Washington State Health Care Authority

Agents for ALS – edaravone (Radicava)

Medical policy no. 74.50.90 Effective Date: July, 1, 2020

Note: New-to-market drugs in this class are non-preferred and subject to this prior authorization (PA) policy. Non-preferred agents in this class, require an inadequate response or documented intolerance due to severe adverse reaction or contraindication to at least TWO preferred agents. If there is only one preferred agent in the class documentation of inadequate response to ONE preferred agent is needed.

Background:

Edaravone is indicated for the treatment of amyotrophic lateral sclerosis. Amyotrophic lateral sclerosis (ALS) is a refractory and progressive disease that causes selective degeneration of upper and lower motor neurons. Commonly known as Lou Gehrig's disease, ALS is characterized by progressive degeneration of motor neurons. "Amyotrophic" refers to muscle atrophy and weakness that signify disease of the lower motor neurons. "Lateral sclerosis" refers to the hardness on palpitation of the lateral columns of the spinal cord on autopsy. In typical ALS presentation, the symptoms are primarily related to muscle weakness, which may begin in the outer extremities or manifest as slurred speech and dysphagia. Over time, the progressive degeneration of motor neurons leads to the inability to control muscle movement, eventually leading to paralysis. The disease is progressive and mean duration of survival is three to five years. Age and a family history of ALS are the sole established risk factors for ALS.

Medical necessity

Drug	*Medical Necessity*
edaravone (Radicava)	**Edaravone (Radicava)** may be considered medically necessary when used for the treatment of: • Amyotrophic lateral sclerosis

Clinical policy:

Clinical Criteria	
Amyotrophic Lateral Sclerosis (ALS) <u>Preferred agents:</u> edaravone (Radicava)	Edaravone (Radicava) may be authorized when **ALL** of the following are met: 1. Client is 18 years of age or older; **AND** 2. Diagnosis of <u>definite</u> or <u>probable ALS</u> based on **ONE** of the following: a. El Escorial World Federation of Neurology criteria (Airlie House criteria); **OR** b. Awaji-Shima criteria; **AND** 3. Prescribed by or in consultation with a neurologist or specialist with expertise in the treatment of ALS; **AND** 4. Score of 2 or better on all 12 items of the revised ALS functional rating scale (ALSFRS-R); **AND** 5. Onset of ALS less than or equal to 2 years; **AND** 6. Patient is receiving riluzole **OR** is not a candidate to receive riluzole due to intolerance or contraindication

	If all of the above criteria are met, the request will be **approved for 6 months**
	Criteria (Reauthorization)
	Edaravone (Radicava) may be reauthorized when **ALL** of the following are met: 1. Patient continues to have a score of 2 or better on all 12 items of ALSFRS-R; **AND** 2. Documentation supporting disease stability or mild progression indicated by a slowing of decline on the ALSFRS-R. If all of the above criteria are met, the request may be **reauthorized for 6 months**

Dosage and quantity limits

Indication	Dose and Quantity Limits
ALS – Initial cycle	• 60 mg IV once daily for 14 days, followed by a 14-day drug-free period
ALS – Subsequent cycle	• 60 mg IV once daily for 10 days within a 14-day period, followed by a 14-day drug-free period

Coding:

HCPCS Code	*Description*
C9493	Injection, edaravone, 1 mg
J1301	Injection, edaravone, 1 mg

Definitions

Term	Description
ALS functional rating scale (revised) (ALSFRS-R)	A commonly used functional rating system for persons with ALS (Cedarbaum, 1999).
Awaji-Shima criteria	Diagnostic criteria used for ALS (Douglass, 2010; Hardiman, 2011)
El Escorial/revised Airlie House criteria (El Escorial is also known as Airlie House)	Diagnostic criteria for ALS (Brooks, 2000; Douglass, 2010). Designed for research purposes to ensure appropriate inclusion of subjects into clinical trials.

Evidence review:

The evidence demonstrating the safety and efficacy of edaravone are described below.

A 36-week confirmatory study (Abe, 2014) was conducted to further evaluate the efficacy and safety of edaravone in subjects with ALS. 206 subjects were randomized to receive either placebo (saline) or edaravone IV infusion. The trial consisted of a 12-week pre-observation period followed by a 24-week treatment period between May 2006 and September 2008 at 29 Japanese sites. Inclusion criteria were: age 20-75 years, diagnosis of definite, probable or probable laboratory-supported ALS, forced vital capacity (FVC) of at least 70%, duration of disease within 3 years, and change in revised ALS functional rate scale (ALSFRS-R) score during the pre-observation period of –1 to –4 points. Exclusion criteria included: reduced respiratory function and complaints of dyspnea; complications that might impact evaluation of drug efficacy, such as Parkinson's disease, schizophrenia and dementia; complications that require hospitalization such as liver, cardiac and renal diseases; infections requiring antibiotics; deteriorated general condition; creatinine clearance 50 ml/min or below; and undergoing cancer treatment. The primary efficacy endpoint was change in ALSFRS-R scores during the

24 weeks of treatment. Upon study completion, data failed to demonstrate the efficacy of edaravone for treatment of ALS. Adverse events occurred in 88.5% (92/104) of subjects in the placebo group and 89.2% (91/102) of subjects the edaravone group. The authors indicated that the results of this trial would be helpful to identify the population for which edaravone could be expected to show efficacy. On the basis of that information, a phase III study was designed.

A phase III trial evaluated the efficacy and safety of edaravone in a 24-week open-label extension period after a 24-week double-blind period (Writing Group, 2017a). A total of 137 subjects were randomized 1:1 to receive edaravone or placebo after a 12-week pre-observation period. Selection criteria included: definite or probable ALS; Japan ALS severity classification grade less than 3; scoring 2 or more points on each single ALSFRS-R item at screening; forced vital capacity 80% or greater; and ALS duration 2 years or less. Most (93%) of these subjects were living independently at the time of screening. Subjects were treated with six cycles of 60 mg edaravone or a matching placebo treatment. The primary efficacy endpoint was a change in ALSFRS-R score at week 24. Safety endpoints included adverse events, adverse drug reactions, and laboratory tests (hematology, blood chemistry, and urinalysis). Upon study completion, the mean change in ALSFRS-R score was –7.50 ± 0.66 (placebo) and –5.01 ± 0.64 (edaravone). Adverse events were similar in both groups (84.1% in the edaravone group and 83.8% 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). There were no serious adverse drug reactions or adverse events that resulted in death. Investigators concluded that subjects meeting the protocol inclusion criteria had less functional loss at 6 months and less quality of life deterioration compared to those receiving placebo treatment. According to the authors, "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 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."

After the phase III trial, an open-label, 24-week extension study was completed to determine the longer-term safety and efficacy of edaravone (Writing Group, 2017b). A total of 123 of the original 137 subjects were randomized to either continue treatment with edaravone (E-E group; n=65) or start edaravone instead of the former placebo (P-E group; n=58). The change in the ALSFRS-R score was –4.1 ± 3.4 and –6.9 ± 5.1 from baseline to the end of the study and –8.0 ± 5.6 and –10.9 ± 6.9 for the 48-week timespan in the E-E group and P-E group, respectively. Common adverse effects for both groups included nasopharyngitis, respiratory disorders, constipation, dysphagia, and contusion. A total of 6 subjects died during the study: 2 in the E-E group and 4 in the P-E group. However, the drug was deemed "not reasonably possible" in causing the deaths. The authors did not find any sudden deterioration in the ALSFRS-R scores or safety concerns, but they noted that "long-term treatment for efficacy and safety remains for a future issue."

Researchers performed a small, 24-week, double-blind, randomized study to determine the safety and efficacy of edaravone for ALS individuals with a Japan ALS severity classification of grade 3 (individuals requiring assistance eating, excreting, or ambulating) (Writing Group; 2017c). A total of 25 individuals were randomized 1:1 to either receive edaravone or a placebo. During the study, edaravone was discontinued for 4 individuals in the edaravone

group and none in the placebo group. At the end of the study, the researchers did not find a statistically significant difference between the two groups for ALSFRS-R scores, %FVC, the Modified Norris scale, amyotrophic lateral sclerosis assessment questionnaire (ALSAQ-40) scores, grip strength, or pinch grip strength. Disease progression occurred in 4 subjects in the edaravone group and 3 subjects in the placebo group. Due to the small study sample, the efficacy and safety of edaravone for ALS grade 3 individuals is inconclusive and needs further study.

References

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History

Date	Action and Summary of Changes
4/8/2020	No changes
2/3/2020	Update existing draft policy
8/2/2018	New policy

Washington State Health Care Authority

Neuromuscular Agents: ALS Agents - Misc

Please provide the information below, please print your answer, attach supporting documentation, sign, date, and return to our office as soon as possible to expedite this request. **Without this information, we may deny the request in seven (7) working days.**

Date of request:	Reference #:	MAS:	
Patient	Date of birth	ProviderOne ID	
Pharmacy name	Pharmacy NPI	Telephone number	Fax number
Prescriber	Prescriber NPI	Telephone number	Fax number

Medication and strength	Directions for use	Qty/Days supply

1. Is this request for a continuation of existing therapy?

   ☐ Yes, subsequent cycle ☐ No, initial cycle

   If yes, does patient have documented disease stability or mild progression indicated by a slowing decline on the ALS functional rating scale (ALSFRS-R)? ☐ Yes ☐ No

2. Does patient have a diagnosis of definite or probable amyotrophin lateral sclerosis (ALS) based on El Escorial World Federation of Neurology (Airlie House) or Awaji-Shima criteria?

   ☐ Yes. Date of onset of ALS: ☐ No. Specify diagnosis:

3. Does patient have a score of two or better on all 12 items for of the ALSFRS-R? ☐ Yes ☐ No

4. Is patient currently taking riluzole? ☐ Yes ☐ No
   If no, is riluzole not tolerated or is contraindicated? ☐ Yes ☐ No

5. Is this prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of ALS? ☐ Yes ☐ No

ALL THE FOLLOWING ARE REQUIRED WITH THIS REQUEST:

- EMG and chart notes confirming diagnosis
- ALSFRS-R assessment

Prescriber signature	Prescriber specialty	Date