

POLICY: Neurology – Radicava® (edaravone intravenous injection – Mitsubishi Tanabe)

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OVERVIEW

Radicava is indicated for the treatment of amyotrophic lateral sclerosis (ALS).¹ It is an anti-oxidative, free radical scavenger which eliminates lipid peroxide and hydroxyl radicals; however, it is unknown exactly how Radicava exerts its therapeutic effect in ALS.¹⁻²

Disease Overview

ALS, also known as Lou Gehrig’s disease, is a rapidly progressive, paralyzing disease characterized by degeneration of upper motor neurons (UMNs) and lower motor neurons (LMNs) in the brain, brainstem, and the spinal cord resulting in muscle weakness.²⁻⁴ Patients with ALS typically present with painless, progressive muscle atrophy and weakness, which eventually leads to paralysis and death, primarily due to respiratory failure. The accurate diagnosis of ALS is challenging and delays in diagnosis are common (average diagnostic delay of 11 to 12 months or more). The El Escorial criteria (used in the clinical studies of Radicava) were developed to standardize the diagnosis of ALS (revised by Airlie House in 1999).³⁻⁵ The average survival following diagnosis of ALS is approximately 3 years; 50% of patients will die within 30 months of symptom onset. However, median survival can range from months to several years and the rate of progression of the disease varies considerably between patients.

Clinical Efficacy

The efficacy of Radicava was established in one Phase III, randomized, double-blind, placebo-controlled, Japanese trial (published) [n = 137].⁶ 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 $\geq 80\%$), 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 compared with placebo.^{1,6} In a separate study involving patients with longer disease duration, reduced respiratory function, and less certain ALS diagnosis, Radicava did not demonstrate benefit vs. placebo.⁷

Guidelines

The American Academy of Neurology (AAN) practice parameter on the care of patients with ALS (last updated 2009; reaffirmed 2014) does not yet address Radicava.⁸⁻⁹ 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 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 (EFNS) guidelines on the clinical management of ALS (2012) also recommend patients be offered treatment with

riluzole as early as possible after diagnosis.¹⁰ However, patients with progressive muscular atrophy, primary lateral sclerosis, or hereditary spastic paraplegia should not be treated with riluzole.

POLICY STATEMENT

Prior authorization is recommended for medical benefit coverage of Radicava. Approval is recommended for those who meet the Criteria and Dosing for the listed indication(s). 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 of the specialized skills required for evaluation and diagnosis of patients treated with Radicava as well as the monitoring required for adverse events and long-term efficacy, approval requires Radicava to be prescribed by or in consultation with a physician who specializes in the condition being treated.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Radicava 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, v, and vi):
- 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.** Patient has a percent-predicted forced vital capacity (FVC) \geq 80% (i.e., has normal respiratory function); AND
 - iv.** Patient has been diagnosed with ALS for \leq 2 years; AND
 - v.** Patient has received or is currently receiving riluzole tablets (Rilutek[®], generics), Tiglutik[®] (riluzole oral suspension), or Exservan[™] (riluzole oral film); AND
 - vi.** Radicava is prescribed by or in consultation with a neurologist, a neuromuscular disease specialist, or a physician specializing in the treatment of ALS.
- B) Patients Currently Receiving Radicava.** Approve if the patient meets ALL of the following (i, ii, and iii):
- i.** Radicava is prescribed by or in consultation with a neurologist, a neuromuscular disease specialist, or a physician specializing in the treatment of ALS; AND
 - ii.** According to the prescriber, the patient continues to benefit from therapy; AND
 - iii.** The patient is not requiring invasive ventilation.

Dosing. Approve the following dosing regimens (A and B):

A) 60 mg intravenous (IV) infusion once daily (QD); 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

Radicava has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval).

1. **Aneurysmal Subarachnoid Hemorrhage.** Radicava is not indicated for the treatment of aneurysmal subarachnoid hemorrhage (SAH).¹ One randomized controlled study (published) [n = 91] evaluated the efficacy of Radicava (formulation/dose not specified) in patients with aneurysmal SAH.¹¹ 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 (P = 0.118). 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 is not indicated for the treatment of myocardial; there are no US or North American studies of Radicava for this indication.¹ One randomized, placebo-controlled, open-label, Japanese study (published) [n = 101] evaluated the effect of Radicava on the long term prognosis in patients experiencing an acute myocardial infarction.¹² Patients were randomized to receive either Radicava (foreign formulation) 30 mg intravenous (IV) or placebo immediately prior to reperfusion. In all patients, successful reperfusion was obtained within 6 hours post-symptom onset. Radicava significantly attenuated the infarct size and incidence of reperfusion arrhythmia compared with placebo (P = 0.035 and P = 0.031, respectively). Further research is warranted to determine if Radicava has a place in therapy in the management of AMI.
3. **Radiation-Induced Brain Injury.** Radicava is not indicated for the treatment of radiation-induced brain injury; there are no US or North American studies of Radicava for this indication.¹ One randomized, open-label, 3-month, Chinese study (published) [n = 137] evaluated the protective effect of Radicava on radiation-induced brain necrosis in patients with nasopharyngeal carcinoma.¹³ Patients were randomized to receive Radicava (foreign formulation) 30 mg intravenous (IV) 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 $\geq 25\%$) was observed in 55.6% of patients who received Radicava (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 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-treated patients vs. 38.5% of placebo-treated patients (P = 0.006). Further research is warranted to determine if Radicava has a place in therapy in the treatment of radiation-induced brain injury.
4. **Retinal Vein Occlusion.** Radicava 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 Radicava for this indication.¹ A single,

small, prospective, Japanese study [published] (n = 47) evaluated the efficacy of Radicava (foreign formulation) in patients with branch retinal vein occlusion undergoing vitrectomy.¹⁴ Patients either received Radicava 30 mg IV 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 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 for this indication.

5. **Sensorineural Hearing Loss.** Radicava is not indicated for the treatment of sensorineural hearing loss; there are no US-based studies of Radicava for this indication.¹ One small, Japanese study evaluated 14 patients with idiopathic sudden sensorineural hearing loss were treated with Radicava (foreign formulation; dose not specified).¹⁵ 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 group and the control group.
6. **Stroke.** Radicava is not FDA-approved for the treatment of patients who have experienced stroke.¹ Radicava has been approved in other countries for this indication and there are some foreign data supporting its use.¹⁶ There are no US-based studies of Radicava for stroke at this time. A systematic review assessed available efficacy data from three clinical trials (n = 496) of Radicava for acute ischemic stroke.¹⁷ These trials compared Radicava 30 mg twice daily IV infusion 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 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 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	Date Reviewed
Annual revision	For patients currently taking Radicava for ALS, criteria were added to require that Radicava continue to be prescribed by or in consultation with a neurologist, neuromuscular disease specialist, or a physician specializing in ALS.	09/12/2018
Early annual revision	Early revision to align with review date of new Radivava PA Policy For patients continuing therapy, approval duration was changed to 6 months (previously was 1 year).	04/10/2019
Annual revision	Amyotrophic Lateral Sclerosis: For the criteria applying to initial therapy diagnosis of amyotrophic lateral sclerosis and for patients currently receiving Radicava who have responded, wording was updated to more generally allow this determination by the prescriber (criteria previously specified this was according to the prescribing physician). Exservan (riluzole oral film) was added as an option for criterion requiring the patient has received or is currently receiving riluzole tablets (Rilutek, generics) or Tiglutik (riluzole oral suspension).	04/08/2020

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 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.**