Clinical Policy: Edaravone (Radicava, Radivaca ORS)

Reference Number: PA.CP.PHAR.343
Effective Date: 01/2018
Last Review Date: 04/2023 Revision Log

Description
Edaravone (Radicava®, Radicava ORS®) is a member of the substituted 2-pyrazolin-5-one class that acts as a free-radical scavenger of peroxyl radicals and peroxynitrite.

FDA approved indication
Radicava and Radicava ORS are indicated for the treatment of amyotrophic lateral sclerosis (ALS).

Policy/Criteria
Provider must submit documentation (which may include office chart notes and lab results) supporting that member has met all approval criteria

It is the policy of PA Health & Wellness® that Radicava is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Amyotrophic Lateral Sclerosis (must meet all)**:**

1. Diagnosis of definite or probable ALS per El Escorial (*see appendix D)*;
2. Prescribed by or in consultation with a neurologist;
3. Age ≥ 18 years;
4. Concomitant use of riluzole (at up to maximally indicated doses) unless contraindicated or clinically significant adverse effects are experienced;
5. Independent living status (defined as patients who can eat a meal, excrete, or move with oneself alone)
6. Forced vital capacity ≥ 80%;
7. Disease duration of ≤ 2 years;
8. Baseline revised ALS Functional Rating Scale (ALSFRS-R) score with ≥ 2 points in each of the 12 items;
9. Dose does not exceed any of the following (a-c):
   a. One of the following (i or ii):
      i. For intravenous administration: 60 mg per day for each treatment cycle;
      ii. For oral administration: 105 mg per day for each treatment cycle;
   b. Initial treatment cycle: daily dosing for 14 days followed by a 14-day drug-free period;
   c. Subsequent treatment cycles: daily dosing for 10 days out of 14-day periods, followed by 14-day drug-free periods.

Approval duration: 6 months

B. Other diagnoses/indications:

1. Refer to PA.CP.PMN.53

II. Continued Therapy

A. Amyotrophic Lateral Sclerosis (must meet all)**:**

1. Currently receiving medication via PA Health & Wellness benefit or member has previously met initial approval criteria or the Continuity of Care policy (PA.LTSS.PHAR.01) applies;
2. Member is responding positively to therapy per prescriber's assessment;
3. If request is for a dose increase, new dose does not exceed both of the following (a and b):
    a. One of the following (i or ii):
        i. For intravenous administration: 60 mg per day for each treatment cycle;
        ii. For oral administration: 105 mg per day for each treatment cycle;
    b. Treatment cycle consisting of daily dosing for 10 days out of 14-day periods, followed by 14-day drug-free periods.

Approval duration: 6 months

B. Other diagnoses/indications (1 or 2)**:**

1. Currently receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.LTSS.PHAR.01) applies.

Approval duration: Duration of request or 6 months (whichever is less); or

2. Refer to PA.CP.PMN.53.

III. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

ALS: amyotrophic lateral sclerosis
ALSFRS-F: revised ALS Functional Rating Scale
FDA: Food and Drug Administration
LMN: lower motor neuron
UMN: upper motor neuron

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
riluzole (Rilutek®)	50 mg PO BID	100 mg/day

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): hypersensitivity to edaravone or any of the inactive ingredients in Radicava and/or Radicava ORS
- Boxed warning(s): none reported

Appendix D: General Information

- Revised El Escorial diagnostic criteria for ALS requires the presence of:
  1. Signs of lower motor neuron (LMN) degeneration by clinical, electrophysiological or neuropathologic examination,
  2. Signs of upper motor neuron (UMN) degeneration by clinical examination, and
  3. Progressive spread of signs within a region or to other regions, together with the absence of:
     a. Electrophysiological evidence of other disease processes that might explain the signs of LMN and/or UMN degenerations; and
     b. Neuroimaging evidence of other disease processes that might explain the observed clinical and electrophysiological signs.
- The definitions of ALS diagnoses provided by the El Escorial criteria are as follows:

	El Escorial criteria, 1994
Definite ALS	Upper and lower motor neuron signs in three regions
Probable ALS	Upper and lower motor neuron signs in at least two regions, with upper motor neuron signs rostral to lower motor neuron signs
Possible ALS	Upper and lower motor neuron signs in one region, upper motor neuron signs alone in two or more regions, or lower motor neuron signs rostral to upper motor neuron signs
Suspected ALS	Lower motor neuron signs only, in two or more regions

- Two pivotal phase III trials that were conducted in Japan were used for the approval of Radicava in the USA. One of the phase III trials of Radicava found no statistically significant difference in delay of ALS progression, but a post-hoc analysis found that a certain subset of patients may benefit. Based on the post-hoc analysis, the second phase III was performed with a much more strict eligibility criteria and found a statistically significant difference in ALS progression in favor of Radicava. Therefore, patients not meeting the strict eligibility criteria at any time (at the time of initial or continued approval) can be assumed that no benefit will be provided by the use of Radicava for the treatment of ALS until further studies support its use in a wider population with ALS.
- The revised ALS Functional Rating Scale (ALSFRS-R) score consists of a total of 12 items and 48 points. It is a physician-generated estimate of the patient's degree of functional impairment. Each item assesses the patient's functional ability on daily tasks, such as walking and hand-writing. Each item is scored from 0 to 4 points, with 0 indicating no ability and 4 indicating normal ability.

IV. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose

ALS	Oral: 105 mg PO in the morning per initial and subsequent treatment cycles below IV: 60 mg IV (60 mg dose as an intravenous infusion over a total of 60 minutes at an infusion rate approximately 1 mg per minute) per initial and subsequent treatment cycles below Treatment cycles for oral and IV administrations: • Initial treatment cycle: daily dosing for 14 days followed by a 14-day drug-free period • Subsequent treatment cycles: daily dosing for 10 days out of 14-day periods, followed by 14-day drug-free periods. • Patients treated with 60 mg of Radicava IV infusion may be switched to 105 mg (5 mL) Radicava ORS using the same dosing frequency.	Oral: 105 mg/day IV: 60 mg/day

V. Product Availability

- Single-dose polypropylene bag for injection: 30 mg/100 mL
- Multi-dose oral suspension: 105 mg/5 mL

VI. References

1. Radicava Prescribing Information. Jersey City, NJ: MT Phrama America, Inc.; November 2022. Available at: www.radicava.com. Accessed January 26, 2023.
2. The Writing Group. Safety and efficacy of edaravone in well defined patients with amyotrophic lateral sclerosis: a randomized, double-blind, placebo-controlled trial. Lancet Neurol. 2017; S1474-4422(17)30115-1.
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. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration. 2014;15(7-8), 610-617.
4. Yoshino H and Kimura A. Investigation of the therapeutic effects of edaravone, a free radical scavenger, on amyotrophic lateral sclerosis (Phase II study). Amyotrophic Lateral Sclerosis. 2006;7(4), 247-251.
5. Anderson PM, Borasio GD, Dengler R, et al. Good practice in the management of amyotrophic lateral sclerosis: Clinical guidelines. An evidence-based review with good practice points. EALSC Working Group. Amyotrophic Lateral Sclerosis. 2007; 8:195-231.
6. Hardiman O, van den Berg LH, and Kiernan MC. Clinical diagnosis and management of amyotrophic lateral sclerosis. Nature Reviews Neurology 2011; 7: 639-649. doi:10.1038/nrneurol.2011.153
7. Takei K, Tsuda K, Takahashi F, et al. An assessment of treatment guidelines, clinical practices, demographics, and progression of disease among patients with amyotrophic lateral sclerosis in Japan, the United States, and Europe. Amyotroph Lateral Scler Frontotemporal Degener 2017; 18: 88–97. DOI: 10.1080/21678421.2017.1361445.

8. Shoesmith C, Abrahao A, Benstead T, et al. Canadian best practice recommendations for the management of amyotrophic lateral sclerosis. CMAJ. 2020 Nov;192(46):E1453-E1468.

Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
C9399	Unclassified drugs or biologicals (edaravone oral suspension)
J1301	Injection, edaravone, 1 mg
J8499	Prescription drug, oral, non chemotherapeutic, nos (edaravone oral suspension)

Reviews, Revisions, and Approvals	Date	Approval Date
2Q 2018 annual review: added continuity of care language; references reviewed and updated.	02/2018	
2Q 2019 annual review: references reviewed and updated.	04/2019	
2Q 2020 annual review: removed Airlie House diagnostic criteria requirement; references reviewed and updated.	04/2020	
2Q 2021 annual review: added Appendix C for contraindications/boxed warnings and hence renamed previous Appendix C to Appendix D; updated section V administration to align with FDA-labeling; references reviewed and updated.	04/2021	
2Q 2022 annual review: references reviewed and updated.	04/2022	
2Q 2023 annual review: added new oral suspension formulation; lowered age limit from 20 years to 18 years per FDA labeling; references reviewed and updated.	04/2023	