# NEW DRUG APPROVAL

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|---|---|
| **Brand Name** | Radicava®, Radicava® ORS |
| **Generic Name** | edaravone |
| **Drug Manufacturer** | Mitsubishi Tanabe Pharma America, Inc. |

## New Drug Approval

FDA approval date: May 12, 2022

Review designation: Priority; Orphan

Type of review: Type 3 - New Dosage Form; New Drug Application (NDA): 215446

Dispensing restriction: N/A

## Place in Therapy

### DISEASE DESCRIPTION & EPIDEMIOLOGY

Amyotrophic lateral sclerosis (ALS), also known as "Lou Gehrig disease," is a neurodegenerative disease of the motor neurons. No single etiology has been proven; rather, multiple pathways (both heritable and sporadic) have been shown to result in unmistakably similar disease entities. ALS necessarily affects both upper and lower motor neurons with variable patterns of onset, most commonly beginning with signs of lower motor neuron degeneration within proximal limbs. As it is a progressive disease, it will eventually lead to paralysis and, inevitably, death. There is no cure for ALS; however, multiple medications and interventions can reduce symptoms and prolong life, sometimes up to 10 or more years.

The incidence of ALS is approximately 1-2.6 cases per 100,000 persons annually, whereas the prevalence is approximately 6 cases per 100 000. The average age of onset of ALS is currently 58-60 years and the average survival from onset to death is 3-4 years. Between October 19, 2010, and December 31, 2011, there were an estimated 12 187 prevalent cases diagnosed with definite ALS in the USA alone. Sporadic ALS (90-95%) constitutes most cases, while the remaining 5-10% are hereditary and termed familial ALS. Sporadic ALS is suspected to involve genetic susceptibility to environmental risk factors.

## Efficacy

The efficacy of Radicava® for the treatment of ALS was established in a 6-month, randomized, placebo controlled, double-blind study conducted in Japanese patients with ALS who were living independently and met the following criteria at screening:

- 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.
- Normal respiratory function (defined as percent-predicted forced vital capacity values of [%FVC] ≥ 80%).
- Definite or Probable ALS based on El Escorial revised criteria.
- Disease duration of 2 years or less.

The study enrolled 69 patients in the Radicava® arm and 68 in the placebo arm. Baseline characteristics were similar between these groups, with over 90% of patients in each group being treated with riluzole.

Radicava® was administered as an intravenous infusion of 60 mg given over a 60-minute period according to the following schedule:

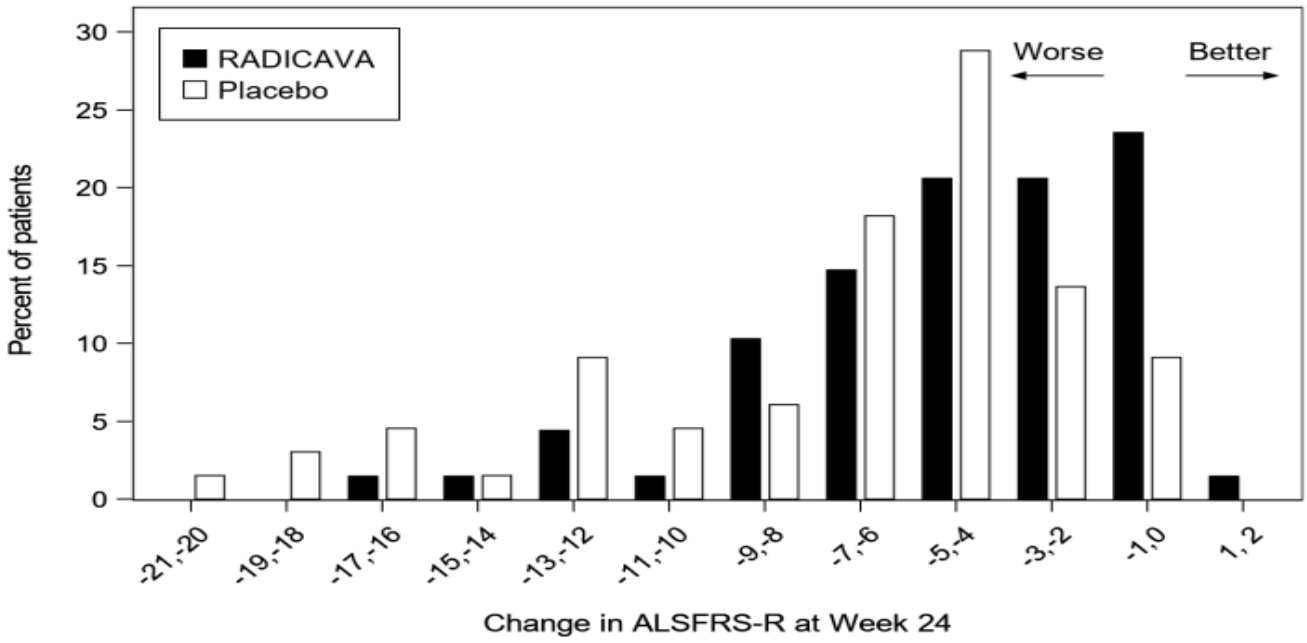
- An initial treatment cycle with daily dosing for 14 days, followed by a 14-day drug-free period (Cycle 1).
- Subsequent treatment cycles with daily dosing for 10 days out of 14-day periods, followed by 14-day drug-free periods (Cycles 2-6).

The primary efficacy endpoint was a comparison of the change between treatment arms in the ALSFRS-R total scores from baseline to Week 24. The ALSFRS-R scale consists of 12 questions that evaluate the fine motor, gross motor, bulbar, and respiratory function of patients with ALS (speech, salivation, swallowing, handwriting, cutting food, dressing/hygiene, turning in bed, walking, climbing stairs, dyspnea, orthopnea, and respiratory insufficiency). Each item is scored from 0-4, with higher scores representing greater functional ability. The decline in ALSFRS-R scores from baseline was significantly less in the Radicava®-treated patients as compared to placebo (see Table 1). The distribution of change in ALSFRS-R scores from baseline to Week 24 by percent of patients is shown in Figure 1.

**Table 1: Analysis of change from baseline to week 24 in ALSFRS-R scores**

| Treatment | Change from Baseline LS Mean ± SE (95% CI) | Treatment Difference (Radicava® – placebo [95% CI]) | *p*- value |
|---|---|---|---|
| Radicava® 60mg | −5.01±0.64 | 2.49 (0.99, 3.98) | 0.0013 |
| Placebo | −7.50±0.66 | | |

**Figure 1: Distribution of Change from Baseline to Week 24 in ALSFRS-R Scores**




## Safety

### ADVERSE EVENTS

Table 2 lists the adverse reactions that occurred in ≥ 2% of patients in the Radicava®-treated group and that occurred at least 2% more frequently than in the placebo-treated group in randomized placebo-controlled ALS trials. The most common adverse reactions that occurred in ≥10% of Radicava®-treated patients were contusion, gait disturbance, and headache.

**Table 2: Adverse Reactions from Pooled Placebo-Controlled Trials[a] that Occurred in ≥ 2% of Radicava®-Treated Patients and ≥ 2% More Frequently than in Placebo Patients**

| Adverse Reaction | Radicava® (N=184) % | Placebo (N=184) % |
|---|---|---|
| Contusion | 15 | 9 |
| Gait disturbance | 13 | 9 |
| Headache | 10 | 6 |
| Dermatitis | 8 | 5 |
| Eczema | 7 | 4 |
| Respiratory failure, respiratory disorder, hypoxia | 6 | 4 |
| Glycosuria | 4 | 2 |
| Tinea infection | 4 | 2 |

[a] Pooled placebo-controlled studies include two additional studies with 231 additional patients, all using the same treatment regimen.

### WARNINGS & PRECAUTIONS

**Hypersensitivity Reactions**- Hypersensitivity reactions (redness, wheals, and erythema multiforme) and cases of anaphylaxis (urticaria, decreased blood pressure, and dyspnea) have been reported in spontaneous post marketing reports with RADICAVA. Patients should be monitored carefully for hypersensitivity reactions. If hypersensitivity reactions occur, discontinue Radicava® and/or Radicava® ORS, treat per standard of care, and monitor until the condition resolves.

**Sulfite Allergic Reactions**- Radicava® and Radicava® ORS contain sodium bisulfite, a sulfite that may cause allergic type reactions, including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown. Sulfite sensitivity occurs more frequently in asthmatic than non-asthmatic people.

### CONTRAINDICATIONS

Radicava® and Radicava® ORS are contraindicated in patients with a history of hypersensitivity to edaravone or any of the inactive ingredients in this product. Hypersensitivity reactions and anaphylactic reactions have occurred.

## Clinical Pharmacology

### MECHANISMS OF ACTION

The mechanism by which Radicava® and Radicava® ORS exert their therapeutic effect in patients with ALS is unknown.

## Dose & Administration

### ADULTS

**Oral dosage:**

Initial cycles: 105 mg orally once daily in the morning after overnight fasting for 14 days followed by a 14-day drug-free period.

Subsequent cycles: 105 mg orally once daily in the morning after overnight fasting administer for 10 days out of 14-day periods followed by 14-day drug-free periods.

**Intravenous dosage:**

Initial cycle: 60 mg once daily for 14 days, followed by a 14-day drug-free period.

Subsequent cycles: 60 mg once daily for 10 days within a 14-day period, followed by a 14-day drug-free period.

### PEDIATRICS

None

### GERIATRICS

Refer to adult dosing.

### RENAL IMPAIRMENT

None

### HEPATIC IMPAIRMENT

None

## Product Availability

### DOSAGE FORM(S) & STRENGTH(S)

- Injection: 30 mg/100 mL in a single-dose polypropylene bag.
- Oral suspension: 105 mg/5 mL in a multi-dose amber glass bottle.