Drug Coverage Policy

Effective Date……7/1/2025
Coverage Policy Number……IP0176
Policy Title……Edaravone Products

Neurology –Edaravone Products

- Radicava® (edaravone intravenous infusion – Mitsubishi Tanabe, generic)
- Radicava ORS® (edaravone oral suspension – Mitsubishi Tanabe)

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment and have discretion in making individual coverage determinations. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Cigna Healthcare Coverage Policy

OVERVIEW
Edaravone intravenous (IV) and Radicava ORS are indicated for the treatment of **amyotrophic lateral sclerosis** (ALS).[1,15]

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

Clinical Efficacy
The efficacy of edaravone IV was evaluated in one Phase III, randomized, double-blind, placebo-controlled, Japanese trial 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-edaravone in patients with FVC ≥ 80% and FVC < 80% was 2.05 and 4.94 which were both statistically significant.[16]

Radicava ORS received FDA-approval under the 505(b)(2) approval pathway which relied upon evaluations of safety and efficacy for Radicava IV.[1]

Guidelines
The American Academy of Neurology (AAN) practice parameter on the care of patients with ALS (last updated 2009; reaffirmed 2023) does not yet address edaravone IV or Radicava ORS.[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.[14] 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.

Medical Necessity Criteria

Policy Statement
Prior Authorization is recommended for prescription benefit coverage of Edaravone IV, Radicava ORS. 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, Radicava ORS as well as the monitoring required for adverse events and long-term efficacy, approval requires Edaravone IV, Radicava ORS to be prescribed by a physician who has consulted with or who specializes in the condition.

Documentation: Documentation is required where noted in the criteria. Documentation may include, but is not limited to, chart notes, laboratory tests, claims records, and/or other information. In subsequent coverage reviews for a patient who has previously met the documentation requirements and related criteria in the *Neurology – Edaravone Products Prior*

Authorization Policy through the Coverage Review Department, and who is requesting reauthorization, the criteria utilized do NOT require resubmission of documentation for reauthorization, except for the criterion requiring documentation of response or benefit to Edaravone IV, Radicava ORS therapy.

Edaravone IV, Radicava ORS are considered medically necessary when the following are met:

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, v, and vi):
     - **i.** Documentation provided that 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.** AND
     - **v.** Patient has received or is currently receiving riluzole tablets, Tiglutik (riluzole oral suspension), or Exservan (riluzole oral film); AND
     - **vi.** The medication is prescribed by or in consultation with a neurologist, a neuromuscular disease specialist, or a physician specializing in the treatment of ALS.
   - **B)** Patient is Currently Receiving Edaravone 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.

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Receipt of sample product does not satisfy any criteria requirements for coverage.

Conditions Not Covered

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive; criteria will be updated as newly published data are available):

1. **Aneurysmal Subarachnoid Hemorrhage.** Edaravone IV and Radicava ORS are 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 and Radicava ORS are not indicated for the treatment of myocardial infarction; there are no US or North American studies of Edaravone IV or Radicava ORS 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 of 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 and Radicava ORS are not indicated for the treatment of radiation-induced brain injury; there are no US or North American studies of Edaravone IV or Radicava ORS 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 and Radicava ORS are 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 or Radicava ORS for this indication.[1,14] 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 and Radicava ORS are not indicated for the treatment of sensorineural hearing loss; there are no US-based studies of Edaravone IV or Radicava ORS 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 and Radicava ORS are 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.

Coding Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPCS Codes	Description
C9399†	Unclassified drugs or biologicals
J1301	Injection, edaravone, 1 mg
J3490†	Unclassified drugs

†Note: Considered Medically Necessary when used to report Edaravone ORS and medical necessity criteria outlined in this Coverage Policy are met.

References

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Revision Details

Type of Revision	Summary of Changes	Date
Annual Review	**Amyotrophic Lateral Sclerosis (ALS).** **Added** Patient has received or is currently receiving riluzole tablets, Tiglutik (riluzole oral suspension), or Exservan (riluzole oral film). **Added** 'Patient is Currently Receiving Edaravone IV or Radicava ORS' criteria. **Updated** policy title from Edaravone.	8/15/2024
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 Products to Neurology – Edaravone Products.	5/1/2025

	Added documentation requirements as noted in the medical necessity criteria. **Updated HCPCS Coding:** **Added** C9399 & J3490 with the following note: Considered Medically Necessary when used to report Edaravone ORS and medical necessity criteria outlined in this Coverage Policy are met.	
Annual Revision	**Amyotrophic Lateral Sclerosis (ALS): The** requirement that patients have 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 function)" was changed to "according to the prescriber, patient has adequate respiratory function and does not require invasive ventilation." Dosing information for IV product only added.	7/1/2025

The policy effective date is in force until updated or retired.