

Clinical Policy: Edaravone (Radicava, Radivaca ORS)

Reference Number: CP.PHAR.343

Effective Date: 07.01.17

Last Review Date: 05.24

Line of Business: Commercial, HIM, Medicaid

[Coding Implications](#)[Revision Log](#)

See [Important Reminder](#) at the end of this policy for important regulatory and legal information.

Description

Edaravone (Radicava[®], Radivaca ORS[®]) is a member of the substituted 2-pyrazolin-5-one class that acts as a free-radical scavenger of peroxy radicals and peroxy nitrite.

FDA Approved Indication(s)

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

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation[®] that Radicava and Radivaca ORS are **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 diagnostic criteria (*see Appendix D*);
2. Prescribed by or in consultation with a neurologist;
3. Age \geq 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, and do not need assistance in everyday life);
6. Percent predicted forced vital capacity (% FVC) \geq 80%;
7. Disease duration of \leq 2 years;
8. Baseline revised ALS Functional Rating Scale (ALSFRS-R) score with \geq 2 points in each of the 12 items;
9. Dose does not exceed any of the following (a, b, and 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. For initial treatment cycle: daily dosing for 14 days followed by a 14-day drug-free period;
 - c. For 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 (must meet 1 or 2):

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
 - a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
 - b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. Amyotrophic Lateral Sclerosis (must meet all):

1. Member meets one of the following (a or b):
 - a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
 - b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B*);
2. Member is responding positively to therapy;
3. Member continues to meet all of the following criteria (a, b, and c):
 - a. Independent living status;
 - b. Percent predicted forced vital capacity (% FVC) \geq 80%;
 - c. Revised ALSFRS-R score with \geq 2 points in each of the 12 items;
4. If request is for a dose increase, new dose does not exceed both of the following (a and b):
 - a. Either 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. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):

- a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
 - b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

- A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid, or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

ALS: amyotrophic lateral sclerosis	FVC: forced vital capacity
ALSFRS-F: revised ALS Functional Rating Scale	LMN: lower motor neuron
FDA: Food and Drug Administration	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 symptoms or 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 revised El Escorial criteria are as follows:

Revised El Escorial criteria	
Clinically definite ALS	Clinical evidence alone of UMN and LMN signs in ≥ 3 regions
Clinically probable ALS	Clinical evidence alone of UMN and LMN signs in ≥ 2 regions with some UMN signs rostral to (above) LMN signs
Clinically probable lab-supported ALS	Clinical signs of UMN and LMN dysfunction in 1 region OR UMN signs in 1 region, and LMN signs defined by EMG criteria in ≥ 2 regions
Clinically possible ALS	Clinical signs of UMN and LMN dysfunction in 1 region OR Isolated UMN signs in ≥ 2 regions OR LMN signs rostral to UMN signs

- 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.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
ALS	<u>Oral</u> : 105 mg PO in the morning per initial and subsequent treatment cycles below	Oral: 105 mg/day IV: 60 mg/day

Indication	Dosing Regimen	Maximum Dose
	<p><u>IV</u>: 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</p> <p>Treatment cycles for oral and IV administrations:</p> <ul style="list-style-type: none"> • 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. <p>Patients treated with 60 mg of Radicava IV infusion may be switched to 105 mg (5 mL) Radicava ORS using the same dosing frequency.</p>	

VI. Product Availability

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

VII. References

1. Radicava Prescribing Information. Jersey City, NJ: MT Pharma America, Inc.; November 2022. Available at: <https://www.radicava.com>. Accessed January 10, 2024.
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.
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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.
9. 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): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2009 Oct 13 (reaffirmed February 2023);73(15):1218-26.
10. Brooks BR, Miller RG, Swash M, et al. El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. Amyotroph Lateral Scler Other Motor Neuron Disord. 2000 Dec;1(5):293-9.

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

Reviews, Revisions, and Approvals	Date	P & T Approval Date
2Q 2020 annual review: no significant changes; revised HIM-Medical Benefit line of business to HIM; references reviewed and updated.	02.25.20	05.20
2Q 2021 annual review: added Appendix C for contraindications/boxed warnings and hence renamed previous Appendix C to Appendix D; references for HIM line of business off-label use revised from HIM.PHAR.21 to HIM.PA.154; updated section V administration to align with FDA-labeling; references reviewed and updated.	02.01.21	05.21
Clarified FVC as percent predicted; lowered age limit from 20 years to 18 years per FDA labeling.	09.23.21	
2Q 2022 annual review: no significant changes; references reviewed and updated.	02.08.22	05.22
RT4: added new oral suspension formulation.	05.18.22	
Template changes applied to other diagnoses/indications and continued therapy section.	09.21.22	
2Q 2023 annual review: no significant changes; references reviewed and updated.	02.03.23	05.23
2Q 2024 annual review: no significant changes; updated Appendix D table of ALS diagnosis definitions per revised El Escorial criteria; references reviewed and updated.	01.10.24	05.24

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. “Health Plan” means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan’s affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

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Note: For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

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