RADICAVA™ (EDARAVONE)

Policy Number: 2019D0062D **Effective Date**: March 1, 2019

Instructions for Use

Table of Contents **Page**

Related Policies

- Provider Administered Drugs – Site of Care Review Guidelines

COVERAGE RATIONALE

See Benefit Considerations

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

I. For **initial therapy**, **all** of the following:
   A. Submission of medical records (e.g., chart notes, previous medical history, diagnostic testing including: imaging, nerve conduction studies, laboratory values) to support[14] 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**
   B. 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**
   C. 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**
   D. Radicava dosing for ALS is in accordance with the United States Food and Drug Administration approved labeling; **and**
   E. Initial authorization will be for no more than 6 cycles (64 doses over 168 days).

II. For **continuation therapy**, **all** of the following:
   A. 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**
   B. Patient is currently receiving Radicava therapy; **and**
   C. Patient is **not** dependent on invasive ventilation or tracheostomy; **and**
   D. Radicava dosing for ALS is in accordance with the United States Food and Drug Administration approved labeling; **and**
   E. Authorization will be for no more than 6 cycles (60 doses over 168 days).

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

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

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]

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 the member specific benefit plan document 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 Coverage Determination Guidelines may apply.

HCPCS Code	Description
J1301	Injection, edaravone, 1 mg

ICD-10 Diagnosis Code	Description
G12.21	Amyotrophic lateral sclerosis

BENEFIT CONSIDERATIONS

Some Certificates of Coverage allow for coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The member specific benefit plan document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances when certain conditions are met. Where such mandates apply, they supersede language in the benefit document or in the medical or drug policy. Benefit coverage for an otherwise unproven service for the treatment of serious rare diseases may occur when certain conditions are met. See the Policy and Procedure addressing the treatment of serious rare diseases.

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," met diagnostic criteria revised EL Escorial for Airlie House. With their baseline disease state, patients also must be able to eat a meal, excrete, or move with oneself alone, and do not need assistance in everyday life. Patients must begin the trial within 3 years after onset of ALS and have a FVC of at least 70%. Patients who complain of dyspnea and have deterioration of respiratory function, among other criteria were excluded from the study. Patients age 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.

There are additional completed studies that have unpublished results on edaravone's efficacy and safety as a treatment for ALS. These studies include, after a 12 week observation period, patients who meet the diagnostic criteria of the revised EL Escorial for Airlie House, have had onset of ALS symptoms less than 2 years, and can still function to the requirements stated in the inclusion criteria. Patients with certain organ and neurological dysfunction, have dyspnea or deteriorating respiratory function were excluded from these studies. The primary outcome measure of each of these trials is the score of the ALSFRS-R. Additional secondary outcome measures include, but not limited to: Period until death or a certain state (i.e., inability to walk alone, failure of arm function, tracheostomy, respirator

installation, tubal feeding replenishment), %FVC, and others. The studies also examine adverse events, drug reactions, laboratory tests and sensory examinations.[11-13]

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Medicare does not have a National Coverage Determination (NCD) for Radicava® (edaravone). Local Coverage Determinations (LCDs) do not exist at this time.

Medicare covers outpatient (Part B) drugs that are furnished "incident to" a physician's service provided that the drugs are not usually self-administered by the patients who take them. See the Medicare Benefit Policy Manual, Chapter 15, §50 - Drugs and Biologicals. (Accessed February 23, 2018)

REFERENCES

1. Radicava [Prescribing Information]. Jersey City, NJ: MT Pharma America, Inc.; May 2017.
2. 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;1:293–299.
3. de Carvalho M, Dengler R, Eisen A, et al. Electrodiagnostic criteria for diagnosis of ALS. Clin Neurophysiol 2008; 119:497–503.
4. Geevasinga N, Menon P, Scherman DB, Simon N, Yiannikas C, Henderson RD, Kiernan MC, and Vucic S. Diagnostic critera in amyotrophic lateral sclerosis: A multicenter prospective study. Neurology. 2016 Aug 16; 87(7): 684-90.
5. Cedarbaum JM, Stambler N, Malta E, Fuller C, Hilt D, Thurmond B, et al. The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. J Neurol Sci. 1999; 169(1): 13–21.
6. Castrillo-Viguera C, Grasso DL, Simpson E, Shefner J, Cudkowicz ME. Clinical significance in the change of decline in ALSFRS-R. Amyotroph Lateral Scler. 2010;11(1-2):178-80.
7. Cedarbaum JM, Mitsumoto H, Ringel S, Florence J, Sanjak M, and Brooks BR. The ALSFRS @ 20: Evolution Of The ALSFRS-R, History, Clinimetric Properties And Future Directions. [poster] [online]. Accessed 18 October 2016.
8. National Institute of Neurological Disorders and Stroke. Amyotrophic Lateral Sclerosis (ALS) Fact Sheet. Retrieved from: https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Amyotrophic-Lateral-Sclerosis-ALS-Fact-Sheet. Accessed on: February 23, 2018.
9. Nagase M, Yamamoto Y, Miyazaki Y, Yoshino H. Increased oxidative stress in patients with amyotrophic lateral sclerosis and the effect of edaravone administration. Redox Rep. 2016 May;21(3):104-12.
10. Abe K, Itoyama Y, Sobue G, Tsuji S, Aoki M, Doyu M, et al. 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; 15(7–8):610–7.
11. Mitsubishi Tanabe Pharma Corporation. Expanded Controlled Study of Safety and Efficacy of MCI-186 in Patients With Amyotrophic Lateral Sclerosis (ALS). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2017 Mar 6]. Available from: https://clinicaltrials.gov/ct2/show/NCT00424463. NLM Identifier: NCT00424463.
12. Mitsubishi Tanabe Pharma Corporation. Efficacy and Safety Study of MCI-186 for Treatment of Amyotrophic Lateral Sclerosis (ALS) Who Met Severity Classification III. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2017 Mar 6]. Available from: https://clinicaltrials.gov/ct2/show/NCT00415519. NLM Identifier: NCT00415519.
13. Mitsubishi Tanabe Pharma Corporation. Phase 3 Study of MCI-186 for Treatment of Amyotrophic Lateral Sclerosis. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2017 Mar 6]. Available from: https://clinicaltrials.gov/ct2/show/NCT01492686. NLM Identifier: NCT01492686.
14. Subcommittee on Motor Neuron Diseases of World Federation of Neurology Research Group on Neuromuscular Diseases, El Escorial "Clinical Limits of ALS" Workshop Contributors. El Escorial World Federation of Neurology criteria for the diagnosis of amyotrophic lateral sclerosis. J Neurol Sci 1994; 124: 96–107.
15. Pharmaceuticals and Medical Devices Agency (2015). First Committee on New Drugs: Report on the Deliberation Results. Radicut. Available from: http://www.pmda.go.jp/files/000212453.pdf.

POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
04/01/2019	Added reference link to the policy titled *Provider Administered Drugs – Site of Care Review Guideline*.
03/01/2019	Reorganized policy template; simplified and relocated *Instructions for Use* and *Benefit Considerations* section. Archived previous policy version 2019D0062C.
01/01/2019	Updated list of applicable HCPCS codes to reflect annual code edits; replaced J3490 with J1301. Policy 2018D0062B archived.
05/01/2018	Annual review. Updated coverage rationale with no changes to clinical intent. Updated CMS statement and references. Approved by National Pharmacy & Therapeutics Committee on 04/18/2018. Policy 2017D0062A archived.
09/01/2017	New policy 2017D0062A. Approved by National Pharmacy & Therapeutics Committee on 05/19/2017.

INSTRUCTIONS FOR USE

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard benefit plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. 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.

This Medical Benefit Drug Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence (Medicare IOM Pub. No. 100-16, Ch. 4, §90.5).

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. 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.