edaravone (Radicava™)

Policy # 00596
Original Effective Date: 12/20/2017
Current Effective Date: 01/11/2021

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider edaravone (Radicava™)‡ for the treatment of amyotrophic lateral sclerosis (ALS) to be **eligible for coverage.****

Patient Selection Criteria

Based on review of available data, the Company may consider edaravone (Radicava) when ALL of the following criteria are met:

- Initial authorization (6 months)
    - Patient has a definite or probable diagnosis of Amyotrophic Lateral Sclerosis (ALS) as defined by the revised El Escorial (Airlie House) criteria; AND
    - Requested dose is ≤60 mg per infusion for ≤14 infusions for the initial month, and ≤10 infusions per month for each subsequent month of treatment; AND
    - Patient has a baseline score of ≥2 points on each item of the ALS Functional Rating Scale-Revised (ALSFRS-R); AND
      *(Note: This criterion is an additional Company requirement, based on clinical trials, for coverage eligibility and will be denied as not medically necessary** if not met.)*
    - Patient has retained normal respiratory function as evidenced by a Forced Vital Capacity (FVC) ≥80% OR decline in respiratory function is better explained by a pulmonary disease process (e.g. COPD, asthma, idiopathic pulmonary fibrosis). In patients with reduced baseline FVC, records may be requested documenting diagnosis of the pulmonary disease process leading to reduced FVC; AND
      *(Note: This criterion is an additional Company requirement, based on clinical trials, for coverage eligibility and will be denied as not medically necessary** if not met.)*

  - Patient has a disease duration of 2 years or less; AND
    *(Note: This criterion is an additional Company requirement, based on clinical trials, for coverage eligibility and will be denied as not medically necessary** if not met.)*
  - Patient is on concurrent therapy with generic riluzole unless contraindicated or previously not tolerated
    *(Note: This criterion is an additional Company requirement, based on clinical trials, for coverage eligibility and will be denied as not medically necessary** if not met.)*
- Re-authorization (6 months)
  - Patient continues to have a score of ≥2 on each item of the ALSFRS-R; AND
    *(Note: This criterion is an additional Company requirement, based on clinical trials, for coverage eligibility and will be denied as not medically necessary** if not met.)*
  - The requested dose is ≤60mg per infusion for ≤10 infusions per month; AND
  - ALSFRS-R score has not decreased more than 6 points from previous baseline 6 months ago
    *(Note: This criterion is an additional Company requirement, based on clinical trials, for coverage eligibility and will be denied as not medically necessary** if not met.)*

When Services Are Considered Not Medically Necessary

The use of edaravone (Radicava) when patient selection criteria (except diagnosis of ALS and dosing of Radicava) are not met is considered to be **not medically necessary.****

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers edaravone (Radicava) for the treatment of any indication other than definite or probable ALS or at a dose other than the dose recommended above to be **investigational.***

Background/Overview

Radicava is indicated for the treatment of ALS. Its mechanism of action is unknown, but is proposed to be related to its antioxidant properties. Oxidative stress has been implicated as an underlying

mechanism in several pathogenic pathways linked to ALS and this drug may provide protection against this oxidative damage. Radicava is an intravenous infusion dosed as a 60 mg infusion over 60 minutes. For the first treatment month, it should be dosed daily for 14 days followed by a 14 day drug-free period. Subsequent treatment cycles involve daily dosing for 10 days out of 14 day periods followed by 14 day drug-free periods. The majority (90%) of patients in pivotal studies of Radicava were on concomitant therapy with riluzole.

ALS is a rapidly progressing, degenerative disease in which the patient's upper and lower motor neurons degenerate leading to loss of motor function. Patients with ALS present with painless, progressive muscle atrophy and weakness, which eventually leads to paralysis. Death due to respiratory failure typically occurs within 3-5 years of diagnosis. Approximately 14,000-15,000 people in the U.S. have ALS. The disease occurs most commonly in people aged 55-75 years. The El Escorial criteria, which were used in the clinical studies of Radicava, were developed to standardize the diagnosis of ALS (see table). Disease progression is monitored using the ALSFRS-R, a 13-question scale that assesses the patient's ability to perform normal daily activities such as speech, handwriting, cutting food, and climbing stairs. Each question is scored on a scale of 0-4 with higher scores representing greater functional ability (see appendix for full scale). The ALSFRS-R score is complemented by a measurement of the FVC which is also used to predict survival and measure disease progression.

Diagnosis	El Escorial Revised Airlie House Criteria
Definite ALS	Upper motor neuron (clinical exam) and lower motor neuron (clinical, electrophysiological or neuropathological exam) signs: • Bulbar region and > 2 spinal regions OR • Three spinal regions
Probable ALS	Upper and lower motor neuron signs in > 2 regions and upper signs rostral to lower signs
Probable ALS – laboratory-supported	• Upper and lower motor neuron signs in one region OR • Upper signs alone in one region and lower signs via electrophysiological criteria of lower motor neuron loss > 2 regions
Possible ALS	• Upper and lower signs in one region OR

	• Upper motor neuron signs alone in > 2 regions OR • Lower motor neuron signs rostral to upper motor neuron signs and unable to prove clinically probably ALS

Source: Data on file. Radicava Product Dossier: Based on AMCP guidelines for formulary submission, version 2.1. MT Pharma America, Inc.; received June 14, 2017

Current treatment guidelines from the American Academy of Neurology do not yet address Radicava. The only other drug approved to treat ALS is riluzole which these guidelines recommend for all patients with ALS unless the risk of fatigue outweighs the modest survival benefits with this drug. The guidelines also address lithium carbonate as a potential treatment option, but state that the data are insufficient to support or discourage its use for ALS. Recommendations for symptomatic management include botulinum toxin type B for patients with refractory sialorrhea and Nuedexta®‡ for pseudobulbar affect.

The European Federation of Neurological Societies also did not address Radicava in their most current guidelines (2012), but recommend riluzole to all patients as early as possible after diagnosis with the caveat that riluzole should not be used for patients with progressive muscular atrophy, primary lateral sclerosis, or hereditary spastic paraplegia.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
Radicava is FDA approved for the treatment of ALS.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, Blue Cross and Blue Shield Association technology assessment program (TEC) and other non-affiliated technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Radicava was approved based on a phase III, randomized, double-blind, placebo-controlled study conducted in Japan. In this study, 137 patients were randomized to receive Radicava or placebo for

24 weeks. This was the second phase 3 study, and was conducted because the first study failed to demonstrate efficacy, but showed a greater magnitude of effect in a subpopulation identified by a post hoc analysis. To be included in this study, patients had to meet extensive inclusion criteria based on the post hoc analysis of the previous study. These criteria included:

- Aged 20-75 years
- ALS of grade 1 or 2 in the Japan ALS Severity Classification (independent living status)
- Definite or probable diagnosis of ALS based on the El Escorial criteria
- Score of ≥2 on each item of the ALS Functional Rating Scale (ALSFRS-R)
- FVC ≥80%
- Disease duration of ≤2 years
- Decrease of 1-4 points in the ALSFRS-R score during a 12-week observation period prior to study randomization
- No history of spinal surgery after onset of ALS
- CrCl >50 mL/min

The primary endpoint was the change from baseline to week 24 in the ALSFRS-R score. Secondary endpoints included the change in FVC, Modified Norris Scale scores, ALS Assessment Questionnaire score (a measure of quality of life), ALS severity classification, and grip and pinch strength. There was found to be significantly less decline in the ALSFRS-R scores in the Radicava group compared with placebo with a change of -5.01 (SE 0.64) vs -7.5 (SE 0.66). The results of the Modified Norris Scale favored Radicava with a least squares mean difference of 4.89, and the ALS Assessment Questionnaire scores demonstrated a significantly lower deterioration in quality of life in the Radicava group. No difference was found in FVC, grip and pinch strength, or ALS severity classification between the Radicava and placebo groups.

Supplemental Information

ALSFRS-R Scale

Score	Description
	1. Speech
4	Normal speech processes
3	Detectable speech disturbance
2	Intelligible with repeating
1	Speech combined with non-vocal communication
	2. Salivation
4	Normal

3	Slight, but definite excess of saliva in mouth; may have nighttime drooling
2	Moderately excessive saliva; may have minimal drooling (during the day)
1	Marked excess of saliva with some drooling
0	Marked drooling; requires constant tissue or handkerchief
3. Swallowing	
4	Normal eating habits
3	Early eating problems—occasional choking
2	Dietary consistency changes
1	Needs supplement tube feeding
0	NPO (exclusively parenteral or enteral feeding)
4. 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
5a. Cutting Food and Handling Utensils (skip if patient has gastrostomy)	
4	Normal
3	Somewhat slow and clumsy, but no help needed
2	Can cut most foods (>50%), although slow and clumsy; some help needed
1	Food must be cut by someone, but can still feed slowly
0	Needs to be fed
5b. Cutting Food and Handling Utensils (WITH gastrostomy only)	
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
6. 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
7. Turning in bed and adjusting bed clothes	
4	Normal function
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
8. Walking	
4	Normal
3	Early ambulation difficulties
2	Walks with assistance
1	Non-ambulatory functional movement
0	No purposeful leg movement
9. Climbing stairs	
4	Normal

3	Slow
2	Mild unsteadiness or fatigue
1	Needs assistance
0	Cannot do
10. Dyspnea	
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
11. Orthopnea	
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 without mechanical assistance
12. Respiratory Insufficiency	
4	None
3	Intermittent use of BiPAP
2	Continuous use of BiPAP during the night
1	Continuous use of BiPAP during day and night
0	Invasive mechanical ventilation by intubation or tracheostomy

References

1. Edaravone (Radicava) [Package Insert]. MT Pharma America. Jersey City, NJ.
2. Miller RG, Jackson CE, Kasarskis EJ, et al. Practice parameter update: the care of the patient with amyotrophic lateral sclerosis: drug, nutritional, and respiratory therapies (an evidence-based review). Neurology. 2009;73:1218-1226.
3. Andersen PM, Abrahams S, Borasio GD, et al. EFNS guidelines on the clinical management of amyotrophic lateral sclerosis (MALS) – revised report of an EFNS task force. Eur J Neurol. 2012;19(3):360-375.
4. Abe K, Aoki M, Tsuji S, et al. on behalf of the edaravone (MCI-186) ALS 19 study group. Safety and efficacy of edaravone in well-defined patients with amyotrophic lateral sclerosis: a randomized, double-blind, placebo-controlled trial. Lancet Neurol. 2017;16:505-512
5. Hardiman O, Van den Berg LH. Edaravone: a new treatment for ALS on the horizon? Lancet Neurol. 2017;16:505-512.
6. Proudfoot M, Jones A, Talbot K, Al-Chalabi A, Turner MR. The ALSFRS as an outcome measure in therapeutic trials and its relationship to symptom onset. 2016 Aug 17;17(5-6):414-425.

7. Nakamara, Y, Kakubari, M, Yoshida, K, Akitmoto, M, Kondo, K An Open-Label, Single-Dose Study to Evaluate the Pharmacokinetic Variables of Edaravone in Subjects with Mild, Moderate, or No Renal Impairment accepted for publication June 27, 2020 Clinical Therapeutics

Policy History

Original Effective Date: 12/20/2017
Current Effective Date: 01/11/2021

12/07/2017	Medical Policy Committee review
12/20/2017	Medical Policy Implementation Committee approval. New Policy
12/06/2018	Medical Policy Committee review
12/19/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged
01/01/2019	Coding update
12/05/2019	Medical Policy Committee review
12/11/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged
12/03/2020	Medical Policy Committee review
12/09/2020	Medical Policy Implementation Committee approval. Removed criterion requiring GFR >50 mL/min based on newly available data.

Next Scheduled Review Date: 12/2021

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2019 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice

medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No codes
HCPCS	J1301
ICD-10 Diagnosis	G12.21

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or

3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.