POLICY: Neurology – Edaravone Intravenous Utilization Management Medical Policy
- Radicava® (edaravone intravenous infusion – Mitsubishi Tanabe)

EFFECTIVE DATE: 1/1/2021
LAST REVISION DATE: 03/19/2025

COVERAGE CRITERIA FOR: All Aspirus Medicare Plans

OVERVIEW
Edaravone intravenous (IV) is indicated for the treatment of **amyotrophic lateral sclerosis** (ALS).[1,16]

Edaravone IV is an anti-oxidative, free radical scavenger which eliminates lipid peroxide and hydroxyl radicals; however, it is unknown exactly how Radicava IV exerts its therapeutic effect in ALS.[1-2]

Of note, Radicava ORS® (edaravone oral suspension) is indicated for the treatment of ALS.[14] Radicava ORS received FDA-approval under the 505(b)(2) approval pathway which relied upon evaluations of safety and efficacy for Radicava IV. Patients treated with Radicava IV may be switched to Radicava ORS using the same dosing frequency.

Clinical Efficacy
The efficacy of edaravone IV was evaluated in one Phase III, randomized, double-blind, placebo-controlled trial conducted in Japan called Study 19 (published) [n = 137].[2] This study enrolled patients who had a "definite" or "probable" diagnosis of ALS (based on El Escorial and revised Airlie House criteria; criteria provided in the Appendix) and were living independently at the time of screening. Patients also were required to have functionally retained most activities of daily living (defined as a score of two points or better on each individual item of the ALS Functional Rating Scale – Revised [ALSFRS-R]), have normal respiratory function (i.e., a percent-predicted forced vital capacity [FVC] value ≥ 80%), and have a disease duration of ≤ 2 years. Overall, 91% of patients were also receiving riluzole. The decline in the ALSFRS-R scores from baseline to Week 24 was statistically significantly less with edaravone IV compared with placebo.[1,2] In a separate study involving patients with longer disease duration, reduced respiratory function, and less certain ALS diagnosis, edaravone IV did not demonstrate benefit vs. placebo.[3]

A post-hoc analysis of Study 19 compared the efficacy of edaravone at week 48 in patients with FVC ≥ 80% vs. patients with FVC < 80%. Patients in both groups had a reduction in the ALSFRS-R score loss vs. placebo patients through week 48. The treatment difference between edavarone-edavarone vs. placebo-edavarone in patients with FVC ≥ 80% and FVC < 80% was 2.05 and 4.94 which were both statistically significant.[17]

Guidelines

The American Academy of Neurology practice parameter on the care of patients with ALS (last updated 2009; reaffirmed 2023) does not yet address edaravone IV.[4-5] The practice parameter states that riluzole is safe and effective for slowing disease progression to a modest degree and should be offered to patients with ALS. However, riluzole may result in fatigue in some patients and if the risk of fatigue outweighs the modest survival benefits, discontinuation of riluzole may be considered. Referral to a specialized multidisciplinary clinic should be considered for patients with ALS to optimize health care delivery, prolong survival, and enhance quality of life. Additionally, noninvasive mechanical ventilation may lengthen survival and can be considered to improve quality of life and slow FVC decline. The European Federation of Neurological Societies guidelines on the clinical management of ALS (2012) also recommend patients be offered treatment with riluzole as early as possible after diagnosis.[6] However, patients with progressive muscular atrophy, primary lateral sclerosis, or hereditary spastic paraplegia should not be treated with riluzole. The European Academy of Neurology guideline on the management of ALS in collaboration with the European Reference Network of Neuromuscular Diseases (2024) do not recommend the use of IV or oral Radicava outside the context of a clinical trial.[15] The interim recommendation states that the evidence will be reviewed and the recommendation will be updated, once the results from the ongoing phase III trial of oral Radicava in Europe are available.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of edaravone IV. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with edaravone IV as well as the monitoring required for adverse events and long-term efficacy, approval requires edaravone IV to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of edaravone IV is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Amyotrophic Lateral Sclerosis (ALS).** Approve for 6 months if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve if the patient meets ALL of the following (i, ii, iii, iv, and v):
     - **i.** According to the prescriber, the patient has a "definite" or "probable" diagnosis of amyotrophic lateral sclerosis (ALS) based on the application of the El Escorial or the revised Airlie House diagnostic criteria; AND
     - **ii.** Patient has a score of two points or more on each item of the ALS Functional Rating Scale – Revised (ALSFRS-R) [i.e., has retained most or all activities of daily living]; AND

iii. According to the prescriber, patient has adequate respiratory function and does not require invasive ventilation; AND
iv. Patient has received or is currently receiving riluzole tablets, Tiglutik (riluzole oral suspension), or Exservan (riluzole oral film); AND
v. The medication is prescribed by or in consultation with a neurologist, a neuromuscular disease specialist, or a physician specializing in the treatment of ALS; OR

B) Patient is Currently Receiving edaravone IV, Radicava IV, or Radicava ORS. Approve if the patient meets ALL of the following (i, ii, and iii):
i. Patient does not require invasive ventilation; AND
ii. According to the prescriber, the patient continues to benefit from therapy; AND
iii. The medication is prescribed by or in consultation with a neurologist, a neuromuscular disease specialist, or a physician specializing in the treatment of ALS.

Dosing. Approve the following dosing regimens (A and B):
A) 60 mg intravenous infusion once daily; AND
B) Treatment Cycles:
i. Initial Cycle: Administer for 14 days followed by a 14-day drug-free period.
ii. Subsequent cycles: Administer for 10 days out of a 14-day period, followed by a 14-day drug-free period.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of edaravone IV is not recommended in the following situations:

1. **Aneurysmal Subarachnoid Hemorrhage.** Edaravone IV is not indicated for the treatment of aneurysmal subarachnoid hemorrhage (SAH).[1] One randomized controlled study (published) [n = 91] evaluated the efficacy of edaravone (formulation/dose not specified) in patients with aneurysmal SAH.[7] At 3 months post-SAH, the incidence of delayed ischemic neurologic deficits (DINDs) in patients treated with edaravone was 10% vs. 21% in patients in a control group; the between-group treatment difference was not significant. In patients who had DINDs, 66% of patients in the control group had a cerebral infarction caused by vasospasm compared with 0% of edaravone -treated patients (P = 0.028). Additional, well-designed clinical studies are needed to establish if edaravone has a role in therapy post-SAH.

2. **Myocardial Infarction.** Edaravone IV is not indicated for the treatment of myocardial infraction; there are no US or North American studies of edaravone IV for this indication.[1] One randomized, placebo-controlled, open-label, Japanese study (published) [n = 101] evaluated the effect of edaravone IV on the long-term prognosis in patients experiencing an acute myocardial infarction.[8] Patients were randomized to receive either edaravone IV (foreign formulation) 30 mg or placebo immediately prior to reperfusion. In all patients, successful reperfusion was obtained within 6 hours post-symptom onset. Edaravone IV significantly attenuated the infarct size and incidence of reperfusion arrhythmia compared with placebo (P = 0.035 and P = 0.031, respectively).

3. **Radiation-Induced Brain Injury.** Edaravone IV is not indicated for the treatment of radiation-induced brain injury; there are no US or North American studies of edaravone IV for this indication.[1] One randomized, open-label, 3-month, Chinese study (published) [n = 137] evaluated the protective

effect of edaravone IV on radiation-induced brain necrosis in patients with nasopharyngeal carcinoma.[9] Patients were randomized to receive edaravone IV (foreign formulation) 30 mg twice daily for 2 weeks (not FDA-approved dosing) + IV corticosteroid therapy or placebo + IV corticosteroid therapy. Following 3 months of therapy, radiologic improvement (reduction in edema of ≥ 25%) was observed in 55.6% of patients who received edaravone IV (n = 40/72) compared with 35.4% of patients treated with placebo (n = 23/65) [P = 0.025]. The area of T1-weighted contrast enhancement was reduced from baseline with both edaravone IV and placebo (-1.67 cm and -1.20 cm, respectively); however, the difference between the treatment arms was not statistically significant. Improvement in neurologic signs and symptoms evaluated by the Late Effects of Normal Tissues – Subjective, Objective, Management, Analytic (LENT/SOMA) scale was also observed in 61.1% of edaravone IV-treated patients vs. 38.5% of placebo-treated patients (P = 0.006). Further research is warranted to determine if edaravone IV has a place in therapy in the treatment of radiation-induced brain injury.

4. **Retinal Vein Occlusion.** Edaravone IV is not indicated for the prevention of macular edema and improvement of visual acuity after arteriovenous sheathotomy in patients with branch retinal vein occlusion; there are no US or North American studies of edaravone IV for this indication.[1] A single, small, prospective, Japanese study [published] (n = 47) evaluated the efficacy of edaravone IV (foreign formulation) in patients with branch retinal vein occlusion undergoing vitrectomy.[10] Patients either received edaravone IV 30 mg at the time of the procedure or no additional therapy. Visual acuity was measured before and 12 months after the procedure. At 12 months following the operation, the logarithm of the minimum angle of resolution (logMAR) units improved from 0.22 to 0.56 logMAR units in patients who had received edaravone IV and from 0.20 to 0.27 logMAR units in patients who did not receive active treatment (P = 0.016). Additional data are needed to support the use of edaravone IV for this indication.

5. **Sensorineural Hearing Loss.** Edaravone IV is not indicated for the treatment of sensorineural hearing loss; there are no US-based studies of edaravone IV for this indication.[1] One small, Japanese study evaluated 14 patients with idiopathic sudden sensorineural hearing loss treated with edaravone IV (foreign formulation; dose not specified).[11] These patients were compared with a control group of 14 patients with similar prognostic factors who had been treated with hyperbaric oxygenation therapy. No significant differences were observed between the edaravone IV group and the control group.

6. **Stroke.** Edaravone IV is not FDA-approved for the treatment of patients who have experienced stroke.[1] Edaravone IV has been approved in other countries for this indication and there are some foreign data supporting its use.[12] There are no US-based studies of edaravone IV for stroke at this time. A systematic review assessed available efficacy data from three clinical trials (n = 496) of edaravone IV for acute ischemic stroke.[13] These trials compared edaravone IV 30 mg twice daily for 14 days + another treatment vs. the other treatment alone within 72 hours of stroke symptom onset. One trial did not find significantly reduced mortality with edaravone IV vs. the control group; the other two studies did not report this endpoint. Overall, there was a significantly higher proportion of patients who had neurologic improvement in the edaravone IV group vs. control.

7. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	04/19/2023
Annual Revision	No criteria changes.	05/15/2024
Aspirus P&T Review	Policy reviewed and approved by Aspirus P&T committee. Annual review process	09/16/2024
Selected Revision	Radicava intravenous (IV) is available as generic edaravone IV. Generic edaravone IV was added to the policy with the same criteria as Radicava IV and brand name "Radicava" was changed to "edaravone" throughout the policy. The name of the policy was changed from Neurology – Radicava IV UM Medical to Neurology – Edaravone IV UM Medical.	01/15/2025
Annual Revision	**Amyotrophic Lateral Sclerosis (ALS):** The requirement that patient has been diagnosed with ALS for ≤ 2 years was removed. The requirement that "patient has a percent-predicted forced vital capacity (FVC) ≥ 80% (i.e., has normal respiratory	03/19/2025

	function)" was changed to "according to the prescriber, patient has adequate respiratory function and does not require invasive ventilation."	
Aspirus P&T Review	Policy reviewed and approved by Aspirus P&T committee. Annual review process	09/15/2025

APPENDIX*

El Escorial criteria for the diagnosis of ALS were initially developed by the World Federation of Neurology (WFN) in 1990. In 1998, the WFN held a workshop for the Research Committee on Motor Neuron Diseases at the Airlie Conference Center in Virginia, which resulted in a revision of the guidelines in 2000. The pivotal study of Radicava IV references the El Escorial criteria updated by the WFN in 2000 (Airlie House). According to these guidelines, the diagnosis of ALS requires:

The presence of:

- Evidence of lower motor neuron (LMN) degeneration by clinical, electrophysiological, or neuropathologic examination; AND
- Evidence of upper motor neuron (UMN) degeneration by clinical examination; AND
- Progressive spread of symptoms or signs within a region or to other regions, as determined by history or examination.

Together with the absence of:

- Electrophysiological or pathological evidence of other disease processes that might explain the signs of LMN and/or UMN degeneration; AND
- Neuroimaging evidence of other disease processes that might explain the observed clinical and electrophysiological signs.

Without pathological confirmation, the diagnosis of ALS may be categorized into levels of certainty using clinical assessment. The following terms are used to describe the categories of diagnostic certainty.

- **Clinically Definite ALS:** defined on clinical evidence alone by the presence of UMN, as well as LMN signs, in the bulbar region and at least two spinal regions or the presence of UMN and LMN signs in three spinal regions.
- **Clinically Probable ALS:** defined on clinical evidence alone by UMN and LMN signs in at least two regions with some UMN signs necessarily rostral to (above) the LMN signs.
- **Clinically Probable ALS – Laboratory-supported:** defined when clinical signs of UMN and LMN dysfunction are in only one region, or when UMN signs alone are present in one region, and LMN signs defined by EMG criteria are present in at least two regions, with proper application of neuroimaging and clinical laboratory protocols to exclude other causes.
- **Clinically Possible ALS:** defined when clinical signs of UMN and LMN dysfunction are found together in only one region or UMN signs are found alone in two or more regions; or LMN signs are found rostral to UMN signs and the diagnosis of Clinically Probable ALS – Laboratory supported cannot be proven by evidence on clinical grounds in conjunction with electrodiagnostic, neurophysiologic, neuroimaging, or clinical laboratory studies. Other diagnoses must have been excluded to accept a diagnosis of Clinically Possible ALS.

*** This appendix is for reference; it is NOT intended that patients meet the above criteria for approval of Radicava IV.**