

RADICAVA™ (EDARAVONE)

Policy Number: PHARMACY 297.4 T2

Effective Date: January 1, 2019

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Related Policy

- [Acquired Rare Disease Drug Therapy Exception Process](#)
- [Specialty Medication Administration - Site of Care Review Guidelines](#)

INSTRUCTIONS FOR USE

This Clinical Policy provides assistance in interpreting Oxford benefit plans. Unless otherwise stated, Oxford policies do not apply to Medicare Advantage members. Oxford reserves the right, in its sole discretion, to modify its policies as necessary. This Clinical Policy is provided for informational purposes. It does not constitute medical advice. The term Oxford includes Oxford Health Plans, LLC and all of its subsidiaries as appropriate for these policies.

When deciding coverage, the member specific benefit plan document must be referenced. The terms of the member specific benefit plan document [e.g., Certificate of Coverage (COC), Schedule of Benefits (SOB), and/or Summary Plan Description (SPD)] may differ greatly from the standard benefit plan upon which this Clinical Policy is based. In the event of a conflict, the member specific benefit plan document supersedes this Clinical Policy. All reviewers must first identify member eligibility, any federal or state regulatory requirements, and the member specific benefit plan coverage prior to use of this Clinical Policy. Other Policies may apply.

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

CONDITIONS OF COVERAGE

Applicable Lines of Business/Products	This policy applies to Oxford Commercial plan membership.
Benefit Type	Medical
Referral Required (Does not apply to non-gatekeeper products)	No
Authorization Required (Precertification always required for inpatient admission)	Yes ^{1,2,3}
Precertification with Medical Director Review Required	Yes ^{1,2,3}
Applicable Site(s) of Service (If site of service is not listed, Medical Director review is required)	All
Special Considerations	<p>¹Precertification with review by a Medical Director or their designee is required.</p> <p>²Participating Providers in the Office Setting: Precertification is required for services performed in the office of a participating provider. Non-Participating/Out-of-Network Providers in the Office Setting: Precertification is not required, but is encouraged for</p>

Special Considerations (continued)

out-of-network services performed in the office. If precertification is not obtained, Oxford will review for out-of-network benefits and medical necessity after the service is rendered.

³Requests for hospital outpatient facility infusion of Radicava require additional precertification with review by a Medical Director or their designee; refer to the policy titled [Specialty Medication Administration - Site of Care Review Guidelines](#).

BENEFIT CONSIDERATIONS

Before using this policy, please check the member specific benefit plan document and any federal or state mandates, if applicable.

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. Refer to: [Acquired Rare Disease Drug Therapy Exception Process](#).

Essential Health Benefits for Individual and Small Group

For plan years beginning on or after January 1, 2014, the Affordable Care Act of 2010 (ACA) requires fully insured non-grandfathered individual and small group plans (inside and outside of Exchanges) to provide coverage for ten categories of Essential Health Benefits ("EHBs"). Large group plans (both self-funded and fully insured), and small group ASO plans, are not subject to the requirement to offer coverage for EHBs. However, if such plans choose to provide coverage for benefits which are deemed EHBs, the ACA requires all dollar limits on those benefits to be removed on all Grandfathered and Non-Grandfathered plans. The determination of which benefits constitute EHBs is made on a state by state basis. As such, when using this policy, it is important to refer to the member specific benefit plan document to determine benefit coverage.

COVERAGE RATIONALE

Radicava (edaravone) is proven and medically necessary for¹ the treatment of amyotrophic lateral sclerosis (ALS) in patients who meet all of the following criteria:

- 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 following:¹⁴ 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 treatment¹³; **and**
 - Submission of medical records (e.g., chart notes, laboratory values) confirming that the patient has a % forced vital capacity (%FVC) $\geq 80\%$ at the start of treatment¹³; **and**
 - Radicava dosing for ALS is in accordance with the United States Food and Drug Administration approved labeling; **and**
 - Initial authorization will be for no more than 6 cycles (64 doses over 168 days).
- For **continuation 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 Food and Drug Administration approved labeling; **and**
 - 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 may apply.

HCPCS Code	Description
J1301	Injection, edaravone, 1 mg

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

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

REFERENCES

The foregoing Oxford policy has been adapted from an existing UnitedHealthcare Pharmacy, Clinical Pharmacy Program that was researched, developed and approved by the UnitedHealth Group National Pharmacy & Therapeutics Committee. [2018D0062B]

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 criteria 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 October 18, 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#267654842>. Accessed 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
01/01/2019	<ul style="list-style-type: none"> Updated list of applicable HCPCS codes: <ul style="list-style-type: none"> Added J1301 (<i>annual code edit</i>) Removed J3490 Archived previous policy version PHARMACY 297.3 T2