endpoints.¹¹

The first phase III study (MCI186-16) was followed by a 36 week extension study (MCI186-17) to investigate the long-term efficacy and safety of edaravone in the FAS group compared to the EESP group. The extension study consisted of a 24-week double-blind comparison followed by 12 weeks of open-label edaravone. Efficacy endpoints were the same as MCI186-16. The intergroup difference between the treatment or placebo group for either the FAS or EESP groups were not statistically significant, however the difference was larger in the EESP (1.85, $p = 0.1127$) than in the FAS (1.16, $p = 0.2176$), similar to findings from MCI186-16.¹² Post-hoc analysis was performed for the dpEESP2y subgroup for the first 24 week placebo-controlled portion of MCI186-17. The difference in ALSFRS-R changes from 24 to 48 weeks between the edaravone and placebo groups was 2.79 ($p = 0.0719$), which was greater than the differences previously reported for the EESP and the FAS. The authors concluded that the post-hoc analysis suggests a potential effect of edaravone between 24 and 48 weeks in those meeting dpEESP2y criteria at baseline.¹³

The Canadian ALS Research Network (CALs) issued a guideline in 2020 providing best practice recommendations for the management of people living with ALS in Canada.¹⁶ CALs provided the following recommendations:

- In a select group of patients, intravenous edaravone has been shown to slow decline on the ALSFRS-R scores compared against intravenous placebo, over a 6-month period (level B). (These patients have shown benefit from edaravone: disease duration < 2 y, FVC $> 80\%$, all ALSFRS-R subcomponents scores > 2 , and demonstrated steady decline in the ALSFRS-R over a 3-mo interval.)
- Evidence for benefit of intravenous edaravone at other stages of ALS has not been demonstrated (Expert Consensus).
- As with any other therapies, individualized goals, risks and benefits should be carefully considered and discussed before intravenous edaravone is initiated (Expert Consensus).

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Radicava is indicated for the treatment of amyotrophic lateral sclerosis (ALS).¹

References

1. Radicava [Prescribing Information]. Jersey City, NJ: Mitsubishi Tanabe Pharma America, Inc.; December 2023.

2. Brooks BR, Miller RG, Swash M, Munsat TL; World Federation of Neurology Research Group on Motor Neuron Diseases. El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Other Motor Neuron Disord* 2000;1:293–299.
3. de Carvalho M, Dengler R, Eisen A, et al. Electrodiagnostic criteria for diagnosis of ALS. *Clin Neurophysiol* 2008; 119:497-503.
4. Geevasinga N, Menon P, Scherman DB, Simon N, Yiannikas C, Henderson RD, Kiernan MC, and Vucic S. Diagnostic criteria in amyotrophic lateral sclerosis: A multicenter prospective study. *Neurology*. 2016 Aug 16; 87(7): 684-90.
5. Cedarbaum JM, Stambler N, Malta E, Fuller C, Hilt D, Thurmond B, et al. The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. *J Neurol Sci*. 1999; 169(1): 13–21.
6. Castrillo-Viguera C, Grasso DL, Simpson E, Shefner J, Cudkowicz ME. Clinical significance in the change of decline in ALSFRS-R. *Amyotroph Lateral Scler*. 2010;11(1-2):178-80.
7. Cedarbaum JM, Mitsumoto H, Ringel S, Florence J, Sanjak M, and Brooks BR. The ALSFRS @ 20: Evolution Of The ALSFRS-R, History, Clinimetric Properties And Future Directions. [poster] [online]. Accessed on: February 6, 2023.
8. National Institute of Neurological Disorders and Stroke. Amyotrophic Lateral Sclerosis (ALS) Fact Sheet. Retrieved from: <https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Amyotrophic-Lateral-Sclerosis-ALS-Fact-Sheet>. Accessed on: January 12, 2024.
9. Nagase M, Yamamoto Y, Miyazaki Y, Yoshino H. Increased oxidative stress in patients with amyotrophic lateral sclerosis and the effect of edaravone administration. *Redox Rep*. 2016 May;21(3):104-12.
10. Abe K, Itoyama Y, Sobue G, Tsuji S, Aoki M, Doyu M, et al. Confirmatory double-blind, parallel-group, placebo-controlled study of efficacy and safety of edaravone (MCI-186) in amyotrophic lateral sclerosis patients. *Amyotroph Lateral Scler Frontotemporal Degener* 2014; 15(7–8):610–7.
11. The Edaravone (MCI-186) ALS 16 Study Group. A post-hoc subgroup analysis of outcomes in the first phase III clinical study of edaravone (MCI-186) in amyotrophic lateral sclerosis, Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration. 2017;18(sup1):11-19.
12. The Writing Group on Behalf of the Edaravone (MCI-186) ALS 17 Study Group. Exploratory double-blind, parallel-group, placebo-controlled extension study of edaravone (MCI-186) in amyotrophic lateral sclerosis, Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration. 2017;18(sup1):20-31.
13. Takahashi F, Takei K, Tsuda K, Palumbo J. Post-hoc analysis of MCI186-17, the extension study to MCI186-16, the confirmatory double-blind, parallel-group, placebo-control006Ced study of edaravone in amyotrophic lateral sclerosis. *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration*. 2017;18(sup1):32-39.
14. Subcommittee on Motor Neuron Diseases of World Federation of Neurology Research Group on Neuromuscular Diseases, El Escorial “Clinical Limits of ALS” Workshop Contributors. El Escorial World Federation of Neurology criteria for the diagnosis of amyotrophic lateral sclerosis. *J Neurol Sci* 1994; 124: 96–107.
15. Pharmaceuticals and Medical Devices Agency (2015). First Committee on New Drugs: Report on the Deliberation Results. Radicut. Available from: <http://www.pmda.go.jp/files/000212453.pdf>.
16. Shoosmith C, Abrahao A, Benstead T, et al. Canadian best practice recommendations for the management of amyotrophic lateral sclerosis. *CMAJ*. 2020;192(46):E1453-E1468. doi:10.1503/cmaj.191721.

Policy History/Revision Information

| Date | Summary of Changes |
|------------|---|
| 05/01/2024 | <p>Coverage Rationale</p> <ul style="list-style-type: none"> • Changed duration for initial authorization from “no more than <i>6 cycles (64 doses over 168 days)</i>” to “no more than 12 months” • Changed duration for reauthorization from “no more than <i>6 cycles (60 doses over 168 days)</i>” to “no more than 12 months” |

| Date | Summary of Changes |
|------|---|
| | <p data-bbox="337 138 643 172">Supporting Information</p> <ul data-bbox="337 176 1138 237" style="list-style-type: none"> <li data-bbox="337 176 1138 205">• Updated <i>References</i> section to reflect the most current information <li data-bbox="337 210 899 237">• Archived previous policy version 2023D0062J |

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

This Medical Benefit Drug Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence ([Medicare IOM Pub. No. 100-16, Ch. 4, §90.5](#)).

UnitedHealthcare may also use tools developed by third parties, such as the InterQual[®] criteria, to assist us in administering health benefits. UnitedHealthcare Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.