RXADVANCE
2 Park Central Drive
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Clinical Policy Title:	edaravone
Policy Number:	RxA.260
Drug(s) Applied:	Radicava™
Original Policy Date:	02/07/2020
Last Review Date:	09/14/2020
Line of Business Policy Applies to:	All lines of business

Background

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. It is indicated for the treatment of amyotrophic lateral sclerosis (ALS).

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
edaravone (Radicava™)	Amyotrophic Lateral Sclerosis	60 mg intravenous 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

Dosage Forms

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

Clinical Policy

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

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 C);*
2. Prescribed by or in consultation with a neurologist;
3. Age 20 years of age or older;

4. Concomitant use of riluzole (at 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. Forced vital capacity of 80% or greater;
7. Disease duration of 2 years or less;
8. Baseline revised ALS Functional Rating Scale (ALSFRS-R) score with 2 points or greater 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
Commercial: 6 months
Medicaid: 6 months

II. Continued Therapy Approval

A. Amyotrophic Lateral Sclerosis (must meet all):

1. Currently receiving medication that has been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy ;
2. Member is responding positively to therapy;
3. Patient continues to meet the following criteria:
    a. Independent living status;
    b. Forced vital capacity of 80% or greater;
    c. Revised ALSFRS-R score with 2 points or greater in each of the 12 items;
4. If request is for a dose increase, new dose does not exceed 60 mg/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
Commercial: 6 months
Medicaid: 6 months

III. Appendices

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 orally twice a day	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: General Information

Revised El Escorial diagnostic criteria for amyotrophic lateral sclerosis 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 amyotrophic lateral sclerosis diagnoses provided by the El Escorial criteria are as follows:

	El Escorial criteria, 1994
Definite amyotrophic lateral sclerosis	Upper and lower motor neuron signs in three regions
Probable amyotrophic lateral sclerosis	Upper and lower motor neuron signs in at least two regions, with upper motor neuron signs rostral to lower motor neuron signs
Possible amyotrophic lateral sclerosis	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 amyotrophic lateral sclerosis	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 edaravone in the USA. One of the phase III trials of edaravone 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 edaravone. 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 edaravone for the treatment of amyotrophic lateral sclerosis until further studies support its use in a wider population with ALS.

The revised amyotrophic lateral sclerosis 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 handwriting. Each item is scored from 0 to 4 points, with 0 indicating no ability and 4 indicating normal ability.

References

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2. 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.
3. 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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5. 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
6. 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
7. Radicava Prescribing Information. Jersey City, NJ: Mitsubishi Tanabe Pharma America; August, 2018. Available at https://www.radicava.com/assets/dist/pdfs/radicava-prescribing-information.pdf. Accessed June 21, 2020.

Review/Revision History	Review/Revised Date	P&T Approval Date
Policy established.	01/2020	02/07/2020
Policy reviewed. 1. Formatting updated. 2. References updated. 3. Clinical Policy Title updated. 4. Drug(s) Applied updated. 5. Line of Business updated. 6. Continued therapy criteria II.A.1 was rephrased to "Currently receiving medication that has been authorized by RxAdvance..."	06/21/2020	09/14/2020