Original Effective Date: 09/01/2017
Current Effective Date: 06/23/2023
Last P&T Approval/Version: 04/26/2023
Next Review Due By: 04/2024
Policy Number: C11528-A

Radicava (edaravone)

PRODUCTS AFFECTED

Radicava (edaravone), Radicava ORS (edaravone)

COVERAGE POLICY

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.
This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Amyotrophic lateral sclerosis (ALS)

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by-case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review.

A. AMYOTROPHIC LATERAL SCLEROSIS (ALS):
1. Documentation supporting the clinical diagnosis of ‘definite ALS’ or ‘probable ALS’ per the revised EL Escorial (Airlie House) diagnostic criteria (See appendix)
AND
2. Baseline ALS Functional Rating Scale-Revised (ALSFRS-R) score of 2 or greater on

each individual item of the scale (12 items; minimum 0 points, maximum 48 points) [DOCUMENTATION REQUIRED]
AND

3. Documentation of duration of disease from the first symptom (any ALS symptom) ≤ 2 years
AND
4. Documentation member has retained normal respiratory function as evidenced by a Forced Vital Capacity (FVC) >80% OR decline in respiratory function is better explained by a pulmonary disease process (e.g., COPD, asthma, idiopathic pulmonary fibrosis). In patients with reduced baseline FVC, records may be requested documenting diagnosis of the pulmonary disease process leading to reduced FVC.
AND
5. Documentation of concomitant use of riluzole (Rilutek) [up to maximally indicated doses (50 mg twice daily)], unless member has a labeled contraindication(s) or clinically significant adverse effects
AND
6. Prescriber attests to (or the clinical reviewer has found that) the member not having any FDA labeled contraindications that haven't been addressed by the prescriber within the documentation submitted for review [Contraindications to edaravone include: Hypersensitivity to edaravone or any of the inactive ingredients in Radicava and/or Radicava ORS]

CONTINUATION OF THERAPY:

A. AMYOTROPHIC LATERAL SCLEROSIS (ALS):

1. Adherence to therapy at least 85% of the time as verified by Prescriber and member's medication fill history (review Rx history for compliance)
AND
2. Documentation of disease stability or mild progression indicating a slowing of decline [i.e., member continues to have a score of 2 or greater on each item of the ALSFRS-R; AND ALSFRS-R score has not decreased more than 6 points total from previous baseline 6 months ago]
AND
3. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity

DURATION OF APPROVAL:

Initial: 6 months; 6 cycles (64 doses over 168 days)
Continuation: 6 months; 6 cycles (60 doses over 168 days)

PRESCRIBER REQUIREMENTS:

Prescribed by, or in consultation with, a board-certified neurologist experienced in the management/treatment of amyotrophic lateral sclerosis (ALS).
[If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests]

AGE RESTRICTIONS:

18 years of age or older

QUANTITY:

60 mg/day IV or 105 mg/day (5 mL) oral suspension
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

PLACE OF ADMINISTRATION:

The recommendation is that oral medications in this policy will be for pharmacy benefit coverage and patient self-administered.

The recommendation is that infused medications in this policy will be for pharmacy or medical benefit coverage administered in a place of service that is a non-hospital facility-based location as per the Molina Health Care Site of Care program.
Note: Site of Care Utilization Management Policy applies for Radicava. For information on site of care, Specialty Medication Administration Site of Care Coverage Criteria (molinamarketplace.com)

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Intravenous, Oral

DRUG CLASS:
ALS Agents - Miscellaneous

FDA-APPROVED USES:
Treatment of amyotrophic lateral sclerosis (ALS)

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

APPENDIX:
Diagnostic criteria
The clinical standard for the diagnosis of ALS is the revised El Escorial World Federation of Neurology criteria, also known as the Airlie House criteria. These criteria were designed for research purposes to ensure appropriate inclusion of patients into clinical trials and allow assignment of diagnostic certainty. They have been further adapted (the Awaji criteria) to better incorporate and electromyography information and improve diagnostic sensitivity.
The El Escorial revised Airlie House diagnostic criteria grades the certainty of the diagnosis based upon 4 clinical grades:

- Clinically “Definite ALS” is defined on clinical evidence alone by the presence of upper motor neuron (UMN), as well as lower motor neuron (LMN) signs, in the bulbar region and at least 2 spinal regions or the presence of UMN and LMN signs in 3 spinal regions.
- Clinically “Probable ALS” is defined on clinical evidence alone by UMN and LMN signs in at least 2 regions with some UMN signs necessarily rostral to (above) the LMN signs.
- Clinically “Probable ALS Laboratory supported” is defined when clinical signs of UMN and LMN dysfunction are in only 1 region, or when UMN signs alone are present in 1 region, and LMN signs defined by electromyography criteria are present in at least 2 regions, with proper application of neuroimaging and clinical laboratory protocols to exclude other causes.
- Clinically “Possible ALS” is defined when clinical signs of UMN and LMN dysfunction are found together in only 1 region or UMN signs are found alone in 2 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.

Note: “Suspected ALS” is deleted from the revised El Escorial Criteria
By the revised El Escorial criteria, diagnosis of ALS requires:

- Presence of evidence of lower motor neuron (LMN) degeneration by clinical, electrophysiologic, or neuropathologic exam evidence of upper motor neuron (UMN)

degeneration by clinical exam progressive spread of symptoms or signs within a region or to other regions, determined by history or exam
- Absence of: electrophysiologic or pathologic evidence of other disease processes that might explain signs of LMN and/or UMN degeneration neuroimaging evidence of other disease processes that might explain observed clinical and electrophysiologic signs

ALS FUNCTIONAL RATING SCALE-REVISED (ALSFRS-R)

ALSFRS-R has been the most widely used composite measure of function in ALS over the last 15 years (Cedarbaum 1999) The ALSFRS-R scale consists of 12 questions that evaluate the fine motor, gross motor, bulbar, and respiratory function of patients with ALS (speech, salivation, swallowing, handwriting, cutting food, dressing/hygiene, turning in bed, walking, climbing stairs, dyspnea, orthopnea, and respiratory insufficiency). Each item is scored from 0 to 4, with higher scores representing greater functional ability.

The ALSFRS-R includes 12 items measuring multiple aspects of daily functioning.

Bulbar	Fine Motor	Gross Motor	Breathing

1. Speech
4. Normal speech processes
3. Detectable speech disturbance
2. Intelligible with repeating
1. Speech combined with nonvocal communication
0. Loss of useful speech

2. Salivation
4. Normal
3. Slight but definite excess of saliva in mouth; may have nighttime drooling
2. Moderately excessive saliva; may have minimal drooling
1. Marked excess of saliva with some drooling
0. Marked drooling; requires constant tissue or handkerchief

3. Swallowing
4. Normal eating habits
3. Early eating problems-occasional choking
2. Dietary consistency changes
1. Needs supplemental tube feeding
0. NPO (exclusively parenteral or enteral feeding)

4. Handwriting
4. Normal
3. Slow or sloppy; all words are legible
2. Not all words are legible
1. Able to grip pen but unable to write
0. Unable to grip pen

5a. Cutting Food / Handling Utensils
4. Normal
3. Somewhat slow and clumsy, but no help needed
2. Can cut most foods, although clumsy and slow; some help needed
1. Food must be cut by someone, but can still feed slowly
0. Needs to be fed

5b. Cutting Food / Handling Utensils (Alt. for patients with Gastrostomy)
4. Normal
3. Clumsy but able to perform all manipulations independently
2. Some help needed with closures and fasteners
1. Provides minimal assistance to caregiver
0. Unable to perform any aspect of task

6. Dressing and hygiene
4. Normal function
3. Independent and complete self-care with effort or decreased efficiency
2. Intermittent assistance or substitute methods
1. Needs attendant for self-care
0. Total dependence

7. Turning in bed
4. Normal
3. Somewhat slow and clumsy, but no help needed
2. Can turn alone or adjust sheets, but with great difficulty
1. Can initiate, but not turn or adjust sheets alone
0. Helpless

8. Walking
4. Normal
3. Early ambulation difficulties
2. Walks with assistance
1. Non-ambulatory functional movement only
0. No purposeful leg movement

9. Climbing stairs
4. Normal
3. Slow
2. Mild unsteadiness or fatigue
1. Needs assistance
0. Cannot do

10. Dyspnea
4. None
3. Occurs when walking
2. Occurs with one or more of the following: eating, bathing, dressing (ADL)
1. Occurs at rest, difficulty breathing when either sitting or lying
0. Significant difficulty, considering using mechanical respiratory support

11. Orthopnea
4. None
3. Some difficulty sleeping at night due to shortness of breath. Does not routinely use more than two pillows
2. Needs extra pillow in order to sleep (more than two)
1. Can only sleep sitting up
0. Unable to sleep

12. Respiratory insufficiency
4. None
3. Intermittent use of BiPAP
2. Continuous use of BiPAP
1. Continuous use of BiPAP during the night and day
0. Invasive mechanical ventilation by intubation or tracheostomy

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:

Amyotrophic Lateral Sclerosis (ALS)

- Also known as Charcot's disease and Lou Gehrig's disease, is a disease of unknown cause characterized by slowly progressive degeneration of upper motor neurons (UMNs) and lower motor neurons (LMNs).
- An adult-onset, neurodegenerative disease characterized by loss of motor neurons in the spinal cord, brainstem, and motor cortex. ALS primarily affects the upper and lower motor neurons and is characterized by muscle weakness, disability, and eventual death, usually from respiratory failure.
- Cause of the disease is unknown, and there is no cure.

- One of the most common neuromuscular diseases worldwide and affects individuals of all races and ethnic backgrounds (NIND 2017). In 2016 the Centers for Disease Control and Prevention estimated that between 14,000 - 15,000 Americans have ALS.
- Most common in individuals 40-60 years old, but younger and older people can develop the disease. Men are more likely to develop ALS than women. Studies suggest an overall ratio of about 1.5 men to every woman who develops ALS in Western countries (ALS Association Epidemiology of ALS and Suspected Clusters)

A diagnosis of ALS is based upon evidence of upper and lower motor neuron signs, relentless disease progression, and the absence of an alternative etiology (Kiernan MC; Brooks BR; AAN 2009). ALS, as with other motor neuron diseases, does not have a diagnostic test that can confirm or entirely exclude its diagnosis.

ALS management is primarily managed with symptomatic treatment and palliative care. There is no known cure for ALS at the present time. There are currently two FDA approved therapies for management of ALS as of May 2017 with the approval of Radicava (edaravone):

1) **Riluzole (Rilutek)** was the first drug to receive FDA approval for ALS (December 1995). Riluzole is an oral formulation that acts to slow the progression of ALS symptoms and prolong survival. The exact mechanism in treating ALS is unknown; however, it is believed to block the release of glutamate from nerve cells thereby reducing the rate of glutamate- induced deterioration in nerve cells resulting in the slowing of initial progression of symptoms.

Riluzole has demonstrated a slight increase overall survival (by 2-3 months), however it has not been shown to have an effect on physical functioning (has not been shown to modulate motor or respiratory function). Clinical studies concluded that Rilutek may increase early survival by two to three months, but it does not improve muscle strength and neurological function and has no effect in later stages of ALS.

Compared with placebo, riluzole may prolong median tracheostomy-free survival by 2-3 months in patients younger than 75 years with definite or probable ALS who have had the disease for less than 5 years and who have a forced vital capacity (FVC) of greater than 60%.

2) **Radicava (edaravone)** received FDA approval on May 5, 2017 for the treatment of patients with ALS. Radicava is the second drug to be approved for treatment of ALS after more than two decades from the first FDA approval of riluzole.

Edaravone is a pyrazolone free radical scavenger. The mechanism by which the drug exerts its therapeutic effects in ALS in unknown. It is theorized to decrease effects of oxidative stress, a likely factor in the onset and progression of ALS. Administration is by IV infusion, requiring it to begiven by a healthcare professional and monitoring for infusion-related reactions.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:
All other uses of Radicava (edaravone) and Radicava ORS (edaravone) are considered experimental/investigational and therefore, will follow Molina's Off-Label policy. Contraindications to edaravone include: patients with a history of hypersensitivity to edaravone or any of the inactive ingredients in Radicava and/or Radicava ORS.

OTHER SPECIAL CONSIDERATIONS:
None

CODING/BILLING INFORMATION

Note: 1) This list of codes may not be all-inclusive. 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

HCPCS CODE	DESCRIPTION
J1301	Injection, edaravone,1mg

AVAILABLE DOSAGE FORMS:
Radicava ORS Starter Kit SUSP 105MG/5ML
Radicava ORS SUSP 105MG/5ML
Radicava SOLN 30MG/100ML (100ml bottle)

REFERENCES

1. Radicava (edaravone) [prescribing information]. Jersey City, NJ: MT Pharma America Inc; May 2022.
2. Brooks BR. El Escorial World Federation of Neurology criteria for the diagnosis of amyotrophic lateral sclerosis. Subcommittee on Motor Neuron Diseases/Amyotrophic Lateral Sclerosis of the World Federation of Neurology Research Group on Neuromuscular Diseases and the El Escorial "Clinical limits of amyotrophic lateral sclerosis" workshop contributors. J Neurol Sci 1994; 124 Suppl:96.
3. Brooks BR, Miller RG, Swash M, et al. World Federation of Neurology Research Group on Motor Neuron Diseases. 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.
4. Abe, K., Itoyama, Y., Sobue, G., Tsuji, S., Aoki, M., & Doyu, M. et al. (2014). 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, 15(7-8), 610-617. doi: 10.3109/21678421.2014.959024
5. Abe, K., Aoki, M., Tsuji, S., Itoyama, Y., Sobue, G., & Togo, M. et al. (2017). Safety and efficacy of edaravone in well defined patients with amyotrophic lateral sclerosis: a randomised, double-blind, placebo-controlled trial. The Lancet Neurology, 16(7), 505-512. doi: 10.1016/s1474-4422(17)30115-1

SUMMARY OF REVIEW/REVISIONS	DATE
REVISION-Notable revisions: Products Affected Required Medical Information Continuation of Therapy Quantity Place of Administration Route of Administration Contraindications/Exclusions/Discontinuation Available Dosage Forms References	Q2 2023
REVISION-Notable revisions: Prescriber Requirements Place of Administration	Q2 2022
Q2 2022 Established tracking in new format	Historical changes on file