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 Mitsubishi Tanabe 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: 3/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

2.1 Dosage Information

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.

2.2 Preparation and Administration Information

RADICAVA is for intravenous infusion only.

Preparation

Do not use if the oxygen indicator has turned blue or purple before opening the package *[see How Supplied/Storage and Handling (16.1, 16.2)]*. Once the overwrap package is opened, use within 24 hours *[see Storage and Handling (16.2)]*.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Administration

Administer each 60 mg dose of RADICAVA injection as two consecutive 30 mg intravenous infusion bags over a total of 60 minutes (infusion rate approximately 1 mg per minute [3.33 mL per minute]).

Promptly discontinue the infusion upon the first observation of any signs or symptoms consistent with a hypersensitivity reaction *[see Warnings and Precautions (5.1, 5.2)]*.

Other medications should not be injected into the infusion bag or mixed with RADICAVA.

3 DOSAGE FORMS AND STRENGTHS

RADICAVA is supplied for intravenous infusion in a single-dose polypropylene bag containing 30 mg of edaravone in 100 mL of clear, colorless aqueous solution.

4 CONTRAINDICATIONS

RADICAVA is contraindicated in patients with a history of hypersensitivity to edaravone or any of the inactive ingredients of this product. Hypersensitivity reactions and anaphylactic reactions have occurred *[see Warnings and Precautions (5.1, 5.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Hypersensitivity reactions (redness, wheals, and erythema multiforme) and cases of anaphylaxis (urticaria, decreased blood pressure, and dyspnea) have been reported in spontaneous postmarketing reports with RADICAVA.

Patients should be monitored carefully for hypersensitivity reactions. If hypersensitivity reactions occur, discontinue RADICAVA, treat per standard of care, and monitor until the condition resolves *[see Contraindications (4)]*.

5.2 Sulfite Allergic Reactions

RADICAVA contains 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 people.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Hypersensitivity Reactions *[see Warnings and Precautions (5.1)]*
- Sulfite Allergic Reactions *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In randomized, placebo-controlled trials, 184 ALS patients were administered RADICAVA 60 mg in treatment cycles for 6 months. The population consisted of Japanese patients who had a median age of 60 years (range 29-75) and were 59% male. Most (93%) of these patients were living independently at the time of screening.

Most Common Adverse Reactions Observed During Clinical Studies

Table 1 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 1: 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 *[see Clinical Studies (14)]*.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of RADICAVA outside of the United States. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Skin and subcutaneous tissue disorders: Hypersensitivity reactions and anaphylaxis.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate data on the developmental risk associated with the use of RADICAVA in pregnant women. In animal studies, administration of edaravone to pregnant rats and rabbits resulted in adverse developmental effects (increased mortality, decreased growth, delayed sexual development, and altered behavior) at clinically relevant doses. Most of these effects occurred at doses that were also associated with maternal toxicity (*see Animal Data*).

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. The background risk for major birth defects and miscarriage in patients with ALS is unknown.

Data

Animal Data

In rats, intravenous administration of edaravone (0, 3, 30, or 300 mg/kg/day) throughout the period of organogenesis resulted in reduced fetal weight at all doses. In dams allowed to deliver naturally, offspring weight was reduced at the highest dose tested. Maternal toxicity was also observed at the highest dose tested. There were no adverse effects on reproductive function in the offspring. A no-effect dose for embryofetal developmental toxicity was not identified; the low dose is less than the recommended human dose of 60 mg, on a body surface area (mg/m^2) basis.

In rabbits, intravenous administration of edaravone (0, 3, 20, or 100 mg/kg/day) throughout the period of organogenesis resulted in embryofetal death at the highest dose tested, which was associated with maternal

toxicity. The higher no-effect dose for embryofetal developmental toxicity is approximately 6 times the recommended human dose (RHD) on a body surface area (mg/m^2) basis.

The effects on offspring of edaravone (0, 3, 20, or 200 mg/kg/day), administered by intravenous injection to rats from GD 17 throughout lactation, were assessed in two studies. In the first study, offspring mortality was observed at the high dose and increased activity was observed at the mid and high doses. In the second study, there was an increase in stillbirths, offspring mortality, and delayed physical development (vaginal opening) at the highest dose tested. Reproduction function in offspring was not affected in either study. Maternal toxicity was evident in both studies at all but the lowest dose tested. The no-effect dose for developmental toxicity (3 mg/kg/day) is less than the RHD on a mg/m^2 basis.

8.2 Lactation

Risk Summary

There are no data on the presence of edaravone in human milk, the effects on the breastfed infant, or the effects of the drug on milk production. Edaravone and its metabolites are excreted in the milk of lactating rats. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for RADICAVA and any potential adverse effects on the breastfed infant from RADICAVA or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness of RADICAVA in pediatric patients have not been established.

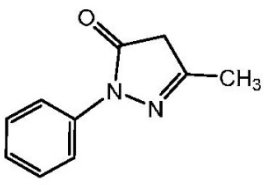
8.5 Geriatric Use

Of the 184 patients with ALS who received RADICAVA in 3 placebo-controlled clinical trials, a total of 53 patients were 65 years of age and older, including 2 patients 75 years of age and older. No overall differences in safety or effectiveness were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

11 DESCRIPTION

The active ingredient in RADICAVA is edaravone, which is a member of the substituted 2-pyrazolin-5-one class. The chemical name of edaravone is [3-methyl-1-phenyl-2-pyrazolin-5-one]. The molecular formula is $C_{10}H_{10}N_2O$ and the molecular weight is 174.20.

The chemical structure is:



Edaravone is a white crystalline powder with a melting point of 129.7°C. It is freely soluble in acetic acid, methanol, or ethanol and slightly soluble in water or diethyl ether.

RADICAVA injection is a clear, colorless liquid provided as a sterile solution.

RADICAVA injection is supplied for intravenous infusion in a polypropylene bag containing 30 mg edaravone in 100 mL isotonic, sterile, aqueous solution, which is further overwrapped with polyvinyl alcohol (PVA) secondary packaging. The overwrapped package also contains an oxygen absorber and oxygen indicator to minimize oxidation. Each bag contains the following inactive ingredients: L-cysteine hydrochloride hydrate (10 mg), sodium bisulfite (20 mg). Sodium chloride is added for isotonicity and phosphoric acid and sodium hydroxide are added to adjust to pH 4.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism by which RADICAVA exerts its therapeutic effect in patients with ALS is unknown.

12.2 Pharmacodynamics

Cardiac Electrophysiology

At a dose 5 times the recommended dose, RADICAVA does not prolong the QT interval to any clinically relevant extent.

12.3 Pharmacokinetics

RADICAVA is administered by IV infusion. The maximum plasma concentration (C_{max}) of edaravone was reached by the end of infusion. There was a trend of more than dose-proportional increase in area under the concentration-time curve (AUC) and Cmax of edaravone. With multiple-dose administration, edaravone does not accumulate in plasma.

Distribution

Edaravone is bound to human serum proteins (92%), mainly to albumin, with no concentration dependence in the range of 0.1 to 50 micromol/L.

Elimination

The mean terminal elimination half-life of edaravone is 4.5 to 6 hours. The half-lives of its metabolites are 2 to 2.8 hours.

Metabolism

Edaravone is metabolized to a sulfate conjugate and a glucuronide conjugate, which are not pharmacologically active. The glucuronide conjugation of edaravone involves multiple uridine diphosphate glucuronosyltransferase (UGT) isoforms (UGT1A6, UGT1A9, UGT2B7, and UGT2B17) in the liver and kidney. In human plasma, edaravone is mainly detected as the sulfate conjugate, which is presumed to be formed by sulfotransferases.

Excretion

In Japanese and Caucasian healthy volunteer studies, edaravone was excreted mainly in the urine as its glucuronide conjugate form (70-90% of the dose). Approximately 5-10% of the dose was recovered in the urine as sulfate conjugate, and only 1% of the dose or less was recovered in the urine as unchanged form. *In vitro*

studies suggest that sulfate conjugate of edaravone is hydrolyzed back to edaravone, which is then converted to the glucuronide conjugate in the human kidney before excretion into the urine.

Specific Populations

Geriatric Patients

No age effect on edaravone pharmacokinetics has been found *[see Use in Specific Populations (8.5)]*.

Patients with Renal Impairment

Following single IV infusion of 30 mg edaravone (half the recommended dosage) over 60 minutes, mean C_{max} and $AUC_{0-\infty}$ of unchanged edaravone were 1.15 and 1.20-fold greater in the subjects with mild renal impairment (eGFR 60-89 mL/min/1.73m^2), and were 1.25 and 1.29-fold greater in the subjects with moderate renal impairment (eGFR 30-59 mL/min/1.73m^2) when compared to subjects with normal renal function, respectively. These changes in exposures are not considered to be clinically significant and therefore no dosage adjustments are necessary in patients with mild to moderate renal impairment. The effects of severe renal impairment on the pharmacokinetics of edaravone have not been studied.

Patients with Hepatic Impairment

Following single IV infusion of 30 mg edaravone (half of the recommended dose) over 60 minutes, mean C_{max} and $AUC0_{-\infty}$ of unchanged edaravone were 1.20 and 1.07-fold greater in the subjects with mild hepatic impairment (Child-Pugh score 5 or 6), were 1.24 and 1.14-fold greater in the subjects with moderate hepatic impairment (Child-Pugh score 7 to 9), and were 1.20 and 1.19-fold greater in the subjects with severe hepatic impairment (Child-Pugh score 10 to 14) when compared to subjects with normal hepatic function, respectively. These changes in exposures are not considered to be clinically significant and therefore no dosage adjustments are necessary in patients with hepatic impairment.

Male and Female Patients

No gender effect on edaravone pharmacokinetics has been found.

Racial or Ethnic Groups

There were no significant racial differences in Cmax and AUC of edaravone between Japanese and Caucasian subjects.

Drug Interaction Studies

The pharmacokinetics of edaravone is not expected to be significantly affected by inhibitors of CYP enzymes, UGTs, or major transporters.

In vitro studies demonstrated that, at clinical dose, edaravone and its metabolites are not expected to significantly inhibit cytochrome P450 enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4), UGT1A1, UGT2B7, or transporters (P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, and OCT2) in humans. Edaravone and its metabolites are not expected to induce CYP1A2, CYP2B6, or CYP3A4 at the clinical dose level of RADICAVA.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

The carcinogenic potential of edaravone has not been adequately assessed.

Mutagenesis

Edaravone was negative in *in vitro* (bacterial reverse mutation and Chinese hamster lung chromosomal aberration) and *in vivo* (mouse micronucleus) assays.

Impairment of Fertility

Intravenous administration of edaravone (0, 3, 20, or 200 mg/kg) prior to and throughout mating in males and females and continuing in females to gestation day 7 had no effect on fertility; however, disruption of the estrus cycle and mating behavior was observed at the highest dose tested. No effects on reproductive function were observed at the lower doses, which are up to 3 times the RHD of 60 mg, on a body surface area (mg/m^2) basis.

14 CLINICAL STUDIES

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:

1. 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; described below])
2. Normal respiratory function (defined as percent-predicted forced vital capacity values of [%FVC] ≥ 80%)
3. Definite or Probable ALS based on El Escorial revised criteria
4. 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:

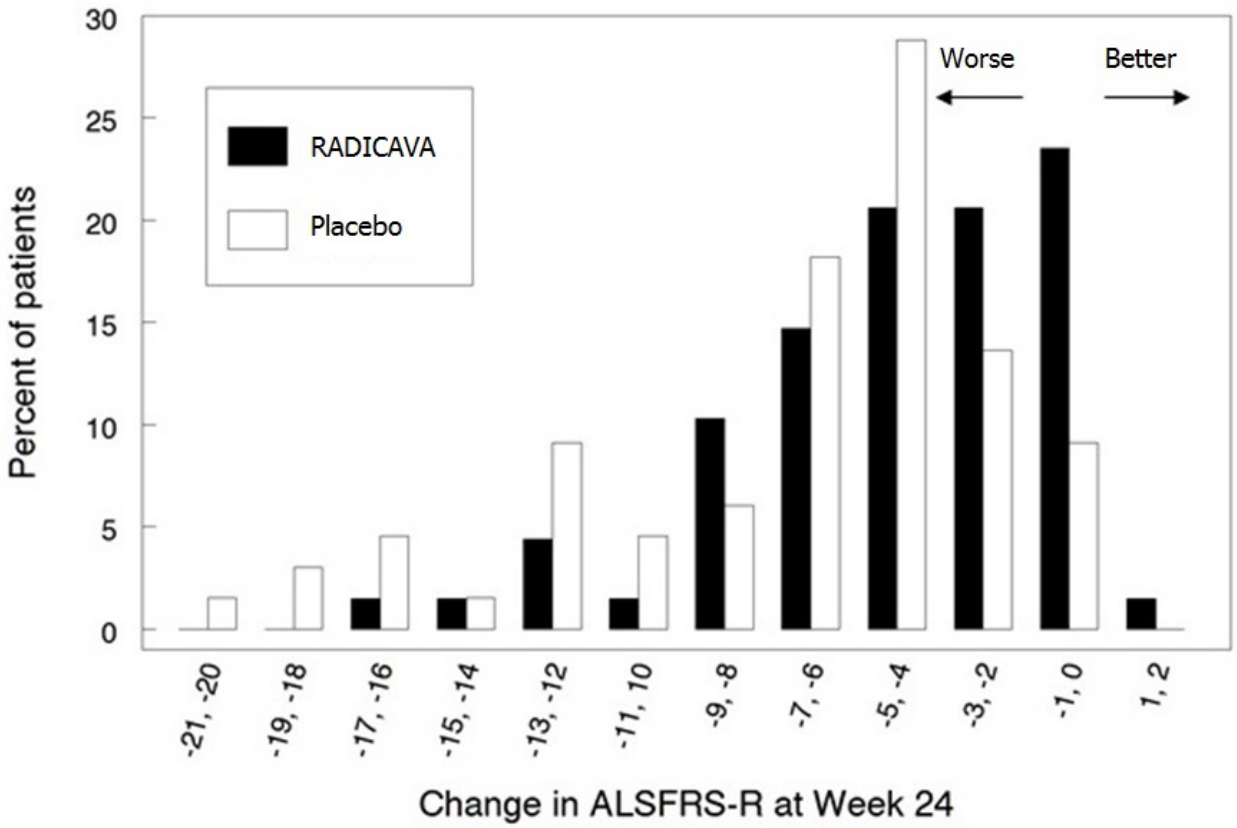
- An initial treatment cycle with daily dosing for 14 days, followed by a 14-day drug-free period (Cycle 1)
- Subsequent treatment cycles with daily dosing for 10 days out of 14-day periods, followed by 14-day drug-free periods (Cycles 2-6).

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 2). The distribution of change in ALSFRS-R scores from baseline to Week 24 by percent of patients is shown in Figure 1.

Table 2: 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



16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

RADICAVA injection is supplied as a 30 mg/100 mL (0.3 mg/mL) clear, colorless, sterile solution for intravenous infusion in single-dose polypropylene bags, each overwrapped with polyvinyl alcohol (PVA) secondary packaging containing an oxygen absorber and oxygen indicator, which should be pink to reflect appropriate oxygen levels *[see Dosage and Administration (2.2) and How Supplied/Storage and Handling (16.2)]*. These are supplied in cartons as listed below.

NDC 70510-2171-1 30 mg/100 mL (0.3 mg/mL) single-dose bag
NDC 70510-2171-2 2 bags per carton

16.2 Storage and Handling

Store at up to 25°C (77°F). Excursions permitted from 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from light. Store in overwrapped package to protect from oxygen degradation until time of use. The oxygen indicator will turn blue or purple if the oxygen has exceeded acceptable levels. Once the overwrap package is opened, use within 24 hours.

17 PATIENT COUNSELING INFORMATION

Advise the patients to read the FDA-approved patient labeling (Patient Information).

Hypersensitivity Reactions

Advise patients to seek immediate medical care if they experience signs or symptoms of a hypersensitivity reaction *[see Warnings and Precautions (5.1)]*.

Sulfite Allergic Reactions

Advise patients about potential for sulfite sensitivity. Inform patients that RADICAVA contains sodium bisulfite, which may cause allergic type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes, and to seek immediate medical care if they experience these signs or symptoms *[see Warnings and Precautions (5.2)]*.

Pregnancy and Breastfeeding

Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during RADICAVA therapy *[see Use in Specific Populations (8.1)]*.

Advise patients to notify their healthcare provider if they intend to breastfeed or are breastfeeding an infant *[see Use in Specific Populations (8.2)]*.

Marketed and distributed by:
Mitsubishi Tanabe Pharma America, Inc., a US subsidiary of Mitsubishi Tanabe Pharma Corporation
525 Washington Blvd., Suite 400,
Jersey City, NJ 07310

65002655 Iss. XX/XXXX

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: 60 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 Mitsubishi Tanabe 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: 3/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

2.1 Dosage Information

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.

2.2 Preparation and Administration Information

RADICAVA is for intravenous infusion only.

Preparation

Do not use if the oxygen indicator has turned blue or purple before opening the package *[see How Supplied/Storage and Handling (16.1, 16.2)]*. Once the overwrap package is opened, use within 24 hours *[see Storage and Handling (16.2)]*.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Administration

Administer a 60 mg dose of RADICAVA injection as an intravenous infusion bag over a total of 60 minutes (infusion rate approximately 1 mg per minute [1.67 mL per minute]).

Promptly discontinue the infusion upon the first observation of any signs or symptoms consistent with a hypersensitivity reaction *[see Warnings and Precautions (5.1, 5.2)]*.

Other medications should not be injected into the infusion bag or mixed with RADICAVA.

3 DOSAGE FORMS AND STRENGTHS

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.

4 CONTRAINDICATIONS

RADICAVA is contraindicated in patients with a history of hypersensitivity to edaravone or any of the inactive ingredients of this product. Hypersensitivity reactions and anaphylactic reactions have occurred *[see Warnings and Precautions (5.1, 5.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Hypersensitivity reactions (redness, wheals, and erythema multiforme) and cases of anaphylaxis (urticaria, decreased blood pressure, and dyspnea) have been reported in spontaneous postmarketing reports with RADICAVA.

Patients should be monitored carefully for hypersensitivity reactions. If hypersensitivity reactions occur, discontinue RADICAVA, treat per standard of care, and monitor until the condition resolves *[see Contraindications (4)]*.

5.2 Sulfite Allergic Reactions

RADICAVA contains 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 people.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Hypersensitivity Reactions *[see Warnings and Precautions (5.1)]*
- Sulfite Allergic Reactions *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In randomized, placebo-controlled trials, 184 ALS patients were administered RADICAVA 60 mg in treatment cycles for 6 months. The population consisted of Japanese patients who had a median age of 60 years (range 29-75) and were 59% male. Most (93%) of these patients were living independently at the time of screening.

Most Common Adverse Reactions Observed During Clinical Studies

Table 1 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 1: 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
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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 *[see Clinical Studies (14)]*.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of RADICAVA outside of the United States. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Skin and subcutaneous tissue disorders: Hypersensitivity reactions and anaphylaxis.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate data on the developmental risk associated with the use of RADICAVA in pregnant women. In animal studies, administration of edaravone to pregnant rats and rabbits resulted in adverse developmental effects (increased mortality, decreased growth, delayed sexual development, and altered behavior) at clinically relevant doses. Most of these effects occurred at doses that were also associated with maternal toxicity (*see Animal Data*).

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. The background risk for major birth defects and miscarriage in patients with ALS is unknown.

Data

Animal Data

In rats, intravenous administration of edaravone (0, 3, 30, or 300 mg/kg/day) throughout the period of organogenesis resulted in reduced fetal weight at all doses. In dams allowed to deliver naturally, offspring weight was reduced at the highest dose tested. Maternal toxicity was also observed at the highest dose tested. There were no adverse effects on reproductive function in the offspring. A no-effect dose for embryofetal developmental toxicity was not identified; the low dose is less than the recommended human dose of 60 mg, on a body surface area (mg/m^2) basis.

In rabbits, intravenous administration of edaravone (0, 3, 20, or 100 mg/kg/day) throughout the period of organogenesis resulted in embryofetal death at the highest dose tested, which was associated with maternal

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The effects on offspring of edaravone (0, 3, 20, or 200 mg/kg/day), administered by intravenous injection to rats from GD 17 throughout lactation, were assessed in two studies. In the first study, offspring mortality was observed at the high dose and increased activity was observed at the mid and high doses. In the second study, there was an increase in stillbirths, offspring mortality, and delayed physical development (vaginal opening) at the highest dose tested. Reproduction function in offspring was not affected in either study. Maternal toxicity was evident in both studies at all but the lowest dose tested. The no-effect dose for developmental toxicity (3 mg/kg/day) is less than the RHD on a mg/m^2 basis.

8.2 Lactation

Risk Summary

There are no data on the presence of edaravone in human milk, the effects on the breastfed infant, or the effects of the drug on milk production. Edaravone and its metabolites are excreted in the milk of lactating rats. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for RADICAVA and any potential adverse effects on the breastfed infant from RADICAVA or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness of RADICAVA in pediatric patients have not been established.

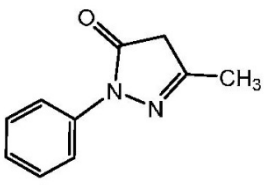
8.5 Geriatric Use

Of the 184 patients with ALS who received RADICAVA in 3 placebo-controlled clinical trials, a total of 53 patients were 65 years of age and older, including 2 patients 75 years of age and older. No overall differences in safety or effectiveness were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

11 DESCRIPTION

The active ingredient in RADICAVA is edaravone, which is a member of the substituted 2-pyrazolin-5-one class. The chemical name of edaravone is [3-methyl-1-phenyl-2-pyrazolin-5-one]. The molecular formula is $C_{10}H_{10}N_2O$ and the molecular weight is 174.20.

The chemical structure is:



Edaravone is a white crystalline powder with a melting point of 129.7°C. It is freely soluble in acetic acid, methanol, or ethanol and slightly soluble in water or diethyl ether.

RADICAVA injection is a clear, colorless liquid provided as a sterile solution.

RADICAVA injection is supplied for intravenous infusion in a polypropylene bag containing 60 mg edaravone in 100 mL isotonic, sterile, aqueous solution, which is further overwrapped with polyvinyl alcohol (PVA) secondary packaging. The overwrapped package also contains an oxygen absorber and oxygen indicator to minimize oxidation. Each bag contains the following inactive ingredients: L-cysteine hydrochloride hydrate (20 mg), sodium bisulfite (40 mg). Sodium chloride is added for isotonicity and phosphoric acid and sodium hydroxide are added to adjust to pH 4.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism by which RADICAVA exerts its therapeutic effect in patients with ALS is unknown.

12.2 Pharmacodynamics

Cardiac Electrophysiology

At a dose 5 times the recommended dose, RADICAVA does not prolong the QT interval to any clinically relevant extent.

12.3 Pharmacokinetics

RADICAVA is administered by IV infusion. The maximum plasma concentration (C_{max}) of edaravone was reached by the end of infusion. There was a trend of more than dose-proportional increase in area under the concentration-time curve (AUC) and Cmax of edaravone. With multiple-dose administration, edaravone does not accumulate in plasma.

Distribution

Edaravone is bound to human serum proteins (92%), mainly to albumin, with no concentration dependence in the range of 0.1 to 50 micromol/L.

Elimination

The mean terminal elimination half-life of edaravone is 4.5 to 6 hours. The half-lives of its metabolites are 2 to 2.8 hours.

Metabolism

Edaravone is metabolized to a sulfate conjugate and a glucuronide conjugate, which are not pharmacologically active. The glucuronide conjugation of edaravone involves multiple uridine diphosphate glucuronosyltransferase (UGT) isoforms (UGT1A6, UGT1A9, UGT2B7, and UGT2B17) in the liver and kidney. In human plasma, edaravone is mainly detected as the sulfate conjugate, which is presumed to be formed by sulfotransferases.

Excretion

In Japanese and Caucasian healthy volunteer studies, edaravone was excreted mainly in the urine as its glucuronide conjugate form (70-90% of the dose). Approximately 5-10% of the dose was recovered in the urine as sulfate conjugate, and only 1% of the dose or less was recovered in the urine as unchanged form. *In vitro*

studies suggest that sulfate conjugate of edaravone is hydrolyzed back to edaravone, which is then converted to the glucuronide conjugate in the human kidney before excretion into the urine.

Specific Populations

Geriatric Patients

No age effect on edaravone pharmacokinetics has been found *[see Use in Specific Populations (8.5)]*.

Patients with Renal Impairment

Following single IV infusion of 30 mg edaravone (half the recommended dosage) over 60 minutes, mean C_{max} and $AUC_{0-\infty}$ of unchanged edaravone were 1.15 and 1.20-fold greater in the subjects with mild renal impairment (eGFR 60-89 mL/min/1.73m^2), and were 1.25 and 1.29-fold greater in the subjects with moderate renal impairment (eGFR 30-59 mL/min/1.73m^2) when compared to subjects with normal renal function, respectively. These changes in exposures are not considered to be clinically significant and therefore no dosage adjustments are necessary in patients with mild to moderate renal impairment. The effects of severe renal impairment on the pharmacokinetics of edaravone have not been studied.

Patients with Hepatic Impairment

Following single IV infusion of 30 mg edaravone (half of the recommended dose) over 60 minutes, mean C_{max} and $AUC_{0-\infty}$ of unchanged edaravone were 1.20 and 1.07-fold greater in the subjects with mild hepatic impairment (Child-Pugh score 5 or 6), were 1.24 and 1.14-fold greater in the subjects with moderate hepatic impairment (Child-Pugh score 7 to 9), and were 1.20 and 1.19-fold greater in the subjects with severe hepatic impairment (Child-Pugh score 10 to 14) when compared to subjects with normal hepatic function, respectively. These changes in exposures are not considered to be clinically significant and therefore no dosage adjustments are necessary in patients with hepatic impairment.

Male and Female Patients

No gender effect on edaravone pharmacokinetics has been found.

Racial or Ethnic Groups

There were no significant racial differences in Cmax and AUC of edaravone between Japanese and Caucasian subjects.

Drug Interaction Studies

The pharmacokinetics of edaravone is not expected to be significantly affected by inhibitors of CYP enzymes, UGTs, or major transporters.

In vitro studies demonstrated that, at clinical dose, edaravone and its metabolites are not expected to significantly inhibit cytochrome P450 enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4), UGT1A1, UGT2B7, or transporters (P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, and OCT2) in humans. Edaravone and its metabolites are not expected to induce CYP1A2, CYP2B6, or CYP3A4 at the clinical dose level of RADICAVA.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

The carcinogenic potential of edaravone has not been adequately assessed.

Mutagenesis

Edaravone was negative in *in vitro* (bacterial reverse mutation and Chinese hamster lung chromosomal aberration) and *in vivo* (mouse micronucleus) assays.

Impairment of Fertility

Intravenous administration of edaravone (0, 3, 20, or 200 mg/kg) prior to and throughout mating in males and females and continuing in females to gestation day 7 had no effect on fertility; however, disruption of the estrus cycle and mating behavior was observed at the highest dose tested. No effects on reproductive function were observed at the lower doses, which are up to 3 times the RHD of 60 mg, on a body surface area (mg/m^2) basis.

14 CLINICAL STUDIES

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:

1. 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; described below])
2. Normal respiratory function (defined as percent-predicted forced vital capacity values of [%FVC] ≥ 80%)
3. Definite or Probable ALS based on El Escorial revised criteria
4. 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:

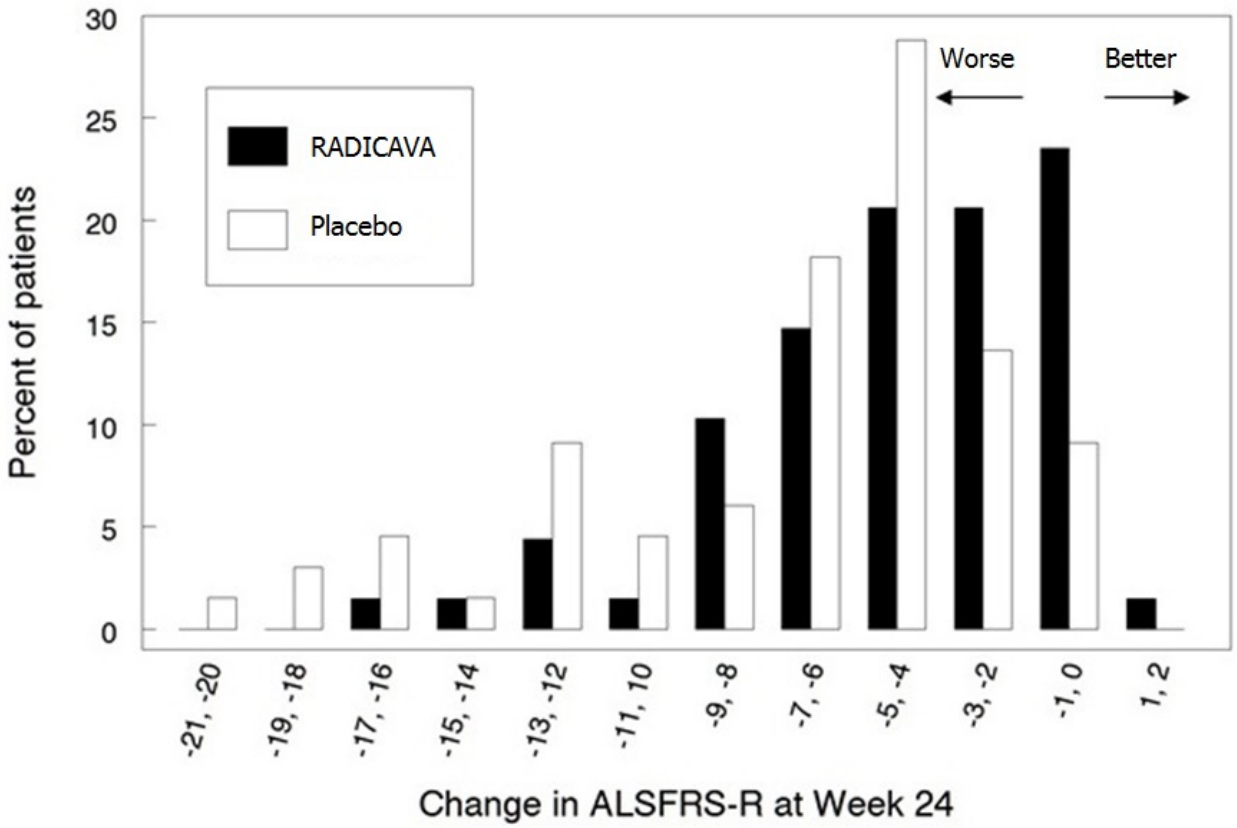
- An initial treatment cycle with daily dosing for 14 days, followed by a 14-day drug-free period (Cycle 1)
- Subsequent treatment cycles with daily dosing for 10 days out of 14-day periods, followed by 14-day drug-free periods (Cycles 2-6).

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 2). The distribution of change in ALSFRS-R scores from baseline to Week 24 by percent of patients is shown in Figure 1.

Table 2: 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



16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

RADICAVA injection is supplied as a 60 mg/100 mL (0.6 mg/mL) clear, colorless, sterile solution for intravenous infusion in a single-dose polypropylene bag, overwrapped with polyvinyl alcohol (PVA) secondary packaging containing an oxygen absorber and oxygen indicator, which should be pink to reflect appropriate oxygen levels *[see Dosage and Administration (2.2) and How Supplied/Storage and Handling (16.2)]*. These are supplied in cartons as listed below.

NDC 70510-2172-0 60 mg/100 mL (0.6 mg/mL) single-dose bag
NDC 70510-2172-1 1 bag per carton

16.2 Storage and Handling

Store at up to 25°C (77°F). Excursions permitted from 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from light. Store in overwrapped package to protect from oxygen degradation until time of use. The oxygen indicator will turn blue or purple if the oxygen has exceeded acceptable levels. Once the overwrap package is opened, use within 24 hours.

17 PATIENT COUNSELING INFORMATION

Advise the patients to read the FDA-approved patient labeling (Patient Information).

Hypersensitivity Reactions

Advise patients to seek immediate medical care if they experience signs or symptoms of a hypersensitivity reaction *[see Warnings and Precautions (5.1)]*.

Sulfite Allergic Reactions

Advise patients about potential for sulfite sensitivity. Inform patients that RADICAVA contains sodium bisulfite, which may cause allergic type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes, and to seek immediate medical care if they experience these signs or symptoms *[see Warnings and Precautions (5.2)]*.

Pregnancy and Breastfeeding

Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during RADICAVA therapy *[see Use in Specific Populations (8.1)]*.

Advise patients to notify their healthcare provider if they intend to breastfeed or are breastfeeding an infant *[see Use in Specific Populations (8.2)]*.

Marketed and distributed by:
Mitsubishi Tanabe Pharma America, Inc., a US subsidiary of Mitsubishi Tanabe Pharma Corporation
525 Washington Blvd., Suite 400,
Jersey City, NJ 07310

65002654 Iss. XX/XXXX

PATIENT INFORMATION

RADICAVA (ra di ká vah)
(edaravone injection)
for intravenous infusion

What is RADICAVA?

RADICAVA is a prescription medicine used to treat people with Amyotrophic Lateral Sclerosis (ALS).
It is not known if RADICAVA is safe and effective in children.

Do not receive RADICAVA if you are allergic to edaravone or any of the ingredients in RADICAVA. See the end of this leaflet for a complete list of ingredients in RADICAVA.

Before you receive RADICAVA, tell your healthcare provider about all of your medical conditions, including if you:

- have asthma.
- are allergic to other medicines.
- are pregnant or plan to become pregnant. It is not known if RADICAVA will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if RADICAVA passes into your breastmilk. You and your healthcare provider should decide if you will receive RADICAVA or breastfeed.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive RADICAVA?

- You will be prescribed RADICAVA by a healthcare provider. RADICAVA will be given by intravenous (IV) infusion into your vein.
- It takes about 1 hour to receive the full dose of RADICAVA.
- Your healthcare provider will tell you how often you will receive RADICAVA.
- Your healthcare provider will monitor you closely during your treatment with RADICAVA.

What are the possible side effects of RADICAVA?

RADICAVA may cause serious side effects including:

1. Hypersensitivity (allergic) reactions. Hypersensitivity reactions have happened in people receiving RADICAVA and can happen after your infusion is finished. Tell your healthcare provider right away or go to the nearest emergency room if you have any of the following symptoms:
   - hives
   - breathing problems
   - itching
   - swelling of the lips, tongue, face
   - dizziness
   - wheezing
   - fainting
2. Sulfite allergic reactions. RADICAVA contains sodium bisulfite, a sulfite that may cause a type of allergic reaction that can be serious and life-threatening. Sodium bisulfite can also cause less severe allergic reactions, for example, asthma episodes, in certain people. Sulfite sensitivity can happen more often in people who have asthma than in people who do not have asthma. Tell your healthcare provider right away or go to the nearest emergency room if you have any of the following symptoms:
   - hives
   - trouble breathing or swallowing
   - itching
   - swelling of the lips, tongue, face
   - dizziness
   - asthma attack (in people with asthma)
   - wheezing
   - fainting

Your healthcare provider will monitor you during treatment to watch for signs and symptoms of all the serious side effects.

The most common side effects of RADICAVA include bruising (contusion), problems walking (gait disturbance), and headache.

These are not all the possible side effects of RADICAVA. Call your healthcare provider for medical advice about side effects. You may report side effects to Mitsubishi Tanabe Pharma America, Inc. at 1-888-292-0058 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

What are the ingredients in RADICAVA?

Active ingredient: edaravone
Inactive ingredients: L-cysteine hydrochloride hydrate, sodium bisulfite, sodium chloride, phosphoric acid, and sodium hydroxide.

Marketed and distributed by: Mitsubishi Tanabe Pharma America, Inc., a US subsidiary of Mitsubishi Tanabe Pharma Corporation, 525 Washington Blvd., Suite 400, Jersey City, NJ 07310

For more information, go to www.Radicava.com or call 1-888-292-0058.

This Patient Information or Medication Guide has been approved by the U.S. Food and Drug Administration Revised or Issued: 11/2018