

Subject: Radicava (edaravone)	Original Effective Date: 9/8/17
Policy Number: MCP-300	Revision Date(s):
Review Date:	

DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP document and provide the directive for all Medicare members.

SUMMARY OF EVIDENCE/POSITION

This policy addresses the coverage of **Radicava (edaravone)** for the treatment of amyotrophic lateral sclerosis (ALS) when appropriate criteria are met.

The intent of the **Radicava (edaravone)** policy is to ensure appropriate selection of patients for therapy based on product labeling, clinical guidelines, and clinical studies. This policy is intended to address coverage criteria that are appropriate for the majority of individuals/members with a particular disease, illness, or condition. Each member's unique clinical circumstances may warrant individual consideration, based on review of applicable medical records.

⌘ Amyotrophic Lateral Sclerosis (ALS)^{Dynamed 2017}

- 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 disease 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 is 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 be given by a healthcare professional and monitoring for infusion-related reactions.

⌘ At the time of this writing, **no trials of Radicava have been conducted in the U.S. and there no U.S. trials are currently registered with ClinicalTrials.gov.** The pivotal clinical trials were conducted in Japan. The FDA requested the manufacturer (MT Pharma America) to file for regulatory approval in the U.S. after it received approval in Japan for ALS in 2015— although there was no U.S. clinical trial data. Perhaps due to the pressing unmet need for treatment of this disease.

⌘ There is insufficient published evidence to assess the safety and efficacy of edaravone for the FDA-approved indication, which includes all patients with ALS. **Clinical benefit has been demonstrated only in patients with mid-stage or earlier disease with preserved respiratory function and assisted ambulatory ability.**

⌘ **The available published phase III evidence is limited to a single trial** conducted in Japan (at 29 sites). **This trial did not meet its primary endpoint** and was not the basis for the FDA approval (Abe et al., 2014). (NCT00330681)

- ◆ Patients (age 20 to 75) were randomized to receive placebo (saline, n=104), or edaravone (n=102) 60mg intravenously per day over the 24-week treatment period.
- ◆ The initial treatment cycle included 14 days of study drug followed by a 14-day observation period, followed by 10 out of 14 days in the administration period in cycles 2 through 6 with a subsequent 14-day observation period.
- ◆ Inclusion criteria:
 - ALS duration of disease of less than 2 years
 - Japanese ALS severity classification of 1 or 2 on a scale of 1 to 5, with 5 being the most severe
 - At least 70% forced vital capacity (FVC)
 - A change in the revised ALSFRS-R score during the 12-week pre-observation period of -1 to -4 points [Refer to Appendix 1 for additional information on ALSFRS-R scale]
 - Participants with reduced respiratory function were excluded.
 - Baseline characteristics were similar between groups

- ◆ **Primary efficacy endpoint.** The endpoint goal of the study was not an increase in overall survival but rather a decrease in rate of worsening of symptoms (decrease in rate of deterioration). The primary efficacy endpoint was the change in ALSFRS-R score compared with placebo during the 24-week treatment period; **this endpoint was not met.** There was no significant difference in the ALSFRS-R scores in the Radicava group compared with placebo.
 - **The authors noted that this study failed to demonstrate efficacy of edaravone to delay the progression of ALS.**
- ◆ *Secondary endpoints were: changes of FVC, grip strength (left/right mean), pinch strength (left/right mean), Modified Norris Scale score, ALSAQ-40 (ALS Assessment Questionnaire), and time to death or a specified state of disease progression (incapable of independent ambulation, loss of function in upper limbs, tracheotomy, artificial respirator with intubation, or tube feeding).*
- ◆ There were no significant differences in the safety profile reported between the treatment groups. The most common adverse events in the Radicava group included gait disturbance (19.6%), nasopharyngitis (21.6%), constipation (12.7%), contusion (11.8%), headache (7.8%), and dysphagia (7.8%).

Post-hoc subgroup analyses of this trial suggested an opportunity to demonstrate efficacy in a more narrowly defined patient population, which led investigators to design 2 additional trials in narrower subsets of patients with ALS. These trials were carried out in Japan (NCT00415519, NCT01492686). **The FDA approval was based on unpublished results on 1 of these trials (NCT01492686, Study MCI186-19):**

⌘ **PIVOTAL TRIAL**

FDA approval of edaravone was based on the pivotal Phase 3 study (NCT01492686, Study MCI186-19), which evaluated 137 people with ALS. Data demonstrated patients who received edaravone for 6 months experienced significantly less decline in physical function (33% reduction or 2.49 ALSFRS-R points; p=0.001).

- ◆ **Primary endpoint:** Change in ALSFRS-R* score from baseline to six months.
Week 24 (6 month) study results: The data demonstrated that patients who received edaravone for six months experienced the following, relative to those who received placebo:
 - ◆ less decline in physical function by 33% compared to placebo
 - ◆ less decline in physical function by 2.49 ALSFRS-R points compared those in the placebo group
- ◆ The most common adverse events were contusion, and dysphagia (16% and 13% of subjects, respectively). Incidence of adverse drug reactions was 2.9% (edaravone) and 7.4% (placebo).

Reference: A 24-Week, Phase III, Double-Blind, Parallel-Group Study of Edaravone (MCI-186) for Treatment of ALS (P3.189). Presented at the American Academy of Neurology Annual Meeting. Vancouver, BC. (Tanaka M, et al.)

- ⌘ In another phase III trial of edaravone in 25 patients with ALS (NCT00415519), investigators reported at conference proceedings that there was no difference in outcomes between Radicava and placebo when treating patients with more advanced disease (i.e., patients who were no longer able to function independently prior to taking the study drug).

- ⌘ The American Academy of Neurology (AAN) Practice Parameter update (2009)

NOTE: The AAN practice parameter for care of patients with ALS does not include recommendations for use of Radicava. The guideline was last reaffirmed in 2014.

CLASSIFICATION: Free Radical Scavenger

Edaravone is a free radical and peroxynitrite scavenger that prevents oxidative damage to cell membranes and may contribute to inhibiting the progression of ALS.

FDA INDICATIONS

⌘ **Amyotrophic lateral sclerosis**

Treatment of amyotrophic lateral sclerosis (ALS)

Available as: 30 mg/100 mL (single-dose polypropylene bag for injection)

FDA Approved: May 2017

♦ *Orphan drug designation for the treatment of ALS*

Black Box Warnings: *None at the time of this writing*

REMS: *No REMS at the time of this writing*

RECOMMENDATIONS/COVERAGE CRITERIA

Radicava (edaravone) may be authorized for members who meet **ALL** of the following criteria [**ALL**]

1. Prescriber specialty [**ONE**]

- ☐ Prescribed by, or in consultation with, a board-certified neurologist experienced in the management/treatment of amyotrophic lateral sclerosis (ALS). Submit consultation notes if applicable.

NOTE: Consultation notes must be submitted for initial request and for continuation of treatment requests at least ONCE annually.

2. Diagnosis/Indication [**ALL**]

Documentation supporting the clinical diagnosis of (includes clinical notes from the member's medical records including any applicable labs and/or tests, supporting the diagnosis) of **ALL** the following criteria: [**ALL**]

- ☐ Diagnosis of '**definite ALS**' or '**probable ALS**' per the revised EL Escorial and Airie House diagnostic criteria

NOTE: Refer to Appendix 1 for additional information on ALS Diagnostic criteria

INFORMATIONAL NOTE: Radicava is approved with a general indication for all patients with ALS; however, the early-onset ALS patients (patients newly diagnosed with definite or probably ALS) had a greater magnitude of effect according to pivotal studies (Study MCI186-19). Clinical benefit has been demonstrated only in patients with mid-stage or earlier disease with preserved respiratory function and assisted ambulatory ability.

- ☐ Diagnosis or onset of ALS has been less than 2 years[†]
- ☐ **Baseline Japanese ALS severity classification grade of less than 3 (grade 1 and 2 meets criterion)** indicating independent living status. A Japanese ALS classification grade is based on the severity of the disease and the grade ranges from 1 to 5 and defined as follows:^{Abe, 2014}
 1. Able to work or perform housework
 2. Independent living but unable to work;
 3. Requiring assistance for eating, excretion or ambulation;
 4. Presence of respiratory insufficiency, difficulty in coughing out sputum or dysphagia; and
 5. Using a tracheostomy tube, tube feeding or tracheostomy positive pressure ventilation

- ☐ **Baseline ALS Functional Rating Scale-Revised (ALSFRS-R) score of 2 or greater** on each individual item of the scale: **> 2 points in each of the 12 items; total 48 points.**[†] Documentation required.

NOTE: Refer to Appendix 1 for additional information on ALS Diagnostic criteria

- ♦ *INFORMATIONAL NOTE: The revised ALSFRS-R score is a physician-generated estimate of the patient's degree of functional impairment. The ALSFRS-R scale is a twelve question evaluation of ALS patients' fine motor, gross motor, bulbar, and respiratory function. Each question has five possible responses, with normal function worth 4 points and the greatest degree of impairment scoring 0 points.*

- ☐ Normal respiratory function[†]: Defined as a percent-predicted forced vital capacity (%FVC) of greater than or equal to 80%. Documentation required.

[†]*INFORMATIONAL NOTE: Rationale for above criteria per Study MCI186-19: The clinical pivotal trial, MCI186-19, studied 137 patients, with 69 receiving Radicava and 68 receiving placebo. Patients had to be diagnosed with ALS within the previous 2 years, and in addition, they had to have normal respiratory function, and had to be able to perform most activities of daily living. They also continued to receive standard of care treatment, which included riluzole.*

3. Age/Gender/Restrictions [ALL]

- ☐ 18 years of age or older
 - ♦ *Safety and efficacy have not been established in pediatric patients*

4. Conventional Therapy/Concurrent Therapy/Other Requirements [ALL]

- ☐ Concomitant use of riluzole (Rilutek) [up to maximally indicated doses (50 mg twice daily or 100 mg/day)] unless member has a labeled contraindication(s)[†] or clinically significant adverse effects.[‡] Documentation required.

[†] *Contraindications to riluzole: Hypersensitivity to riluzole or any component of the formulation*

[‡] *Warnings/Precautions to riluzole:*

- *Hepatic effects: May cause drug-induced hepatic injury (including fatality); asymptomatic elevations of hepatic transaminases may also occur. Elevations of transaminases may occur within 3 months of use. Use is not recommended in patients who develop hepatic transaminases more than 5 times the upper limit of normal. Monitor for signs and symptoms of hepatic injury every month for the first 3 months and periodically thereafter; discontinue use if evidence of hepatic dysfunction occurs (e.g., elevated bilirubin).*
- *Neutropenia: Severe neutropenia has been reported (ANC less than 500/mm³) within the first 2 months of therapy. Evaluate patients with febrile illnesses.*
- *Pulmonary disorders: Interstitial lung disease (ILD), including hypersensitivity pneumonitis, has occurred. Discontinue therapy immediately if ILD occurs.*

INFORMATIONAL NOTE: Rationale for above criteria per Study MCI186-19

5. Contraindications/Exclusions/Discontinuations

Authorization will not be granted if ANY of the following conditions apply [ANY]

- ☐ Non-FDA approved indications
- ☐ Hypersensitivity to Radicava (edaravone) or any component of the formulation
 - ◆ *The most common adverse reported by subjects receiving edaravone were contusion and gait disturbance. Radicava is also associated with serious risks that require immediate medical care, such as hives, swelling, or shortness of breath, and allergic reactions to sodium bisulfite, an ingredient in the drug. Sodium bisulfite may cause anaphylactic symptoms that can be life-threatening in people with sulfite sensitivity.*

Exclusions [ANY]

- ☐ Younger than 18 years

6. Labs/Reports/Documentation required [ALL]

All documentation for determination of medical necessity must be submitted for review. Prescriber to submit documentation as indicated in the criteria above, including but not limited to chart notes, applicable lab values and/or tests, adverse outcomes, treatment failures, or any other additional clinical information or clinical notes from the member's medical records supporting the diagnosis. Letters of support and/or explanation are often useful, but are not sufficient documentation unless ALL specific information required by this MCP is included.

NOTE: Additional documentation, rationale, and/or supporting evidence may be requested for review as deemed necessary or appropriate by Molina Medical/Pharmacy staff.

CONTINUATION OF THERAPY

Radicava (edaravone) may be authorized for continuation of therapy if meet **ALL** of the following criteria are met: **[ALL]**

1. Initial Coverage Criteria [ALL]

- ☐ Member currently meets ALL initial coverage criteria
- ☐ Subsequent authorizations will require the Member to have an office visit and re-assessment for this condition annually to determine if continuation of treatment with requested medication is medically necessary. Chart notes or consultation notes (if applicable) must be submitted for initial request and for continuation of treatment requests at least ONCE annually.

2. Compliance [ALL]

- ☐ Adherence to therapy at least 85% of the time as verified by Prescriber and member's medication fill history (review Rx history for compliance), including:
 - ☐ Adherent to the prescribed medication regimen
 - ☐ Tolerance to therapy
 - ☐ No severe adverse reactions or drug toxicity

NOTE: Therapy may be discontinued due to poor adherence upon recommendation of the Molina Medical Director when adherence < 85% has been demonstrated in at least two months during the course of therapy

NOTE: History of non-compliance or non-adherence as verified by member's medication fill history or prescription drug profile may result in continuation of therapy request not being authorized. [MOLINA MEDICAL/PHARMACY REVIEWER TO VERIFY]

3. Labs/Reports/Documentation required [ALL]

Radicava (edaravone) therapy may be authorized when therapy has demonstrated efficacy as evidenced by an improvement in disease activity after initial therapy documentation by: **[ALL]**

- ☐ Disease stability or mild progression indicating a slowing of decline on the ALSFRS-R (no rapid disease progression while on therapy, no significant toxicity, etc.)

4. Discontinuation of Treatment [ANY]

Discontinue treatment if ANY of the following conditions applies: **[ANY]**

- ☐ Intolerable adverse effects or drug toxicity [including but not limited to: hypersensitivity reactions, sulfite allergic reactions, confusion, etc.]
- ☐ Persistent and uncorrectable problems with adherence to treatment
- ☐ Poor response to treatment as evidenced by physical findings and/or clinical symptoms
- ☐ Contraindications
 - ☐ Non-FDA approved indications
 - ☐ Hypersensitivity to Radicava (edaravone) or any component of the formulation
- ☐ Exclusions **[ANY]**
 - ☐ Younger than 18 years

5. Labs/Reports/Documentation required [ALL]

All documentation for determination of medical necessity must be submitted for review. Prescriber to submit documentation as indicated in the criteria above, including but not limited to chart notes, applicable lab values and/or tests, adverse outcomes, treatment failures, or any other additional clinical information or clinical notes from the member's medical records supporting the diagnosis. Letters of support and/or explanation are often useful, but are not sufficient documentation unless ALL specific information required by this MCP is included.

NOTE: Additional documentation, rationale, and/or supporting evidence may be requested for review as deemed necessary or appropriate by Molina Medical/Pharmacy staff.

ADMINISTRATION, QUANTITY LIMITATIONS, AND AUTHORIZATION PERIOD

Consult the manufacturer's labeling for more detailed information on dosage and administration of this drug, cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and monitoring.

1. Recommended Dosage [ALL]

Dose prescribed is the FDA recommended dose for 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: [ALL]

- ☐ **Initial treatment cycle:** 60 mg IV infusion once daily for 14 days, followed by a 14-day drug-free period
- ☐ **Subsequent treatment cycles:** 60 mg IV infusion once daily for 10 days within a 14-day period, followed by a 14-day drug-free period

2. Authorization Limit [ALL]

- ☐ Quantity limit: 60 mg/day
 - ☐ 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
- ☐ Duration authorization: [ALL]
 - ☐ Initial: 6 months; 6 cycles (64 doses over 168 days)
 - ☐ Continuation: 6 months; 6 cycles (64 doses over 168 days)
- ☐ Continuation of treatment: Re-authorization is required every **6 months** to determine effectiveness of therapy and continued need based on documented positive clinical response. Subsequent renewals will be authorized upon verification of marked clinical improvement demonstrated by objective improvement in these selected markers. *Refer to 'Continuation of Therapy' section.*

3. Route of Administration [ALL]

- ☐ Radicava (edaravone) is considered a **provider-administered** medication via intravenous (IV) use only.
- ☐ Site of Administration

Molina Healthcare supports administering injectable medications in various settings, provided that those services are furnished in the **most appropriate and cost-effective setting** that are supportive of the member's medical condition and unique needs. The decision on the most appropriate setting for administration is based on the member's current medical condition and any required monitoring or additional services that may coincide with the delivery of the specific medication as directed by the FDA-approved labeling.

 - Radicava (edaravone) may be administered in a **home-based infusion, physician office setting, infusion center** (independent infusion therapy provider, retail pharmacy with infusion services)
 - Inpatient and hospital outpatient infusion: Reserve only for cases where home-based or physician office setting is not appropriate. An inpatient admission for the sole purpose of edaravone infusion is not medically necessary.

- ❑ If member meets all criteria and approval for therapy is granted, medication will be dispensed by a specialty pharmacy vendor at the discretion of Molina Healthcare. Self-administered medications may not be dispensed for self-administration and billed through the medical benefit by a provider. These agents must be dispensed through a participating pharmacy.

COVERAGE EXCLUSIONS

This policy addresses the coverage of **Radicava (edaravone)** for the treatment of amyotrophic lateral sclerosis (ALS) when appropriate criteria are met.

All other uses of **Radicava (edaravone)** that are not an FDA-approved indication or not included in the 'Coverage Criteria' section of this policy are considered experimental/investigational or not a covered benefit of this policy. This subject to change based on research and medical literature, or at the discretion of Molina Healthcare.

*Pharmaceutical samples: The use of pharmaceutical samples (from the prescriber or manufacturer assistance program) will not be considered when evaluating the medical condition, prior prescription history, or as continuation of therapy.

**FDA-approved indication does not, in itself, dictate coverage. Molina Clinical Policy may not recommend coverage for all FDA-approved indications. Please review this Policy in its entirety for indications covered by Molina Healthcare.*

SUMMARY OF EVIDENCE

PIVOTAL TRIAL

Efficacy and Safety Study of MCI-186 for Treatment of the Patients with Amyotrophic Lateral Sclerosis (ALS) 2
FDA approval of edaravone was based on the six-month results a randomized, placebo-controlled, double-blind Phase 3 study (MCI-186-19) study which evaluated the efficacy and safety of edaravone in a 24-week open-label extension period after a 24-week double-blind period (NCT01492686).

Data demonstrated patients who received edaravone for 6 months experienced significantly less decline in physical function (33% reduction or 2.49 ALSFRS-R points; $p=0.001$).^{Takana et al. 2016}

- ◆ The study enrolled 137 subjects (n=137): 69 patients in the Radicava arm and 68 in the placebo arm.
 - ◆ Subjects randomized in 1:1 ratio to receive Radicava 60mg intravenously for 60 minutes or placebo for six-months
 - ◆ Ages: 20 Years to 75 Years (Adult, Senior)
- ◆ All study patients had to meet all of the following criteria at screening:
 - ◆ Functionality retained most activities of daily living (defined as scores of 2 points or better on each individual item of the ALS Functional Rating Scale – Revised [ALSFRS-R])
 - ◆ Normal respiratory function (defined as percent-predicted forced vital capacity [%FVC] values of greater than or equal to 80%)
 - ◆ Definite or probable ALS based on the El Escorial revised criteria
 - ◆ Disease duration of 2 years or less

Baseline characteristics were similar between these groups, with over 90% of patients in each group being treated with riluzole.

- ◆ Patients who met the criteria were randomized to receive either edaravone 60 mg intravenously (IV) or placebo for 6 cycles (4 weeks per cycle with 2 weeks on, 2 weeks off). 90% of patients in both the edaravone and placebo group were also receiving treatment with riluzole. Radicava was administered as an IV infusion of 60 mg given over a 60-minute period according to the following schedule:
 - Subsequent treatment cycles with daily dosing for 10 days out of 14-day periods, followed by 14-day drug-free periods (Cycles 2 to 6)
- ◆ Primary endpoint of the study was a comparison of change in treatment arms in the ALSFRS-R score from baseline to week 24. The revised ALSFRS was used to measure disease status and levels of disability in patients with ALS. **The endpoint of the study was not an increase in overall survival but rather a decrease in the rate of worsening of symptoms (decrease in rate of deterioration)**
- ◆ Results
At week 24 (6 months): **Data demonstrated patients who received edaravone for six months experienced less decline in physical function-- by 33 percent or 2.49 ALSFRS-R points (p=0.0013) compared to those in the placebo group.**
- ◆ The most common adverse events were contusion, and dysphagia (16% and 13% of subjects, respectively). Incidence of adverse drug reactions was 2.9% (edaravone) and 7.4% (placebo).
- ◆ Conclusion The clinical trial investigators concluded edaravone showed efficacy in a small subset of patients (i.e. those meeting the criteria noted above) and ‘there is no indication that edaravone might be effective in a wider population of patients with ALS who do not meet the criteria.’

⌘ **Safety.** The most common adverse events associated with edaravone are contusion, gait disturbance, and headache. Adverse events observed post FDA approval of edaravone include hypersensitivity reactions and anaphylaxis. Edaravone is contraindicated in patients with history of hypersensitivity to edaravone or any of its inactive ingredients.

⌘ The Writing Group (Lancet 2017)

The following was concluded on behalf of the Edaravone (MCI0186) ALS 19 Study Group:

- Post-hoc analysis of these data revealed that patients in an early stage with definite or probable diagnosis of ALS, defined by the revised El Escorial criteria, who met a select set of inclusion criteria showed a greater magnitude of effect than did the full study population.
- Edaravone showed efficacy in a small subset of people with ALS who met criteria identified in post-hoc analysis of a previous phase 3 study, showing a significantly smaller decline of [ALS Functional Rating Scale] ALSFRS-R score compared with placebo. There is no indication that edaravone might be effective in a wider population of patients with ALS who do not meet the criteria.

HAYES

At the time of this writing in August 2017, a Hayes assessment addressing the management of amyotrophic lateral sclerosis with edaravone (Radicava) is not available; however a ‘Prognosis Overview’ is available.

◆ **Riluzole 100 mg/day may prolong survival by about 2-3 months (Level 2 [mid-level] evidence)**^{Dynamed}

- based on Cochrane review with borderline statistical significance
- systematic review of 4 randomized controlled trials of riluzole with 1,477 adults with ALS
- comparing median survival with riluzole 100 mg vs. placebo
 - 15.5 months vs. 13.2 months in meta-analysis of 2 homogeneous trials with 631 patients ($p = 0.042$)
 - 14.8 months vs. 11.8 months in meta-analysis including third trial with 168 older patients with more advanced disease ($p = 0.056$), but limited by heterogeneity ($p < 0.0001$)
- riluzole 100 mg associated with decreased mortality at 1 year in analysis of 3 trials with 799 patients ($p = 0.0036$, NNT 11)
 - risk ratio 0.78 (95% CI 0.65-0.92)
 - NNT 7-29 with 44% mortality in control group
 - results limited by significant heterogeneity ($p = 0.05$)
- fourth trial from Japan with 195 patients had no significant differences in multiple clinical outcomes and did not report survival-specific data
- riluzole associated with small but significant beneficial effect on bulbar and limb function but not on muscle strength in analysis of 3 trials with 731 patients
- elevated serum alanine transferase (ALT) (> 3 times upper limit of normal), nausea, and asthenia significantly more frequent with riluzole
- minimal data on quality of life
- Authors' conclusions: **Riluzole 50 mg twice a day is reasonably safe and probably prolongs median survival by about two to three months in patients with amyotrophic lateral sclerosis.**
- Reference: *Cochrane Database of Systematic Reviews 2012, Issue 3. Art. No.: CD001447*

CLINICAL PRACTICE GUIDELINES

**Guidelines have not addressed the role of edaravone (Radicava) as of this writing in August 2017*

Evidence-based guidelines for the clinical management of ALS have been published by the European Federation of Neurological Societies and the American Academy of Neurology:

American Academy of Neurology (AAN)

In October 2009, the AAN published a 2-part, evidence-based Practice Parameter update about the care of patients with ALS. These publications updated the 1999 evidence-based practice parameter.

Practice parameter update: The care of the patient with ALS: multidisciplinary care, symptom management, and cognitive/behavioral impairment (an evidence-based review) (AAN 2009)

- ◆ ALS management is primarily symptomatic treatment and palliative care
- ◆ treatment to slow disease progression
 - ◆ riluzole 50 mg twice daily recommended for slowing disease progression in ALS (AAN Level A)
 - riluzole 100 mg/day may prolong survival by about 2-3 months (level 2 [mid-level] evidence)
 - consider withholding riluzole in those patients who develop fatigue as a side effect (AAN Level C)

NOTE: This review addresses riluzole, lithium, nutrition, and respiratory care. Radicava has not been addressed in the practice parameter at the time of this writing in August 2017.

AAN 2008 grading system for recommendations

Levels of evidence

Level A: established as effective, ineffective, or harmful (or established as useful/predictive or not useful/predictive) for given condition in specified population (requires at least 2 consistent Class I studies)

Level B: probably effective, ineffective, or harmful (or probably useful/predictive or not useful/predictive) for given condition in specified population (requires at least 1 Class I study or at least 2 consistent Class II studies)

Level C: possibly effective, ineffective, or harmful (or possibly useful/predictive or not useful/predictive) for given condition in specified population (requires at least 1 Class II study or at least 2 consistent Class III studies)

European Federation of Neurological Societies (EFNS)

EFNS task force on management of amyotrophic lateral sclerosis: guidelines for diagnosing and clinical care of patients and relatives (EFNS 2005)

*GPP=Good Practice Point

- ALS patients should be offered treatment with riluzole 50 mg twice daily (Class 1A, GPP)
- Patients treated with riluzole should be monitored regularly for safety (Class 1A, GPP).
- Treatment should be initiated as early as possible after the patient has been informed of the diagnosis taking into account expected therapeutic benefits and potential safety issues (class 1A). Realistic expectations for treatment effects and potential side effects should be discussed with the patient and caregivers. (GPP)
- Treatment with riluzole should be considered in PMA and PLS patients who have a first degree relative with ALS. (GPP)

DEFINITIONS

N/A

APPENDIX

Appendix 1: DIAGNOSTIC CRITERIA

The El Escorial criteria were developed in 1994 by the World Federation of Neurology for research and clinical trial purposes. These guidelines were subsequently revised in recognition of the importance of laboratory testing, and were renamed the Airlie House criteria in 1998. The role of neurophysiology in diagnostic categorization has been further revised, and a subsidiary set of indicators—the Awaji-Shima criteria—was introduced in 2008, use of which improved diagnostic sensitivity without increasing false-positive rates

REVISED EL ESCORIAL CRITERIA: World Federation of Neurology consensus diagnostic criteria

The El Escorial Criteria (EEC) were developed in 1990 by the World Federation of Neurology and revised in 2000 to standardize the diagnosis of ALS for clinical research studies.

Currently, the ALS diagnostic criteria with the broadest international acceptance are the El Escorial revised Airlie House diagnostic criteria (Motor Neuron Diseases Research Group of the World Federation of Neurology) that were proposed in 1998. These criteria allow assignment of diagnostic certainty and were designed for research purposes to ensure appropriate inclusion of patients into clinical trials.

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

References

- 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.*
- 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.*

AWAJI-SHIMA CRITERIA

The Awaji-shima criteria simplify the EEC and classify the certainty level of the diagnosis into one of three categories: clinically definite, probable, and possible.

- ◆ **Clinically definite ALS** is defined on clinical or electrophysiological evidence, demonstrated by the presence of upper and lower motor neuron signs in the bulbar region and at least two spinal regions, or the presence of upper and lower motor neuron signs in three spinal regions.
- ◆ **Clinically probable ALS** is defined on clinical or electrophysiological evidence, demonstrated by upper and lower motor neuron signs in at least two spinal regions, with some upper motor neuron signs necessarily rostral to the lower motor neuron signs.
- ◆ **Clinically possible ALS** is defined on clinical or electrophysiological signs of upper and lower motor neuron dysfunction in only one region, or upper motor neuron signs alone in two or more regions, or lower motor neuron signs rostral to upper motor neuron signs.

Reference: de Carvalho M, Dengler R, Eisen A, et al. Electrodiagnostic criteria for diagnosis of ALS. Clin Neurophysiol 2008;119(3):497–503

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	

Reference: Cedarbaum JM, Stambler N, Malta E, et al. The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. BDNF ALS Study Group (Phase III). J Neurol Sci. 1999; 169(1-2):13-21.

CODING INFORMATION: THE CODES LISTED IN THIS CLINICAL POLICY ARE FOR INFORMATIONAL PURPOSES ONLY. LISTING OF A SERVICE OR DEVICE CODE IN THIS POLICY DOES NOT IMPLY THAT THE SERVICE DESCRIBED BY THIS CODE IS A COVERED OR NON-COVERED. COVERAGE IS DETERMINED BY THE BENEFIT DOCUMENT. THIS LIST OF CODES MAY NOT BE ALL INCLUSIVE AND 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.

CPT	Description
NA	

HCPCS	Description
J3490	Unclassified drug [Radicava (edaravone)]

ICD-10	Description [For dates of service on or after 10/01/2015]
G12.21	Amyotrophic lateral sclerosis

REFERENCES

Package Insert, FDA, Drug Compendia

Radicava [Prescribing Information]. Jersey City, NJ: MT Pharma America, Inc.; May 2017.

Drug Facts and Comparisons. Facts and Comparisons eAnswers [online]. Clinical Drug Information LLC, 2017. Available from Wolters Kluwer Health, Inc. [via subscription only]

Clinical Pharmacology [Internet]. Radicava (edaravone). Available from: <http://www.clinicalpharmacology.com/> [via subscription only]. Accessed August 2017

Micromedex® Healthcare Series [Internet database]. DRUGDEX® Evaluations. Radicava (edaravone). Greenwood Village, CO: Thomson Micromedex. Available at: <http://www.micromedexsolutions.com/micromedex2/librarian>. June 2017.

ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine; 2000 Feb 29 - [cited June 2017]. Available from: <http://clinicaltrials.gov/>.

CLINICAL TRIALS, DEFINITIONS, PEER-REVIEWED PUBLICATIONS

[DEFINITION] Brooks BR, Miller RG, Swash M, Munsat TL, 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](#)

[DEFINITION] Castrillo-Viguera C, Grasso DL, et al. Clinical significance in the change of decline in ALSFRS-R. Amyotroph Lateral Scler. 2010;11(1-2):178-80.

[DEFINITION] Cedarbaum JM, Stambler N, Malta E, Fuller C, Hilt D, Thurmond B, Nakanishi A. The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. BDNF ALS Study Group (Phase III). J Neurol Sci 1999;169:13-21

[DEFINITION] de Carvalho M, Dengler R, Eisen A, et al. Electrodiagnostic criteria for diagnosis of ALS. Clin Neurophysiol 2008; 119:497-503.

[DEFINITION] Geevasinga N, Menon P, Scherman DB, Simon N, Yiannikas C, Henderson RD, Kiernan MC, and Vucic S. Diagnostic criteria in amyotrophic lateral sclerosis: A multicenter prospective study. *Neurology*. 2016 Aug 16; 87(7): 684-90.

[DEFINITION] Kiernan MC, Vucic S, Cheah BC, et al. Amyotrophic lateral sclerosis. *Lancet*. 2011 Mar 12;377(9769):942-55

Huisman MH, de Jong SW, van Doormaal PT, et al. Population based epidemiology of amyotrophic lateral sclerosis using capture-recapture methodology. *J Neurol Neurosurg Psychiatry* 2011;82(10):1165–1170

Miller RG, Mitchell JD, et al. Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND). *Cochrane Database Syst Rev*. 2007 Jan 24. CD001447.

Elman LB, McCluskey L. Diagnosis of amyotrophic lateral sclerosis and other forms of motor neuron disease. UpToDate Inc., April 2017. Accessed August 2017

DynaMed Plus [Internet]. Ipswich (MA): EBSCO Information Services. 1995 - . Record No. 116744, Amyotrophic lateral sclerosis (ALS); [updated 2017 Feb 05, cited August 2017]; [about 22 screens]. Available from <http://www.dynamed.com/login.aspx?direct=true&site=DynaMed&id=116744>. Registration and login required.

The Writing Group. Safety and efficacy of edaravone in well-defined patients with amyotrophic lateral sclerosis: a randomized, double-blind, placebo-controlled trial. *The Lancet Neurology* (2017) Available at: [http://www.thelancet.com/journals/laneur/article/PIIS1474-4422\(17\)30115-1/abstract](http://www.thelancet.com/journals/laneur/article/PIIS1474-4422(17)30115-1/abstract). Accessed on August 2017.

Clinical Trials

- Abe K, et al. Edaravone ALS Study Group. Confirmatory double-blind, parallel-group, placebo-controlled study of efficacy and safety of edaravone (MCI-186) in amyotrophic lateral sclerosis patients. *Amyotroph Lateral Scler Frontotemporal Degener*. 2014 Dec;15(7-8):610-7. doi: 10.3109/21678421.2014.959024. Epub 2014 Oct 6. <https://clinicaltrials.gov/ct2/show/record/NCT00330681>
- Yoshino H, Kimura A. Investigation of the therapeutic effects of edaravone, a free radical scavenger, on amyotrophic lateral sclerosis (Phase II study). *Amyotroph Lateral Scler*. 2006; 7(4):241-245.
- Tanaka, Masahiko, et al. A Double-Blind, Parallel-Group, Placebo-Controlled, 24-Week, Exploratory Study of Edaravone (MCI-186) for the Treatment of Advanced Amyotrophic Lateral Sclerosis (ALS)(P3. 191). *Neurology* 86.16 Supplement (2016): P3-191 Accessed August 2017

GOVERNMENT AGENCIES, PROFESSIONAL SOCIETIES, AND OTHER AUTHORITATIVE PUBLICATIONS

National Institute of Neurological Disorders (NIND) Amyotrophic Lateral Sclerosis Fact Sheet. Available at: http://www.ninds.nih.gov/disorders/amyotrophiclateralsclerosis/detail_ALS.htm Accessed August 2017

ALS Association Epidemiology of ALS and Suspected Clusters. <http://www.alsa.org/als-care/resources/publications-videos/factsheets/epidemiology.html>. Accessed August 2017

Miller RG, Mitchell JD, Moore DH. Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND). *Cochrane Database of Systematic Reviews* 2012, Issue 3. Art. No.: CD001447. DOI: 10.1002/14651858.CD001447.pub3.

American Academy of Neurology

Miller RG, Jackson CE, Kasarskis EJ, et al. Practice Parameter update: The care of the patient with amyotrophic lateral sclerosis: Multidisciplinary care, symptom management, and cognitive/behavioral impairment (an evidence-based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology Neurology 2009;73:1227-1233

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; 73:1218-1226

Thurman DJ, Stevens JA, Rao JK. Assessing patients in a neurology practice for risk of falls (an evidence-based review) : Report of the Quality Standards Subcommittee of the American Academy of Neurology Neurology 2008;70;473

European Federation of Neurological Societies (EFNS)

Andersen PM, et al. EFNS task force on management of amyotrophic lateral sclerosis: guidelines for diagnosing and clinical care of patients and relatives. European J of Neurology 2005;12:921-938

Andersen PM, et al. EFNS guidelines on the Clinical Management of Amyotrophic Lateral Sclerosis (MALS) - revised report of an EFNS task force. Eur J Neurol 2011;19(3) 360-375