Drug and Biologic Coverage Policy

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Edaravone

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Related Coverage Resources

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Coverage Policy

Edaravone (Radicava™) is considered medically necessary when ALL of the following criteria are met:

- Documented diagnosis of definite or probable amyotrophic lateral sclerosis (ALS) based on El Escorial – Revised (Airlie House) criteria
- Prescribed by, or in consultation with, a neurologist
- Functionality retained most activities of daily living (defined as scores of 2 points or better on each individual item of the ALS Functional Rating Scale – Revised [ALSFRS-R] [i.e., a minimum score of 24])
- Normal respiratory function (defined as percent-predicted forced vital capacity values of [%FVC] of at least 80%)
- Disease duration of 2 years or less

Initial authorization is up to 6 months.

Edaravone (Radicava) is considered medically necessary for continued use when the following are met:

- Documented diagnosis of definite or probable amyotrophic lateral sclerosis (ALS) based on El Escorial – Revised (Airlie House) criteria
- Attestation of beneficial clinical response
- Prescribed by, or in consultation with, a neurologist

- Individual is not dependent on continuous invasive ventilation or tracheostomy.

Reauthorization for up to 12 months.

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Edaravone (Radicava) is considered experimental, investigational or unproven for ANY other use including the following:
- Acute intracerebral hemorrhage
- Acute ischemic stroke

Note: Receipt of sample product does not satisfy any criteria requirements for coverage.

FDA Approved Indications

FDA Approved Indication
Radicava is indicated for the treatment of amyotrophic lateral sclerosis (ALS).

Recommended Dosing

FDA Recommended Dosing
The recommended dosage of Radicava is an intravenous infusion of 60 mg administered over a 60-minute period according to the following schedule:
- An initial treatment cycle with daily dosing for 14 days, followed by a 14-day drug-free period
- Subsequent treatment cycles with daily dosing for 10 days out of 14-day periods, followed by 14-day drug-free periods.

Drug Availability
Radicava is supplied for intravenous infusion in a single-dose polypropylene bag containing 60 mg of edaravone in 100 mL of clear, colorless aqueous solution.

General Background

Disease Overview
Amyotrophic lateral sclerosis is a progressive, neuromuscular disease characterized by degeneration and death of upper motor neurons (UMN) and lower motor neurons (LMN). Clinical presentation is widely variable depending on the spinal cord segment, limb, or cranial nerve affected. Signs and symptoms related to LMN loss include weakness, atrophy, and fasciculations, while UMN loss can result in dysarthria, dysphagia, hyperreflexia, emotional lability, and spasticity (i.e., bulbar symptoms). Asymmetric limb weakness is the most common presenting symptom of ALS. Patients suffer from both UMN and LMN symptoms as the disease progresses, but sensory neurons are not affected. (Valadi, 2015) Some degree of cognitive impairment occurs in up to 40% of patients with ALS including frontotemporal dementia (FTD) in about 14%. Ultimately, widespread paralysis occurs, and respiratory muscles are affected, leading to death. (Salameh, 2015; Valadi, 2015) The median survival from time of symptom onset is about 3 years, but can range from less than 1 year to over 10 years. (Salameh, 2015; Valadi, 2015)

A diagnosis of ALS requires evidence of UMN loss based on clinical examination; evidence of LMN loss based on clinical, neuropathological (i.e., muscle biopsy), or electrophysiological (i.e., electromyography or nerve conduction study) examination; and progression of disease based on spread of signs and symptoms throughout the body over time. (Valadi, 2105) Neuroimaging and cerebral spinal fluid (CSF) evaluation are performed mainly to rule out other disorders. (Salameh, 2015; Valadi, 2015) The El Escorial – Revised criteria, also known as the Airlie House criteria, are commonly used to categorize patients based on the certainty of the diagnosis of ALS.

(Belsh, 2000) The 4 categories, from most to least certain, include clinically definite, clinically probable, clinically probable with laboratory support, and clinically possible ALS. (Belsh, 2000)

Pharmacology

The mechanism of action of edaravone in the treatment of ALS is not known. It is thought to be neuroprotective and may also protect endothelial and myocardial cells from oxidative damage. (Ikeda, 2015; Takahashi, 2009) Patients with ALS have increased markers of oxidative stress (e.g., protein carbonyl, 3-nitrotyrosine, 8-hydroxyguanine), and oxidative stress due to production of free radicals likely contributes to the disease process. (Nagase, 2016; Petrov, 2017) Edaravone is a free radical scavenger and has antioxidant effects. (Ikeda, 2015; Nagase, 2016) It donates an electron to lipid peroxide and hydroxyl radicals thereby preventing free radical formation and neuronal damage. (Takahashi, 2015)

Professional Societies/Organizations

European Federation of Neurological Societies (EFNS) published the most recent guidelines for management of ALS in 2012. The guidelines focus on the importance of offering treatment with riluzole to prolong survival, and providing multidisciplinary care, symptomatic treatment, respiratory support, enteral nutrition, and communication support systems to improve quality of life. Riluzole is recommended for all patients as soon as possible after the diagnosis of ALS is confirmed. Survival is prolonged by approximately 3 months in patients taking riluzole. No other therapies are recommended to prolong survival or slow disease progression in ALS. (Andersen, 2012) Edaravone was not yet approved for ALS when the guidelines were developed, and its place in therapy is not discussed.

The American Board of Internal Medicine's (ABIM) Foundation Choosing Wisely® Initiative

No recommendations are available for edaravone (Radicava).

Centers for Medicare & Medicaid Services - National Coverage Determinations (NCDs)

There are no CMS National Coverage Determinations for edaravone (Radicava).

Clinical Efficacy

The efficacy of edaravone for the treatment of ALS was evaluated based on outcomes related to functional decline, quality of life, and markers of oxidative stress. There are no data to support prolonged survival with edaravone. No published studies evaluated use of edaravone for longer than 6 months, and the product labeling does address how long to continue therapy. Table 1 summarizes the Revised ALS Functional Rating Scale (ALSFRS-R) and other efficacy endpoints used to measure functional decline in the studies. Two randomized, double-blind studies compared edaravone with placebo (Abe, 2014; ALS 19 Study Group, 2017) and 1 open-label, prospective study compared the rate of functional decline before and after initiating edaravone therapy. (Yoshino, 2006) Patients were permitted to continue riluzole therapy in all 3 trials evaluating edaravone, and no studies have directly compared the efficacy of edaravone monotherapy with riluzole monotherapy.

Table 1. Efficacy Outcomes used in Clinical Trials Evaluating Edaravone for ALS[a]

Outcome	Description
Revised ALS Functional Rating Scale (ALSFRS-R)	• Validated questionnaire to assess functional ability • Includes 12 items to assess function in 4 domains: fine motor activity, gross motor activity, nutrition, and respiratory function • Each item is scored from 0 to 4 points and the total score ranges from 0 to 48 points • Higher scores indicate better function • A difference of decline in ALSFRS-R score of ≥ 20% is typically considered clinically significant • Scores typically decline linearly over time
ALS Assessment Questionnaire (ALSAQ-40)	• Questionnaire completed by patients to assess subjective well-being • Includes 5 domains: ADLs/independence (10 items), communication (7 items), eating and drinking (3 items), emotional reactions (10 items), and physical mobility (10 items)

	• Patients rate their difficulty with each item from 1 (never difficult) to 5 (cannot do it at all) • Total scores range from 40 to 200 points • Lower scores indicate better well-being
Modified Norris Scale	• Used to evaluate bulbar (e.g., speech, swallowing) and limb function • Total scores range from 0 to 102 points • Bulbar scale scores range from 0 to 39 points • Limb scale scores range from 0 to 63 points • Higher scores indicate better function
Japanese ALS Severity Score	Scores range from 1 to 5 1 = able to work or complete housework 2 = able to live independently but not able to work 3 = assistance required for ambulation, eating, or toileting 4 = respiratory insufficiency (i.e., dysphagia or difficulty coughing out sputum) 5 = feeding tube or tracheostomy required

a Data derived from Abe, 2014; ALS 19 Study Group, 2017; Castrillo-Viguera, 2011; MT Pharma America, Inc., 2017; Oxford University Innovation website, 2016; Yoshino, 2006
Abbreviations: ADLs = activities of daily living; ALS = amyotrophic lateral sclerosis

Patients (N = 137) in the ALS 19 Study Group with early-stage ALS were randomized to edaravone or placebo. Strict inclusion criteria (i.e., ALS symptom onset ≤ 2 years, FVC ≥ 80%, score of ≥ 2 points on each of the 12 ALSFRS-R items, definite or probable ALS based on diagnostic criteria) were selected based on results of an analysis that identified disease characteristics associated with a better response to edaravone in a previous study. Baseline characteristics were similar in both treatment groups. The primary outcome was change in functional decline according to the ALSFRS-R score after 6, four-week cycles of treatment. Patients who received at least 1 dose of study medication, at least 1 post-baseline ALSFRS-R assessment, and completed treatment cycle 3 were included in the primary efficacy analysis. The last observation carried forward (LOCF) method was used to account for missing data in patients who discontinued between cycle 3 and cycle 6. Patients who discontinued before the end of cycle 3 (n = 3) were not included in the primary efficacy analysis. The ALSFRS-R score declined significantly less with edaravone (least-squares mean [LSM] -5.01 points) than with placebo (LSM 7.5 points, P = 0.0013). Edaravone remained superior to placebo in sensitivity and post-hoc analyses using different methods to account for missing data. Total Modified Norris Scale scores and ALSAQ-40 scores were better in patients taking edaravone than in those taking placebo (P ≤ 0.0393). There were no statistically significant between-group differences in other secondary outcomes (i.e., FVC, grip strength, pinch strength, or limb and bulbar scale subscores of the Modified Norris Scale). No patients in either group died during the study. Two patients taking edaravone reached a prespecified milestone of disease progression (1 patient lost meaningful speech, 1 patient required tracheostomy) compared with 6 patients taking placebo (1 patient required a feeding tube, 2 patients lost independent ambulation, 3 patients lost meaningful speech), but the between-group difference was not statistically significant. (ALS 19 Study Group, 2017)

Abe et al compared edaravone 60 mg with placebo in 206 patients with definite, probable, or probable – laboratory-supported ALS. Inclusion criteria was less strict than in the ALS-19 Study Group and included patients with a longer disease duration (up to 3 years) and lower FVC (≥ 70%). The primary outcome was change in functional decline according to the ALSFRS-R score after 6, four-week cycles of treatment. Patients who received at least 1 dose of study medication, at least 1 post-baseline ALSFRS-R assessment, and completed treatment cycle 3 were included in the primary efficacy analysis. The LOCF method was used to account for missing data in patients who discontinued between cycle 3 and cycle 6, but the authors did not report how many patients discontinued during this time frame. Overall dropouts were similar in both treatment groups. There were no statistically significant differences in the decline in ALSFRS-R, FVC, ALSAQ-40 or modified Norris scale scores. The between-group difference in ALSFRS-R was greatest in the subgroup of patients with definite ALS (2 points) compared with probable ALS (0.9 points) and probable laboratory supported ALS (0.4 points), although there were no statistically significant between group differences in any subgroup. The sample size was calculated based on an anticipated between-group difference in ALSFRS-R of 2 points, but the actual difference was 0.65 points, so the study may not have had adequate power to detect a statistically significant difference. About 25% of patients in each group had an ALSFRS-R change of 0 or -1 points during the treatment period, indicating patients had more slowly progressive disease than anticipated. This may also have contributed to the

difference between the edaravone and placebo groups. More patients in edaravone group (n = 32) died or reached a milestone of disease progression compared with placebo (n = 27), but the difference was not statistically significant. The authors concluded that edaravone may be more beneficial in patients with less severe ALS symptoms at baseline, and in those with a higher certainty of diagnosis (i.e., definite or probable, but not probable – laboratory-supported ALS). (Abe, 2014)

Yoshino et al conducted a nonrandomized study evaluating edaravone in 19 patients with ALS. The first 5 patients to enroll in the study received edaravone 30 mg, and the remaining patients received edaravone 60 mg. The 30 mg dose was chosen to establish safety of edaravone in ALS patients because it is half the dose already approved for ischemic stroke in Japan. Each patient served as their own control. The primary outcome was the rate of decline in the ALSFRS R during the 6 months prior to study enrollment versus during the 6 month study period. One patient in the edaravone 30 mg group and 2 patients in the edaravone 60 mg group di did not have ALSFRS-R scores available and were not included in the efficacy analysis. The change in the mean ALSFRS-R score was less (-2.3 points) during therapy with edaravone 60 mg compared with prior to initiating therapy (-4.7 points, P = 0.039). There were no statistically significant differences before and after initiation of therapy with edaravone 30 mg. Markers of oxidative stress (i.e., concentration of 3-nitrotyrosine in the cerebral spinal fluid) were reduced during treatment with edaravone 60 mg, and were undetectable in almost all patients by the end of cycle 6 (actual values not reported). Diarrhea was the only adverse event reported that was thought to be related to edaravone, and it resolved over time with continued therapy. (Yoshino, 2006)

Off Label Uses

AHFS Drug Information 2019 Edition does not support any off-label uses of edaravone (Radicava).

Experimental, Investigational, Unproven Uses

Several studies have evaluated edaravone in other conditions associated with oxidative stress, and it is approved to prevent nerve damage following acute ischemic stroke in Japan. Systematic reviews have concluded that additional data from large randomized controlled trials are needed evaluating the use of edaravone in acute ischemic stroke (Feng, 2011) or acute intracerebral hemorrhage (Yang, 2011).

Coding/ Billing Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Covered when medically necessary:

HCPCS Codes	Description
J1301	Injection, edaravone, 1 mg

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