Drug and Biologic Coverage Policy

Effective Date **10/1/2023**
Next Review Date… **10/1/2024**
Coverage Policy Number **IP0176**

Edaravone

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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. 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.

Overview

This policy supports medical necessity review for the following edaravone products:

- **Radicava®** (edaravone) intravenous injection
- **Radicava ORS®** (edaravone) oral suspension

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

Medical Necessity Criteria

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

1. **Amyotrophic Lateral Sclerosis (ALS).** Individual meets **ALL** of the following criteria (A, B, C, D, and E):
    A. Documented diagnosis of "definite" or "probable" amyotrophic lateral sclerosis (ALS) based on El Escorial – Revised (Airlie House) criteria

B. Individual has retained most activities of daily living (defined as a score of 2 points or better on each item of the ALS Functional Rating Scale – Revised [ALSFRS-R] [for example, a minimum score of 24])
C. Individual has normal respiratory function (defined as percent-predicted forced vital capacity values [% FVC] of at least 80%)
D. Individual has a disease duration of 2 years or less
E. Medication is prescribed by or in consultation with a neurologist, a neuromuscular disease specialist, or a physician specializing in the treatment of ALS

Intravenous Dosing. **BOTH** of 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.

Reauthorization Criteria

Edaravone (Radicava, Radicava ORS) are considered medically necessary for continued use when **ALL** of the following criteria are met (1, 2, 3, and 4):
1. Documented diagnosis of "definite" or "probable" amyotrophic lateral sclerosis (ALS) based on El Escorial – Revised (Airlie House) criteria
2. According to the prescriber, the individual continues to benefit from therapy
3. Individual is not dependent on invasive ventilation
4. Medication is prescribed by or in consultation with a neurologist, a neuromuscular disease specialist, or a physician specializing in the treatment of ALS

Authorization Duration

Initial approval duration: up to 6 months.
Reauthorization approval duration: up to 12 months.

Conditions Not Covered

Any other use is considered experimental, investigational or unproven, including the following (this list may not be all inclusive):

1. **Aneurysmal Subarachnoid Hemorrhage**
Radicava IV and Radicava ORS are not indicated for the treatment of aneurysmal subarachnoid hemorrhage (SAH).[1,14] One randomized controlled study (published) [n = 91] evaluated the efficacy of Radicava (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 Radicava 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 Radicava-treated patients (P = 0.028). Additional, well-designed clinical studies are needed to establish if Radicava has a role in therapy post-SAH.

2. **Myocardial Infarction**
Radicava IV and Radicava ORS are not indicated for the treatment of myocardial infarction; there are no US or North American studies of Radicava IV or Radicava ORS for this indication.[1,14] One randomized, placebo-controlled, open-label, Japanese study (published) [n = 101] evaluated the effect of Radicava IV

on the long term prognosis in patients experiencing an acute myocardial infarction.[8] Patients were randomized to receive either Radicava IV (foreign formulation) 30 mg or placebo immediately prior to reperfusion. In all patients, successful reperfusion was obtained within 6 hours post-symptom onset. Radicava 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**
   Radicava IV and Radicava ORS are not indicated for the treatment of radiation-induced brain injury; there are no US or North American studies of Radicava IV or Radicava ORS for this indication.[1,14] One randomized, open-label, 3-month, Chinese study (published) [n = 137] evaluated the protective effect of Radicava IV on radiation-induced brain necrosis in patients with nasopharyngeal carcinoma.[9] Patients were randomized to receive Radicava 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 Radicava 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 Radicava 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 Radicava IV-treated patients vs. 38.5% of placebo-treated patients (P = 0.006). Further research is warranted to determine if Radicava IV has a place in therapy in the treatment of radiation-induced brain injury.

4. **Retinal Vein Occlusion**
   Radicava 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 Radicava IV or Radicava ORS for this indication.[1,14] A single, small, prospective, Japanese study [published] (n = 47) evaluated the efficacy of Radicava IV (foreign formulation) in patients with branch retinal vein occlusion undergoing vitrectomy.[10] Patients either received Radicava 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 Radicava 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 Radicava IV for this indication.

5. **Sensorineural Hearing Loss**
   Radicava IV and Radicava ORS are not indicated for the treatment of sensorineural hearing loss; there are no US-based studies of Radicava IV or Radicava ORS for this indication.[1,14] One small, Japanese study evaluated 14 patients with idiopathic sudden sensorineural hearing loss were treated with Radicava 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 Radicava IV group and the control group.

6. **Stroke**
   Radicava IV and Radicava ORS are not FDA-approved for the treatment of patients who have experienced stroke.[1,14] Radicava 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 Radicava IV for stroke at this time. A systematic review assessed available efficacy data from three clinical trials (n = 496) of Radicava IV for acute ischemic stroke.[13] These trials compared Radicava 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 Radicava 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 Radicava IV group vs. control.

Coding

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
J1301	Injection, edaravone, 1 mg

Background

OVERVIEW
Radicava intravenous (IV) and Radicava ORS are indicated for the treatment of **amyotrophic lateral sclerosis** (ALS).[1,14]

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 Radicava IV was evaluated in one Phase III, randomized, double-blind, placebo-controlled, Japanese trial (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 Radicava IV compared with placebo.[1,2] In a separate study involving patients with longer disease duration, reduced respiratory function, and less certain ALS diagnosis, Radicava IV did not demonstrate benefit vs. placebo.[3]

Radicava ORS received FDA-approval under the 505(b)(2) approval pathway which relied upon evaluations of safety and efficacy for Radicava IV.[14]

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 Radicava 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.

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 or Radicava ORS.**

References

1. Radicava™ intravenous infusion [prescribing information]. Jersey City, NJ: Mitsubishi Tanabe; December 2021.
2. Abe K, Aoki M, Tsuji S, et al. on behalf of the edaravone (MCI-186) ALS 19 study group. Safety and efficacy of edaravone in well defined patients with amyotrophic lateral sclerosis: a randomized, double-blind, placebo-controlled trial. Lancet Neurol. 2017;16:505-512.
3. Abe K, Itoyama Y, Sobue G, 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):610-617.
4. Miller RG, Jackson CE, Kasarskis EJ, et al. Practice parameter update: the care of the patient with amyotrophic lateral sclerosis: multidisciplinary care, symptom management, and cognitive/behavioral impairment (an evidence-based review). Neurology. 2009;73(15):1227-1233.
5. Miller RG, Jackson CE, Kasarskis EJ, et al. Practice parameter update: the care of the patient with amyotrophic lateral sclerosis: drug, nutritional, and respiratory therapies (an evidence-based review). Neurology. 2009;73:1218-1226.
6. Andersen PM, Abrahams S, Borasio GD, et al. EFNS guidelines on the clinical management of amyotrophic lateral sclerosis (MALS) – revised report of an EFNS task force. Eur J Neurol. 2012;19(3):360-375.

7. Munakata A, Ohkuma H, Nakano T, et al. Effect of a free radical scavenger, edaravone, in the treatment of patients with aneurysmal subarachnoid hemorrhage. Neurosurgery. 2009;64(3):423-428.
8. Tsujita K, Shimomura H, Kaikita K, et al. Long-term efficacy of edaravone in patients with acute myocardial infarction. Circ J. 2006;70(7):832-837.
9. Tang Y, Rong X, Hu W, et al. Effect of edaravone on radiation-induced brain necrosis in patients with nasopharyngeal carcinoma after radiotherapy: a randomized controlled trial. J Neurooncol. 2014;120(2):441-447.
10. Maeno T, Tano R, Takenaka H, et al. Edaravone (MCI-186) is effective as a free radical scavenger following arteriovenous sheathotomy for treatment of macular edema associated with branch retinal vein occlusion. Br J Ophthalmol. 2009;93(11):1479-1482.
11. Sano H, Kamijo T, Ino T, et al. Edaravone, a free radical scavenger, in the treatment of idiopathic sudden sensorineural hearing loss with profound hearing loss. Auris Nasus Larynx. 2010;37(1):42-46.
12. Data on file. Radicava™ Product Dossier: Based on AMCP guidelines for formulary submission, version 2.1. MT Pharma America, Inc.; received June 14, 2017.
13. Feng S, Yang Q, Liu M, et al. Edaravone for acute ischaemic stroke. Cochrane Database Syst Rev. 2011;12:CD007230.
14. Radicava ORS® oral suspension [prescribing information]. Jersey City, NJ: Mitsubishi Tanabe; May 2022.

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