Clinical Policy: Edaravone (Radicava)

Reference Number: ERX.SPA.155
Effective Date: 09.01.17
Last Review Date: 05.20
Line of Business: Commercial, Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Edaravone (Radicava™) 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(s)

Radicava is 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.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ 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 criteria (*see Appendix D)*;
2. Prescribed by or in consultation with a neurologist;
3. Age ≥ 20 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 members who can eat a meal, excrete, or move with oneself alone, and do not need assistance in everyday life);
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 60 mg per day for:
   a. Initial treatment cycle: daily dosing for 14 days followed by a 14-day drug-free period;
   b. 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 ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

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

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
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. Forced vital capacity ≥ 80%;
c. ALSFRS-R score with ≥ 2 points in each of the 12 items;

4. If request is for a dose increase, new dose does not exceed 60 mg per day for each 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 (must meet 1 or 2)**:**

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

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 policy – ERX.PA.01 or evidence of coverage documents.

IV. 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 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): a history of hypersensitivity to edaravone or any of the inactive ingredients in Radicava
- 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

	El Escorial criteria, 1994
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 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	60 mg IV (2 consecutive 30 mg intravenous infusion bags) over 60 minutes at an infusion rate of approximately 1 mg/3.33mL per minute) as follows: • 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	60 mg/day

VI. Product Availability

Single-dose polypropylene bag for injection: 30 mg/100 mL

VII. References

1. Radicava Prescribing Information. Jersey City, NJ: MT Phrama America, Inc.; July 2019. Available at: www.radicava.com. Accessed February 25, 2020.
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

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created	05.17	08.17
2Q 2018 annual review: removed Airlie House diagnostic criteria requirement; references reviewed and updated.	02.02.18	05.18
2Q 2019 annual review: no significant changes; references reviewed and updated.	02.05.19	05.19
2Q 2020 annual review: no significant changes; references reviewed and updated.	02.25.20	05.20

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.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. 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.