Drug Use Research & Management Program
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New Drug Evaluation: Edaravone injection, intravenous

Date of Review: July 2018
Generic Name: edaravone

End Date of Literature Search: 04/30/2018
Brand Name (Manufacturer): Radicava® (MT Pharma America, Inc.)
Dossier Received: yes

Research Questions:

1. What is the efficacy of edaravone compared to placebo or currently available treatments for amyotrophic lateral sclerosis (ALS)?
2. Is edaravone safe for treatment of ALS?
3. Are there any subgroups (based on age, gender, ethnicity, comorbidities, disease duration or severity) that would particularly benefit or be harmed from treatment with edaravone?

Conclusions:

- There is insufficient evidence to determine if edaravone has any significant impact on functional status or disease progression in all ALS patients beyond 6 months. One small study of 137 patients over 24 weeks in early-stage Japanese ALS patients demonstrated a 2.49 difference on a 48-point ALSFRS-R scale [0 (worst) to 48 (normal)] compared to placebo [2.49 +/- 0.76 (95% CI, 0.99 to 3.98); P = 0.001].[1]
- There is insufficient evidence to evaluate the long-term safety of edaravone. The safety population included a total of 368 patients. Mortality rates were similar and serious adverse events were fewer in edaravone group versus placebo (1.1% and 2.2%; 17.4% and 22.3%, respectively).[2] The most common adverse events with edaravone treatment were contusion (15%), gait disturbance (13%), and headache (8%).[2]
- There is insufficient evidence to compare edaravone to any other ALS therapies or in specific subpopulations other than Japanese patients.

Recommendations:

- Recommend implementation of prior authorization criteria for edaravone (**Appendix 2**).

Background:

Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's or Charcot's disease, is the most common degenerative and fatal motor neuron disease.[3] The Centers for Disease Control and Prevention (CDC) has estimated there are over 12,000 people in the United States with ALS or roughly 5 cases per 100,000 individuals.[4] ALS affects more males than females at a ratio of 1.7:1.[4] ALS symptoms typically do not develop until 50 years of age, and the disease is typically diagnosed between 55 and 65 years of age. Although there is variation in ALS presentation and progression, the average life expectancy is two to five years from the time of diagnosis.[4] Only about 10% of ALS patients live more than 10 years from disease onset.[5] The clinical standard for diagnosis of ALS is the Revised El Escorial World Federation of Neurology criteria which requires evidence of degeneration and dysfunction of upper motor neuron (UMN) and lower motor

neurons (LMN).[6] Early stages of ALS are marked by muscle stiffness, asymmetric limb weakness, cramping and fatigue.[6] Twenty percent of ALS patients exhibit bulbar symptoms such as slurred speech and dysphagia.[7] As ALS progresses, selective degeneration of upper and lower motor neurons eventually results in loss of coordination and muscle strength leading to complete paralysis, respiratory failure, and death.[7] Up to 30% of ALS patients may experience significant cognitive or psychological impairment as well as depression and mood imbalance.[8] Based on claims data, Oregon Medicaid has 105 identified cases of ALS, 54 of whom are in the Fee-For-Service (FFS) program. Claims data is unable to distinguish between the various stages of ALS.

The etiology of ALS is largely unknown, however, mitochondrial abnormalities, signs of oxidative stress, and elevated 3-nitrotyrosine and protein carbonyl levels have been observed in many patients.[3,9] Established risk factors for development of ALS are age and family history. Around 90% of ALS cases are sporadic (SALS) and affect individuals in their late 50s to early 60s. Only 10% of ALS cases are familial ALS (FALS) which typically emerge a decade earlier in the patient's 40s to early 50s.[4,9] Siblings and children of ALS patients are at increased risk of developing FALS.[3,9] One-fifth of FALS cases have revealed mutations in the copper/zinc ion-binding superoxide dismutase (SOD1) gene.[3,9,10] SOD1 has been theorized to be one of the protective enzymes responsible for the destruction of free superoxide radicals in the body and is required to block free-radical-induced DNA damage and prevent oxidative stress.[3,9,10] However, the direct link between SOD1 mutation and motor neuron degeneration of FALS patients is unclear as cases may also be linked to other mutations in Transactive Response DNA Binding Protein (TARDBP), Fused in Sarcoma (FUS), and Angiogenin (ANG) proteins.[3,9,10] There are no clinical laboratory tests that confirm diagnosis of nongenetically determined ALS.[6]

There is no cure for ALS and effective management is primarily focused on symptomatic and supportive care for the patient's physical, emotional and psychological needs.[11] Therapy outcomes which are of clinical value to ALS patients include mobility, muscle strength, quality of life, disease progression, and mortality. A variety of tools and clinical measures have been employed to manage and monitor ALS patients at various stages of functional decline.[11,12] Guidelines from the American Academy of Neurology (AAN) recommend noninvasive ventilation (NIV) and percutaneous endoscopic gastrostomy (PEG) as important but underutilized treatments for ALS patients.[11] Noninvasive ventilation may be useful at earlier stages of ALS for the treatment of respiratory insufficiency in order to lengthen survival, slow forced vital capacity decline, and improve patient quality of life .[13] Spirometry with forced vital capacity (FVC) has been commonly used to diagnose diaphragmatic weakness and symptom progression in ALS patients.[13] Due to the loss of motor function, the majority of patients will eventually require assistance with activities of daily living (ADL).[13] PEG has been utilized in feeding to help stabilize patient weight and prolong survival.[11] The Respiratory Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) is a tool widely used by clinicians to assess disease progression in ALS patients.[14] The ALSFRS-R enables clinicians to score the patient's physical function on a scale from 0 (worst) to 48 (normal).[14] The ALSFRS-R has been considered by some to be an improvement over the original ALSFRS due to its incorporation of 3 additional questions regarding dyspnea, orthopnea, and the need for respiratory support.[14,15] Some studies have used changes in the ALSFRS-R to make survival predictions.[16] However, there has been criticism regarding use of the ALSFRS-R scale because it may not be sensitive to heterogeneity in ALS disease progression especially among multiple domains over short time periods.[12,14] An additional validity concern of the ALSFRS-R is its reduced sensitivity for detection of change in low-functioning ALS patients as well as the potential for scores to be affected by mood or effort.[12,17] The minimum clinically important difference (MCID) on the ALSFRS-R score is unclear.[17] Changes in the ALSFRS-R have been correlated with patient-perceived changes of physical, emotional, and social function, but patients may be unable to perceive an intervention effect until its impact on the ALSFRS-R is 9 points or more.[18] Clinical trials have shown that the ALSFRS-R consistently declines at a rate of -0.92 units per month in ALS patients.[19] Surveys of clinicians estimate that an ALSFRS-R slope change (score vs. time) by 20-25% or more would be considered clinically meaningful.[19] Other measurements of function in ALS patients have also included strength testing to evaluate limb function.[12]

Pharmacological treatment options to slow disease progression are few, and there is no evidence that FALS or SALS patients respond better to any particular available therapy.[20] Gamma aminobutyric acid (GABA) modulators and recombinant human insulin-like growth factor-1 (IGF-1) have been studied to improve

function or survival in adult ALS patients, but there is insufficient evidence available to support use of either agent to mitigate the degenerative effects of the disease.[20,21,22] Until recently, the glutamate inhibitor riluzole was the only agent FDA approved for ALS treatment.[2] The AAN and National Institute for Heath and Care Excellence (NICE) guidelines have both recommended that riluzole be offered to ALS patients by a neurological specialist to slow disease progression.[11,23] A 2011 updated Cochrane Review examined the efficacy of riluzole in prolonging survival and in delaying the use of surrogates to sustain survival.[24] Evidence from four RCTs of acceptable methodological quality with 1477 ALS patients were reviewed.[24] Three of the four studies with full data on tracheostomy-free survival were compared.[24] Riluzole 100 mg per day provided a benefit for the homogeneous group of patients in the first two trials (hazard ratio (HR) 0.80, 95% confidence internal (CI) 0.64 to 0.99, P= 0.042).[24] The third trial included older patients with more advanced disease, however, the pooled treatment effects were still significant (HR 0.84, 95% CI 0.698 to 0.997, P= 0.046).[24] The results indicated that riluzole therapy for ALS patients was associated with an increased median survival benefit of 11.8 to 14.8 months versus placebo.[24] The exact mechanism for the therapeutic benefit of riluzole in ALS has not been determined. Assessment of functional improvement with the ALSFRS-R tool was not performed in riluzole-treated patients.[24]

Clinical Efficacy:

Edaravone is a free radical scavenger indicated for the treatment of adults with ALS.[2] Edaravone is thought to hinder functional nerve cell deterioration through the reduction of oxidative stress to the cell membranes.[23] The specific mechanism by which edaravone may function in the treatment of ALS in unknown.[2] Edaravone's utility in the treatment of ALS was first recognized in Japan and Korea, then approved for use in the United States in May 2017 as an orphan drug.[1,25] See **Appendix 1** for Highlights of Prescribing Information from the manufacturer, including indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations. The clinical trial by Abe et al. (Study 19) which contributed to edaravone's FDA approval in ALS patients is described below and evaluated in **Table 3**.

Key prognostic factors used to develop inclusion and exclusion criteria for Study 19 were initially identified through post-hoc analysis of a failed phase 3, randomized, double-blind, parallel-group, placebo-controlled trial of edaravone in Japanese ALS patients (n=206).[25,26] The primary efficacy end point was the mean change in ALSFRS-R score.[25] The study was unable to find a statistically significant different ALSFRS-R score between placebo and edaravone at 24 weeks [placebo -6.35 ± 0.84 vs. edaravone -5.70 ± 0.85 (95% CI, -0.90 to 2.19, p = 0.411)], but data from this trial was used to develop inclusion and exclusion criteria in Study 19.[25,26]

Study 19, was a fair-quality, 24-week, phase 3, double-blind, placebo-controlled, RCT (n=137) which evaluated the efficacy and safety of edaravone in a specific ALS population of independently-living Japanese patients.[1] The trial applied stricter enrollment critiera than the previous study. Subjects were required to undergo a 12-week pre-observational screening period to establish baseline function. Only participants with a diagnosis of definite or probable ALS with a disease duration of less than or equal to 2 years (rather than <3 years), a score of 2 or more on all items in the ALSFRS-R, and a FVC of at least 80% (rather than $\geq$70%) were allowed to complete the study.[1] The baseline characteristics between edaravone and placebo groups were generally well matched. Subjects had a mean disease duration of 1.1 years, the majority (72%) had a baseline disease severity of 2 on the 5 point Japanese ALS severity scale (5 = most severe), and 91% were on concomitant riluzole therapy (see **Table 3** for additional inclusion criteria and baseline characteristics).[1] Patients were randomized 1:1 to receive six cycles of 60 mg edaravone IV once-daily for 14 days followed by 14 days off drug or a matching placebo treatment.[1] All subsequent cycles (cycles 2-6) were 10 of 14 days on drug, followed by 14 days off drug.[1] The primary outcome measure was the least-squares mean change in ALSFRS-R score from baseline to 24 weeks (or at discontinuation if after cycle 3 of 6).[1]

At 24 weeks, edaravone patients demonstrated a statistically significant least squares mean difference in the ALSFRS-R score versus placebo from baseline through cycle 6 (-5.01 vs. -7.5, respectively), with an intergroup adjusted mean difference of 2.49 (95% CI, 0.99 to 3.98; P = 0.001).[1] Though statistically

significant, a -5.01 unit decline did not appear to meet the threshold for a clinically important change in the ALSFRS-R score compared to the expected -5.52 unit decline over 6 months cited in other medical studies.[18,19] Additionally, the outcome measure did not reach the 9-point or more ALSFRS-R improvement threshold reported to be discernable by patients.[18] It is unclear why placebo-treated patients in Study 19 declined at a much faster rate than expected. The ALSFRS-R measurement tool may not be sensitive to changes over a short-term trial, and therefore, the clinical relevance is unclear.

The study had several unanswered questions related to the integrity of the trial and applicability to the general ALS population. The study sponsor, Mitsubishi Tanabe Pharma Corporation, was involved in the study design, study monitoring, data collection and management, statistical analysis, data interpretation, and writing of the draft report of the analysis.[1] The 12-week observational period protocol details were not reported. Concealment of allocation and randomization procedure details were not fully disclosed. Only subjects with >80% FVC at baseline were included in the trial while those with scores of 3 or less on ALSFRS-R items for dyspnea, orthopnea, or respiratory insufficiency were excluded. Therefore, the efficacy of edaravone in treating more advanced ALS patients with respiratory issues is unknown. The inter-rater reliability of clinician ALSFRS-R score assessment was unclear and at least one patient evaluation at the end of cycle 2 was excluded from the efficacy analysis due to inadequate clinician training. The secondary endpoints of percent of FVC, Modified Norris Scale scores, grip strength, and pinch strength yielded mixed results, and the analyses were not statistically adjusted for multiplicity *a priori*. Additionally, there is no evidence that edaravone had any effect on patient survival. The trial was conducted entirely in Japan, therefore, efficacy rates for non-Asian populations is unknown. Overall, edaravone demonstrated uncertain clinical benefit in a small, select group of Japanese patients with early ALS. Until further studies are published to support use in a wider ALS population, the clinical effectiveness of edaravone for Oregon Medicaid patients is unclear.

Clinical Safety:

A total of 349 patients received edaravone in the ALS clinical trials, 306 patients received edaravone for at least 6 months (6 cycles), and 98 patients received edaravone for at least 12 months (12 cycles).[27] Safety analyses from pooled controlled clinical trials (n=368) showed no major imbalances between edaravone and placebo groups.[2,27] A similar mortality rate was observed in edaravone- versus placebo-treated patients [4/184 (2.2%) vs. 2/184 (1.1%), respectively].[27] All 6 patient deaths were due respiratory failure attributed to disease progression and not drug-related as judged by authors and the FDA.[26] Discontinuation rates due to adverse events were higher overall in placebo-treated patients (5%) than in edaravone-treated patients (2%) with the main driver related to respiratory, thoracic, and mediastinal disorders.[2,27] Serious adverse events (SAE) were reported more frequently in placebo treated patients (22%) than edaravone-treated patients (17%; statistical significance not reported) with dysphagia listed as the most common occurrence at similar rates in both edaravone and placebo groups (9.8% and 10.3%, respectively).[27] No SAEs were identified as distinctly drug-related.[2,27] The most common adverse events in at least 5% of the edaravone-treated subjects that occurred at 2% or higher frequency compared to placebo included contusion, gait disturbance, headache, eczema, and contact dermatitis (**Table 1**).[2,27] Since the trials were of short duration and included small numbers of patients with early stages of ALS, the long-term safety effects remain unknown.

Table 1. Selected Adverse Reactions with an Incidence in ≥5% of Edaravone-treated Patients and ≥2% than Placebo [2,27]

	Edaravone (n=184)	Placebo (n=184)
Contusion	15%	9%
Gait disturbance	13%	9%
Headache	8%	5%
Eczema	7%	2%
Dermatitis, contact	6%	3%

Patients should be monitored for hypersensitivity and sulfite reactions.[27] The limited ECG data provided did not identify a QT prolongation signal, and there was no thorough QT (TQT) study performed.[27] No REMS was required for edaravone.[27]

No look-alike/sound-alike error risk potential was identified.

Table 2. Pharmacology and Pharmacokinetic Properties.[2,27,28]

Parameter	
Mechanism of Action	Edaravone is a member of the substituted 2-pyrazolin-5-one class. The mechanism for therapeutic effects in amyotrophic lateral sclerosis is uncertain.
Oral Bioavailability	N/A – administered as an intravenous infusion
Distribution and Protein Binding	Albumin: 92%
Elimination	Renal excretion: 1% unchanged; 70% to 90% as the glucuronide form; and 5% to 10% as the sulfate conjugate
Half-Life	4.5 to 6 hours
Metabolism	Metabolized to a sulfate conjugate and a glucuronide conjugate in the liver and kidney which are not pharmacologically active.

Comparative Endpoints:

Clinically Relevant Endpoints:

1) Functional or symptom improvement
2) Quality of life
3) Disease progression
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Change in ALSFRS-R score (baseline to cycle 6)

Table 3. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Abe et al., 2017 (Study 19)[1] Radicava FDA Medical Review[27] Radicava FDA Summary Review[2] Radicava FDA Statistical Review[26] Phase 3 MC, DB, PC, RCT	1. Edaravone 60 mg IV infusion 2. Placebo (saline) IV infusion Cycle 1: once daily x 14 consecutive days followed by a 2-week drug-free period; in Cycle 2 and thereafter, once daily x 10 days within a 2-week period followed by a 2-week drug-free period. All patients completing 6 cycles of therapy were offered the option of continuing open-label treatment with edaravone for an additional 6 cycles.	Demographics: •57% male •67% of patients < 65 years of age •98% diagnosed with sporadic ALS (as opposed to familial) •60% of patients with probable ALS diagnosis •72% Grade 2 ALS severity (according to Japanese ALS Severity Classification, grade 1-5, 5 = most severe) •91% concomitant riluzole use •Mean baseline ALSFRS > 43 Key Inclusion Criteria: -Age 20-75 yo -Independent living status (grade 1 or 2 in the Japan ALS Severity Classification) -Decrease in the Revised ALS Functional Rating Scale (ALSFRS-R) score of 1-4 during a 12 week obs period -Scores ≥ 2 on all 12 items of ALSFRS-R -FVC > 80% -Definite or probable ALS (according to the El Escorial and revised Airlie House criteria) -Duration of disease from first sign of any ALS symptom, is 2 years or less.	ITT: 1. 69 2. 68 mITT: 1. 68 2. 66 Attrition: 1. 2 (3%) 2. 8 (12%)	Primary Endpoint: Least-squares mean change (± standard error) in the ALSFRS-R score at the end of cycle 6 or at discontinuation: Edaravone: -5.01 ± 0.64 Placebo: -7.50 ± 0.66 LSMD: 2.49 ± 0.76 (95% CI, 0.99 to 3.98); P = 0.001 Secondary Endpoints: Change in Percent FVC Edaravone: -15.61 ± 2.41 placebo: -20.40 ± 2.48 LSMD: 4.78 ± 2.84 (95% CI, -0.83 to 10.40), p=0.0942 Change in total Modified Norris Scale score (0-102 [best]) Edaravone: -15.92 ± 1.97 Placebo: -20.80 ± 2.06 LSMD: 4.89 ± 2.35 (95% CI, 0.24 to 9.54), p=0.0393 FDA statistical review[26] p=0.052 Change in grip strength(kg) – Mean for left and right hands Edaravone: -4.08 ± 0.54 placebo: -4.19 ± 0.56 LSMD: 0.11 ± 0.64; (95% CI, -1.15 to 1.38); p = 0.8583 Change in pinch strength(kg) – Mean for left and right hands Edaravone: -0.78 ± 0.14 placebo: -0.88 ± 0.14 LSMD: 0.10 ± 0.16 (95% CI, -0.23 to 0.42); p = 0.5478 Change in ALSAQ-40 score (200-40 [best]) Edaravone: 17.25 ± 3.39	N/A N/A NS N/A NS NS NS	Outcome: Death Edaravone: 2.2% Placebo: 1.1% Death within 6-month extension period Edaravone: 4% Placebo 4% SAE: Edaravone: 17% Placebo: 22% Discontinuation due to AEs: Edaravone: 2.2% Placebo: 5.4%	N/A N/A N/A N/A	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Minimization method used with stratification for ALS diagnosis; baseline characteristics balanced; method of allocation concealment not described Performance Bias: Unclear. Edaravone and placebo were provided in ampules that were indistinguishable in appearance and packaging; patients unable to access the key code until unblinding; investigators masked to treatment groups but had key code access Detection Bias: Unclear. Funder and investigators were privy to access key code so whether blinding was successful or not was unknown Attrition Bias: Low. Few patients with missing data at the end of Cycle 6, data imputed by LOCF; differential attrition 6%; sensitivity analysis performed Reporting Bias: High Patient censoring rules not disclosed; The study funder (Mitsubishi Tanabe Pharma Corporation) was involved in study design, study monitoring, data collection and management, statistical analysis, data interpretation, and writing of the draft report of the study; most investigators received personal fees or were paid employees of Mitsubishi Tanabe; not all clinicians assessing ALSFRS-R score had adequate training which lead to at least one patient's analysis being excluded; did not address multiplicity of secondary endpoints *a priori*; secondary endpoint of time to death/disease progression not reported in table **Applicability**: Patient: Highly selective inclusion criteria limits applicability to a broader population; All Japanese patients with ALS Severity Score in categories 1 or 2; excluded patients with respiratory dysfunction and advanced ALS. Intervention: Efficacy assessed at multiple instances before pre-observation, at baseline before the start

		Key Exclusion Criteria: -Score ≤ 3 on ALSFRS-R items for dyspnea, orthopnea, or respiratory insufficiency -Spinal surgery history after ALS onset -CrCl ≤ 50mL/min		placebo: 26.04 ± 3.53 LSMD: -8.79 ± 4.03 (95% CI, -16.76 to -0.82); p = 0.0309 Number of events involving death or certain disease progression events (death, disability of independent ambulation, loss of upper limbs function, tracheotomy, use of respirator, use of tube feeding, loss of useful speech) Edaravone: 2 Placebo: 6 Log-rank test, P = 0.1284 Generalized Wilcoxon test, P = 0.1415	N/A NS			of Cycle 1, and after the 2-week observation period of each treatment cycle; No supratherapeutic dose/exposure studied; Most subjects were concurrent users of rizuole, and changes in dose or regimen were not permitted Comparator: Placebo appropriate to determine efficacy. Comparison with riluzole may have been a more meaningful comparator to establish place in therapy. Outcomes: Short term subjective scale used to assess speed of decline at early stage ALS; No established MCID for ALSFRS-R; Trial was not designed to detect a survival difference as survival trials require large numbers of patients studied for long periods Setting: All 31 sites in Japan
Abbreviations: AE = adverse events; ARR = absolute risk reduction; ALSAQ40 = Amyotrophic Lateral Sclerosis Assessment Questionnaire; ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale – Respiratory; CI = confidence interval; CrCl = creatinine clearance; FVC = forced vital capacity; ITT = intention to treat; LOCF = last observation carried forward; LSMD = least squares mean difference; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; obs = observational; PP = per protocol; SAE = serious adverse events; YO = years old							

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28. Radicava (edaravone injection) [prescribing information] Jersey City, NJ, MT Pharma America, Inc; 2017

Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use RADICAVA safely and effectively. See full prescribing information for RADICAVA.

RADICAVA (edaravone injection), for intravenous use
Initial U.S. Approval: 2017

INDICATIONS AND USAGE

RADICAVA is indicated for the treatment of amyotrophic lateral sclerosis (ALS) (1)

DOSAGE AND ADMINISTRATION

The recommended dosage is 60 mg administered as an intravenous infusion over 60 minutes as follows:

- Initial treatment cycle: daily dosing for 14 days followed by a 14-day drug-free period
- Subsequent treatment cycles: daily dosing for 10 days out of 14-day periods, followed by 14-day drug-free periods. (2)

DOSAGE FORMS AND STRENGTHS

Injection: 30 mg/100 mL in a single-dose polypropylene bag (3)

CONTRAINDICATIONS

Patients with a history of hypersensitivity to edaravone or any of the inactive ingredients in RADICAVA (4)

WARNINGS AND PRECAUTIONS

- Hypersensitivity Reactions: Advise patients to seek immediate medical care (5.1)
- Sulfite Allergic Reactions: RADICAVA contains sodium bisulfite, which may cause allergic type reactions (5.2)

ADVERSE REACTIONS

Most common adverse reactions (at least 10% and greater than placebo) are contusion, gait disturbance, and headache (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact MT Pharma America, Inc. at 1-888-292-0058 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 5/2017

Edaravone (Radicava™)

Goal(s):

- To encourage use of riluzole which has demonstrated mortality benefits.
- To ensure appropriate use of edaravone in populations with clinically definite or probable amytrophic lateral sclerosis
- To monitor for clinical response for appropriate continuation of therapy

Length of Authorization:

Up to 12 months

Requires PA:

- Edavarone (pharmacy and physician administered claims)

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for continuation of therapy of previously approved FFS criteria (after which patient has completed 6-month trial)?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3
3. Is this a treatment for amyotrophic lateral sclerosis (ALS)?	**Yes**: Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Is the diagnosis funded by OHP?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; not funded by the OHP.
5. Is the patient currently on riluzole therapy, OR have a documented contraindication or intolerance to riluzole?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
6. Is the medication being prescribed by or in consultation with a neurologist?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Does the patient have documented percent-predicted forced vital capacity (%FVC) ≥ 80%?	**Yes:** Record lab result. Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Is there a baseline documentation of the revised ALS Functional Rating Scale (ALSFRS-R) score with ≥2 points in each of the 12 items?	**Yes:** Record baseline score. (0 [worst] to 48 [best]) Approve for 6 months based on FDA-approved dosing.*	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is the medication being prescribed by or in consultation with a neurologist?	**Yes**: Go to #2	**No:** Pass to RPh. Deny; medical appropriateness
2. Has the prescriber provided documentation that the use of Radicava (edarvone) has slowed in the decline of functional abilities as assessed by a Revised ALS Functional Rating Scale (ALSFRS-R) with no decline more than expected given the natural disease progression (5 points from baseline over 6 months)?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness Use clinical judgment to approve for 1 month to allow time for appeal. MESSAGE: "Although the request has been denied for long-term use because it is considered medically inappropriate, it has also been APPROVED for one month to allow time for appeal."
3. Does the patient have documented percent-predicted forced vital capacity (%FVC) ≥ 80%?	**Yes:** Record lab result. Go to #4	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
4. Is there a documentation of the revised ALS Functional Rating Scale (ALSFRS-R) score with ≥2 points in each of the 12 items?	**Yes:** Record score. (0 [worst] to 48 [best]) Approve for 12 months.	**No:** Pass to RPh. Deny; medical appropriateness

* = see below for summary of FDA-approved dosage and administration. Consult FDA website for prescribing information details at www.fda.gov

P&T/DUR Review: 7/18 (DE)
Implementation: 8/15/18

***Dosage and Administration:**

60 mg (two consecutive 30 mg infusion bags) IV infusion over 60 minutes

- Initial treatment cycle: daily dosing for 14 days followed by a 14-day drug-free period
- Subsequent treatment cycles: daily dosing for 10 days out of 14-day periods, followed by 14-day drug-free period