09-J2000-82

Original Effective Date: 09/15/17

Reviewed: 08/10/22

Revised: 09/15/22

Next Review: 12/14/22

Subject: Edaravone (Radicava)

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Dosage/ Administration	Position Statement	Billing/Coding	Reimbursement	Program Exceptions	Definitions
Related Guidelines	Other	References	Updates		

DESCRIPTION:

Approximately 12,000 to 15,000 individuals in the United States have amyotrophic lateral sclerosis (ALS). Also known as Lou Gehrig's disease, ALS is a progressive, neurodegenerative disease that attacks neurons controlling voluntary muscles. While symptom onset is gradual, those with ALS eventually lose the ability to walk, talk, eat, and ultimately, breathe without ventilator support. The majority of patients with ALS die within 3 to 5 years of developing symptoms. Currently, there is no cure for ALS and treatment is limited to symptom control and supportive therapies. Riluzole is the only other approved treatment that has shown to be modestly effective and is currently recommended by the American Academy of Neurology for use in ALS to slow the disease process.

Edaravone (Radicava), a free radical scavenger and antioxidant, was approved by the U.S. Food and Drug Administration (FDA) in May 2017 for the treatment of ALS. Edaravone may provide neuroprotection against oxidative stress; however, the exact mechanism of action in ALS is unknown.

The safety and efficacy of edaravone were evaluated in subjects diagnosed with "definite ALS", "probable ALS", or "probable-laboratory-supported ALS" (as defined by revised EL Escorial for Airlie House criteria) in a double-blind, parallel-group, placebo-controlled Phase III study published in 2014 by Abe and colleagues. Subjects were required to be able to eat, excrete, move independently, and not need assistance in everyday life. Subjects were excluded if the onset of ALS symptoms was beyond three years of study enrollment and if forced vital capacity (FVC) was less than 70%.

Subjects were randomized edaravone 60 mg daily (n=120) or placebo (n=104). A single treatment cycle consisted of 14 days of study drug administration period followed by a 14-day observation period. Study drugs were administered every day for 14 days in the administration period of the first cycle, and for 10 out of 14 days in the administration periods of cycles 2 to 6. The end of the administration period in each cycle was followed by a 14-day observation period. The primary endpoint was the change in ALSFRS-R score. 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).

The primary endpoint of changes in ALSFRS-R during the 24-week treatment were -6.35±0.84 in the placebo group (n=99) and -5.70±0.85 in the edaravone group (n=100), with a difference of 0.65±0.78 (p=0.411). The primary outcome of inter-group difference in the change of the ALSFRS-R at the end of treatment was not statistically significant. Of all secondary outcomes, edaravone only showed statistically significant benefit over placebo in pinch strength (-1.03±0.15 placebo vs. -0.83±0.15 edaravone; difference of 0.20±0.14; p=0.165). There were no significant differences in the safety profile reported between the two experimental groups.

Post-hoc analysis of data revealed that a subset of patients showed a greater magnitude of effect than the fully study population. A subsequent Phase III, randomized, parallel-group study was designed and later published in 2017 by Abe and collegues to evaluate edaravone (n=69) vs placebo (n=68) in a population meeting these criteria. Participants were included if they had a definite or probable diagnosis of ALS, scored 2 points or more on all 12 items of ALSFRS-R, had an FVC of 80% or more, and had a disease duration of 2 years or less. Patients were randomized to receive 60 mg intravenous edaravone or intravenous saline placebo for 6 cycles (4 weeks per cycle with 2 weeks on, 2 weeks off) for a total treatment duration of 24 weeks. In cycle 1, the study drug or placebo was administered once per day for 14 days within a 14 day period, followed by the drug-free period. In cycle 2 and thereafter, the study drug or placebo was administered for 10 days within a 14 day period, followed by a 2 week drug-free period.

For the primary outcome, the change in ALSFRS-R score was -5·01 (SE 0·64) in the edaravone group and -7·50 (0·66) in the placebo group. The least-squares mean difference between groups was 2·49 (SE 0·76, 95% CI 0·99-3·98; p=0·0013) in favor of edaravone. Treatment-emergent adverse events were similar between the groups.

POSITION STATEMENT:

Comparative Effectiveness

The FDA has deemed edaravone (Radicava) oral suspension to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

Site of Care: If edaravone (Radicava) IV infusion is administered in a hospital-affiliated outpatient setting, additional requirements may apply depending on the member's benefit. Refer to 09-J3000-46: Site of Care Policy for Select Specialty Medications.

Initiation of edaravone (Radicava) **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. Indication for use is treatment of amyotrophic lateral sclerosis (ALS)
2. Member's diagnosis of ALS meets either of the following categories of clinical diagnostic certainty (defined by the revised El Escorial/Arlie House criteria) – documentation from the medical record and all relevant diagnostic testing (e.g., imaging, nerve conduction studies) must be provided:
    a. Clinically Definite ALS
        i. Presence of upper motor neuron (UMN), as well as lower motor neuron (LMN) signs, in the bulbar region and at least two spinal regions **OR** the presence of UMN and LMN signs in three spinal regions
    b. Clinically Probable ALS

i. Presence of UMN and LMN signs in at least two regions with some UMN signs necessarily rostral to (above) the LMN signs

3. Member has a disease duration of two years or less – documentation from the medical record must be provided
4. Member's baseline (i.e., within 60 days of initiation of edaravone) ALS Functional Rated Scale-Revised (ALSFRS-R) score is 2 or higher in **ALL** ALSFRS-R criteria (see Table 1) – documentation from the medical record must be provided
5. Edaravone will be used in combination with riluzole (unless contraindicated or previously tried and not tolerated)
6. Edaravone is prescribed and supervised by a board certified (or board eligible) neurologist
7. Dose does not exceed:
    a. IV infusion:
        i. Initial: 60 mg daily for 14 days followed by a 14 day drug free period
        ii. Maintenance: 60 mg daily for 10 days out of a 14 day period followed by a 14 day drug free period
    b. Oral suspension:
        i. Initial: 105 mg daily for 14 days followed by a 14 day drug free period
        ii. Maintenance: 105 mg daily for 10 days out of a 14 day period followed by a 14 day drug free period

Approval duration: 6 months

Continuation of edaravone (Radicava) **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. Authorization/reauthorization has been previously approved by Florida Blue or another health plan in the past two years for treatment of ALS, **OR** the member has previously met all indication-specific criteria
2. Member's diagnosis of ALS meets either of the following categories of clinical diagnostic certainty based on clinical criteria (defined by the revised El Escorial/Arlie House criteria) – documentation from the medical record and all relevant diagnostic testing (e.g., imaging, nerve conduction studies) must be provided:
    a. Clinically Definite ALS
        i. Presence of upper motor neuron (UMN), as well as lower motor neuron (LMN) signs, in the bulbar region and at least two spinal regions **OR** the presence of UMN and LMN signs in three spinal regions
    b. Clinically Probable ALS
        i. Presence of UMN and LMN signs in at least two regions with some UMN signs necessarily rostral to (above) the LMN signs

3. Member's current (i.e., within 30 days) ALS Functional Rated Scale-Revised (ALSFRS-R) score is 2 or higher in **ALL** ALSFRS-R criteria (see Table 1) – documentation from the medical record must be provided
4. Member had a disease duration of two years or less when edaravone was first initiated – documentation from the medical record must be provided
5. Edaravone is prescribed and supervised by a board certified (or board eligible) neurologist
6. Dose does not exceed
    a. IV infusion: 60 mg daily for 10 days out of a 14 day period followed by a 14 day drug free period
    b. Oral suspension: 105 mg daily for 10 days out of a 14 day period followed by a 14 day drug free period

Approval duration: 1 year

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- IV Infusion
    - 60 mg administered as an intravenous
    - 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
- Oral Suspension
    - 105 mg (5 mL) taken orally or via feeding tube in the morning after overnight fasting, and food should not be consumed for 1 hour after administration except water
    - 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

Dose Adjustments

- None

Drug Availability

- Injection: 30 mg/100 mL in a single-dose polypropylene bag
- Oral suspension: 105 mg/5 mL in a multi-dose amber glass bottle

PRECAUTIONS:

Boxed Warning

- None

Contraindications

- Patients with a history of hypersensitivity to edaravone or any of the inactive ingredients

Precautions/Warnings

- Hypersensitivity Reactions: Advise patients to seek immediate medical care
- Sulfite Allergic Reactions: contains sodium bisulfite, which may cause allergic type reaction

BILLING/CODING INFORMATION:

HCPCS Coding

J1301	Injection, edaravone, 1 mg
J8499	Prescription drug, oral, non-chemotherapeutic, Not Otherwise Specified

ICD-10 Diagnosis Codes That Support Medical Necessity

G12.21	Amyotrophic lateral sclerosis

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date. The Site of Care Policy for Select Specialty Medications does not apply to Medicare Advantage members.

DEFINITIONS:

Clinically Definite ALS is defined on clinical evidence alone by the presence of UMN, as well as LMN signs, in the bulbar region **and** at least two spinal regions or the presence of UMN and LMN signs in three spinal regions.

Clinically Probable ALS is defined on clinical evidence alone by UMN and LMN signs in at least two regions with some UMN signs necessarily rostral to (above) the LMN signs

RELATED GUIDELINES:

None applicable

OTHER:

Table 1: ALS functional rating scale (revised) (ALSFRS-R)

Speech	4 Normal speech processes 3 Detectable speech disturbance 2 Intelligible with repeating 1 Speech combined with nonvocal communication 0 Loss of useful speech
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
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)
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
Cutting food and handling utensils (patients without gastrostomy)	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
Cutting food and handling utensils (alternate scale 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
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

Turning in bed and adjusting bed clothes	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
Walking	4 Normal 3 Early ambulation difficulties 2 Walks with assistance 1 Nonambulatory functional movement 0 No purposeful leg movement
Climbing stairs	4 Normal 3 Slow 2 Mild unsteadiness or fatigue 1 Needs assistance 0 Cannot do
Dyspnea (new)	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
Orthopnea (new)	4 None 3 Some difficulty sleeping at night due to shortness of breath, does not routinely use more than two pillows 2 Needs extra pillows in order to sleep (more than two) 1 Can only sleep sitting up 0 Unable to sleep
Respiratory insufficiency (new)	4 None 3 Intermittent use of BiPAP 2 Continuous use of BiPAP during the night 1 Continuous use of BiPAP during the night and day 0 Invasive mechanical ventilation by intubation or tracheostomy

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 8/13/22.

GUIDELINE UPDATE INFORMATION:

09/15/17	New Medical Coverage Guideline.
01/15/18	Review and revision to guideline; position statement, references.
01/01/19	Revision: HCPCS code updates. Added J1301 and removed C9493.
01/15/19	Review and revision to guideline; updating references.
11/11/19	Revision to guideline consisting of adding a reference to the Site of Care Policy for Select Specialty Medications and updating the Program Exceptions.
01/15/20	Review and revision to guideline; updating references.
01/15/21	Review and revision to guideline; updating references.
01/15/21	Review and revision to guideline; updating references.
09/15/22	Revision to guideline; updated position statement, dosing, coding