Radicava® (Edaravone)

Policy Number: CS2023D0062K
Effective Date: April 1, 2023

Instructions for Use

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Application

This Medical Benefit Drug Policy does not apply to the states listed below; refer to the state-specific policy/guideline, if noted:

State	Policy/Guideline
Florida	Refer to the state's Medicaid clinical policy
Indiana	Radicava® (Edaravone) (for Indiana Only)
Kansas	Refer to the state's Medicaid clinical policy
Louisiana	Radicava® (Edaravone) (for Louisiana Only)
North Carolina	None
Ohio	Radicava® (Edaravone) (for Ohio Only)
Texas	Refer to drug specific criteria found within the Texas Medicaid Provider Procedures Manual

Coverage Rationale

Radicava (edaravone) is proven and medically necessary for the treatment of amyotrophic lateral sclerosis (ALS) in patients who meet all of the following criteria:[1]

- For initial therapy, all of the following:
  - Submission of medical records (e.g., chart notes, previous medical history, diagnostic testing including: imaging, nerve conduction studies, laboratory values) to support the diagnosis of "definite" or "probable" ALS per the El Escorial/revised Airlie House diagnostic criteria, and prescribed by, or in consultation with, a neurologist with expertise in the diagnosis of ALS; and
  - Submission of the most recent ALS Functional Rating Scale-Revised (ALSFRS-R) score confirming that the patient has scores ≥ 2 in all items of the ALSFRS-R criteria at the start of treatment;[13] and
  - Submission of medical records (e.g., chart notes, laboratory values) confirming that the patient has a % forced vital capacity (%FVC) ≥ 80% at the start of treatment;[13] and
  - Radicava dosing for ALS is in accordance with the United States Food and Drug Administration (FDA) approved labeling; and
  - Initial authorization will be for no more than 6 cycles (64 doses over 168 days)

- For continuation of therapy, all of the following:
  - Diagnosis of “definite” or “probable” ALS per the El Escorial/revised Airlie House diagnostic criteria, and prescribed by, or in consultation with, a neurologist with expertise in the diagnosis of ALS; and
  - Patient is currently receiving Radicava therapy; and
  - Patient is not dependent on invasive ventilation or tracheostomy; and
  - Radicava dosing for ALS is in accordance with the United States FDA approved labeling; and
  - Authorization will be for no more than 6 cycles (60 doses over 168 days)

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by federal, state, or contractual requirements and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS Code	Description
J1301	Injection, edaravone, 1 mg

Diagnosis Code	Description
G12.21	Amyotrophic lateral sclerosis

Background

Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, is a rapidly progressive, invariably fatal neurological disease that attacks neurons responsible for controlling voluntary muscles. The disease belongs to a group of disorders known as motor neuron diseases, which are characterized by the gradual degeneration and death of motor neurons. Eventually, all muscles under voluntary control are affected. Individuals lose their strength and the ability to move their arms, legs, and body. When muscles in the diaphragm and chest wall fail, individuals lose the ability to breathe without ventilatory support. Individuals with ALS usually survive for only 3 to 5 years from the onset of symptoms. However, about 10 percent of those with ALS survive for 10 or more years.[8]

The mechanism by which Radicava (edaravone) exerts its therapeutic effect in patients with ALS is unknown.[1] It has been characterized as a free radical scavenger, which is thought to block radicals that mediate both neuronal and vascular damage.[9-10]

Clinical Evidence

The efficacy and safety of edaravone for amyotrophic lateral sclerosis (ALS) was examined in a double-blind, parallel-group, placebo-controlled, phase III trial.[10] The 36-week confirmatory trial consisted of a 12-week pre-observation period followed by a 24-week treatment period. The eligible patient population included those who were diagnosed with ALS as defined as "definite ALS," "probable ALS" or "probable-laboratory-supported ALS," based on the revised El Escorial World Federation of Neurology criteria, also known as Airlie House criteria. With their baseline disease state, patients also must have been able to eat a meal, excrete, or move with oneself alone, and did not need assistance in everyday life. Patients must have begun the trial within 3 years after onset of ALS and have a FVC of at least 70%. Patients who complained of dyspnea and had deterioration of respiratory function, among other criteria were excluded from the study. Patients aged 20 to 75 were randomized to receive either placebo (saline, n = 104), or edaravone (n = 102) 60mg intravenously per day. 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. Primary efficacy 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). 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 results with primary outcome, the inter-group difference in the change of the ALSFRS-R at the end of treatment, was not statistically significant. Of all of the 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. The authors admit that this study failed to demonstrate efficacy of edaravone to delay the progression of ALS.[10]

For post-hoc analysis, two subpopulations were identified in which edaravone might be efficacious, the efficacy-expected subpopulation (EESP), and the definite/probable EESP 2 years (dpEESP2y) subpopulation. The EESP group was defined by scores of ≥ 2 points on all 12 items of the ALSFRS-R and a %FVC ≥ 80% at baseline. The dpEESP2y group, in addition to EESP criteria, had definite or probable ALS diagnosed by El Escorial revised criteria, and disease duration of ≤ 2 years. The primary endpoint for the efficacy analysis was the change in the ALSFRS-R score during a 24-week treatment period. Secondary endpoints included %FVC, Modified Norris Scale score, and ALS Assessment Questionnaire (ALSAQ-40) score. The full analysis set (FAS) included 205 patients (104 patients in the placebo group and 101 patients in the edaravone group). The EESP group included 104 patients (50 patients in the placebo group and 54 patients in the edaravone group). The dpEESP2y group included 72 patients (32 patients in the placebo group and 40 patients in the edaravone group). Results showed intergroup differences of the least-queries mean change in the ALSFRS-R score were 0.65 (p = 0.4108) in the FAS, 2.2 (p = 0.036) in EESP, and 3.01 (p = 0.027) in the dpEESP2y. The analysis showed a significant intergroup difference in both the EESP and dpEESP2y, with larger differences for dpEESP2y than for the EESP group. Similar differences were also seen for secondary endpoints.[11]

The first phase III study (MCI186-16) was followed by a 36 week extension study (MCI186-17) to investigate the long-term efficacy and safety of edaravone in the FAS group compared to the EESP group. The extension study consisted of a 24-week double-blind comparison followed by 12 weeks of open-label edaravone. Efficacy endpoints were the same as MCI186-16. The intergroup difference between the treatment or placebo group for either the FAS or EESP groups were not statistically significant, however the difference was larger in the EESP (1.85, p = 0.1127) than in the FAS (1.16, p = 0.2176), similar to findings from MCI186-16.[12] Post-hoc analysis was performed for the dpEESP2y subgroup for the first 24 week placebo-controlled portion of MCI186-17. The difference in ALSFRS-R changes from 24 to 48 weeks between the edaravone and placebo groups was 2.79 (p = 0.0719), which was greater than the differences previously reported for the EESP and the FAS. The authors concluded that the post-hoc analysis suggests a potential effect of edaravone between 24 and 48 weeks in those meeting dpEESP2y criteria at baseline.[13]

The Canadian ALS Research Network (CALS) issued a guideline in 2020 providing best practice recommendations for the management of people living with ALS in Canada.[16] CALS provided the following recommendations:

- In a select group of patients, intravenous edaravone has been shown to slow decline on the ALSFRS-R scores compared against intravenous placebo, over a 6-month period (level B). (These patients have shown benefit from edavarone: disease duration < 2 y, FVC > 80%, all ALSFRS-R subcomponents scores > 2, and demonstrated steady decline in the ALSFRS-R over a 3-mo interval.)
- Evidence for benefit of intravenous edaravone at other stages of ALS has not been demonstrated (Expert Consensus).
- As with any other therapies, individualized goals, risks and benefits should be carefully considered and discussed before intravenous edaravone is initiated (Expert Consensus).

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Radicava is indicated for the treatment of amyotrophic lateral sclerosis (ALS).[1]

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Policy History/Revision Information

Date	Summary of Changes
04/01/2023	**Application** *Texas* • Replaced instruction to "refer to the state's Medicaid clinical policy" with "refer to the drug-specific criteria found within the *Texas Medicaid Provider Procedures Manual*" **Supporting Information** • Updated *Clinical Evidence* and *References* sections to reflect the most current information • Archived previous policy version CS2022D0062J

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. The UnitedHealthcare Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.