PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrRADICAVA®

(edaravone oral suspension)

105mg/5mL

and

(edaravone injection)

Solution, 30mg/100mL (0.3mg/mL), intravenous administration

ATC code: N07XX14

Manufactured by:

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

RADICAVA (injection) and RADICAVA (oral suspension) are indicated for the treatment of patients with amyotrophic lateral sclerosis (ALS).

Pediatrics < 18 years of age

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

Geriatrics ≥ 65 years of age

Evidence from clinical studies and experience suggests that use in the geriatric population is not associated with differences in safety or effectiveness (see **7 WARNINGS AND PRECAUTIONS, Special populations, 7.1.4 Geriatrics**).

2 CONTRAINDICATIONS

Edaravone is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container (see **7 WARNINGS AND PRECAUTIONS, Hypersensitivity Reactions)**. For a complete listing, see **6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING**.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Switching from RADICAVA (injection) to RADICAVA (oral suspension)

Patients treated with 60 mg of RADICAVA (injection) may be switched to 105 mg (5 mL) RADICAVA (oral suspension) using the same dosing frequency. Upon switching to RADICAVA (oral suspension), patients should follow RADICAVA (oral suspension) dosing recommendations with regard to food consumption.

4.2 Recommended Dose and Dosage Adjustment

RADICAVA (***oral suspension***)

The recommended dose of RADICAVA (oral suspension) is 105 mg (5 mL) taken orally or via a feeding tube [Nasogastric (NG) tube or Percutaneous Endoscopic Gastrostomy (PEG) tube] 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.

RADICAVA (oral suspension) should be taken in the morning after fasting overnight for at least 8 hours and waiting at least 1 hour before eating or drinking anything except water.

For patients who are unable to fast overnight, the required fasting interval can be shortened depending on the type of meal (see Table 1 for specific fasting conditions, and see **10 CLINICAL PHARMACOLOGY and PATIENT MEDICATION INFORMATION, How to take RADICAVA (oral suspension)**.

Table 1: RADICAVA (oral suspension) Administration Relative to Type of Food Consumption

Type of food/caloric supplement consumed	Fasting time before and after RADICAVA (oral suspension) dose administration with regard to meal type
High-fat meal (800-1000 calories, 50% fat)	8 hours before administration and one hour after administration
Low-fat meal (400-500 calories, 25% fat)	4 hours before administration and one hour after administration
Caloric supplement (250 calories, e.g., protein drink)	2 hours before administration and one hour after administration

RADICAVA (injection)

The recommended dosage of RADICAVA (injection) 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.

No dosage adjustment is required in patients with hepatic impairment or mild and moderate renal impairment (see 10 **CLINICAL PHARMACOLOGY, Special Populations and Conditions, Hepatic Insufficiency; Renal Insufficiency**).

4.4 Administration

RADICAVA (***oral suspension***)

Take RADICAVA (oral suspension) using a 5 mL oral syringe that is provided to the patient with the product. Shake the RADICAVA (oral suspension) bottle vigorously up and down for at least 30 seconds before use.

RADICAVA (oral suspension) can be administered by mouth or via feeding tube. Silicone and polyvinyl chloride (PVC) feeding tubes can be used.

Administration via	Tube Type (Tube diameter)	Flush volume
Nasogastric tube	Silicone, PVC (12-16 Fr)	30 mL
Gastrostomy tube	Silicone, PVC (12-24 Fr)	30 mL

Before and after administration with a feeding tube, flush the tube with 30 mL (1 ounce) of water.

For complete details, refer to the **PATIENT MEDICATION INFORMATION, How to take RADICAVA (oral suspension)** *and* **Instructions for Use***.*

RADICAVA (injection)

Preparation
RADICAVA (injection) is a ready to use sterile solution to be administered by intravenous infusion only.

Do not use if the oxygen indicator has turned blue or purple before opening the package (see **12 SPECIAL HANDLING INSTRUCTIONS**). Once the overwrap package is opened, use within 24 hours (see **12 SPECIAL HANDLING INSTRUCTIONS**).

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if the solution is cloudy, discoloured or contains particles.

Administration
Administer each 60 mg dose of RADICAVA (injection) using two consecutive 30 mg [100 mL per bag] intravenous infusion bags over a total of 60 minutes (infusion rate approximately 1 mg per minute [200 mL per hour]).

Promptly discontinue the infusion upon the first observation of any signs or symptoms consistent with a hypersensitivity reaction (see **7 WARNINGS AND PRECAUTIONS, Hypersensitivity Reactions**).

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

4.5 Missed Dose

In case of a missed dose of RADICAVA (oral suspension), take the next dose as soon as possible after the time of the missed dose. Do not double the daily dose.

5 OVERDOSAGE

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Suspension / 105 mg / 5 mL	L-cysteine hydrochloride hydrate, phosphoric acid, polyvinyl alcohol, simethicone emulsion, sodium bisulfite, sodium hydroxide, sorbitol, xanthan gum, purified water
Intravenous	Sterile Solution / 30 mg / 100 mL	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

6.1 Physical Characteristics

RADICAVA (oral suspension)

RADICAVA (oral suspension) is a white to off-white suspension in a multi-dose child resistant 60 mL amber glass bottle which is supplied as two configurations:

Unit of sale	Package configuration
RADICAVA (oral suspension) Starter Kit	Carton of two (2) inner cartons, each containing of one (1) bottle of 35 mL (105 mg/5 mL dose), two (2) oral dosing syringes and one bottle adapter.
RADICAVA (oral suspension) Kit	One carton of one (1) bottle of 50 mL (105 mg/5 ml dose), two (2) oral dosing syringes and one (1) bottle adapter

RADICAVA (injection)

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.

7 WARNINGS AND PRECAUTIONS

Neurologic

An imbalance of neurologic adverse events, such as gait disturbance, have been reported in placebo-controlled clinical trials (see **8.2 Clinical Trial Adverse Reactions**). Neurological findings were also observed in dogs and monkeys administered edaravone (see **16 NON-CLINICAL TOXICOLOGY,**

Neurotoxicity).

Sensitivity/Resistance

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 (injection). Based on the spontaneous post marketing reports, it appears RADICAVA (injection) can cause anaphylactic reactions.

Patients should be monitored carefully for hypersensitivity reactions. If hypersensitivity reactions occur, discontinue RADICAVA (injection) / RADICAVA (oral suspension), treat per standard of care and monitor until the condition resolves. (see **2 CONTRAINDICATIONS**).

Sulfite Allergic Reactions:

RADICAVA (injection) / RADICAVA (oral suspension) 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 people with asthma.

Skin

A higher incidence of skin-related adverse events was identified in RADICAVA (injection) patients compared to placebo patients in pooled placebo-controlled clinical trials (26% RADICAVA; 19% placebo), including eczema (7% RADICAVA; 2% placebo), dermatitis contact (6% RADICAVA; 3% placebo), rash (4% RADICAVA; 2% placebo), and erythema (3% RADICAVA; 2% placebo). There was also one case of toxic skin eruption on RADICAVA (injection). Based on the clinical trial reports, it appears RADICAVA (injection) can cause skin reactions.

7.1 Special Populations

7.1.1 Pregnant Women

There are no adequate data on the developmental risk associated with the use of RADICAVA (injection) / RADICAVA (oral suspension) 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 behaviour) at clinically relevant doses. Most of these effects occurred at doses that were also associated with maternal toxicity (see **16 NON-CLINICAL TOXICOLOGY, Reproduction**).

7.1.2 Breast-feeding

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. Precaution should be exercised because edaravone can be excreted in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for RADICAVA (injection) / RADICAVA (oral suspension) and any potential adverse effects on the breastfed infant from RADICAVA (injection) / RADICAVA (oral suspension).

7.1.3 Pediatrics < 18 years of age

Safety and effectiveness of RADICAVA (injection) / RADICAVA (oral suspension) in pediatric patients have not been established.

7.1.4 Geriatrics ≥ 65 years of age

Of the 184 patients with ALS who received RADICAVA (injection) 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.

Of the 185 patients with ALS who received RADICAVA (oral suspension) in an open label clinical trial, a total of 65 patients were 65 years of age and older, including 6 patients 75 years of age and older.

No overall differences in safety or effectiveness were observed between these patients and younger patients.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most common adverse reactions with RADICAVA in pooled placebo-controlled trials were contusion, gait disturbance, and headache.

Discontinuation due to an adverse event occurred in 2% (4/184) of RADICAVA (injection) patients vs 5% (10/184) of patients on placebo in pooled placebo-controlled trials. Discontinuation due to an adverse event occurred in 6% (11/185) of RADICAVA (oral suspension) patients in an open-label safety trial.

Overall, 4 patients (2%) on RADICAVA (injection) and 2 (1%) patients on placebo died during pooled placebo-controlled trials. All deaths in the trials were from respiratory disorder/failure. Six (3%) patients on RADICAVA (oral suspension) died during an open-label safety trial. The majority of deaths in the trial were from respiratory failure including 3 patients on RADICAVA (oral suspension).

8.2 Clinical Trial Adverse Reactions:

RADICAVA (injection)

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials, therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real world use.

The safety profile of RADICAVA (injection) was compared to placebo in 3 clinical trials:

- Two double-blind, randomized, placebo-controlled studies in patients with grade 1-2 ALS (Japanese severity classification). From these 2 studies, 171 patients received RADICAVA and 160 of the 171 patients completed the placebo-controlled period (6 months).
- One double-blind, randomized, placebo-controlled study in 25 patients with grade 3 ALS. Thirteen patients received RADICAVA and 9 of the 13 patients completed the 6-month trial.

In these double-blind randomized, placebo-controlled trials, patients were administered RADICAVA (injection) 60 mg (n=184) or placebo (n=184) in treatment cycles for 6 months of which 169 RADICAVA (injection) and 162 patients on placebo completed 6 months of treatment. 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.

The safety profile of RADICAVA (oral suspension) was evaluated in an open-label safety study in ALS patients (n=185). Of the 185 patients that received RADICAVA (oral suspension), 160 patients completed 6 months (interim analysis). The population consisted of White (58%), Japanese (35%), Asian – not Japanese (2%), and Black (2%) patients. The median age was 61 years (range 22-75) and 64% of patients were male.

Most Common Adverse Reactions Observed During Clinical Trials

Table 3: Adverse Reactions from Pooled Placebo-Controlled Trials[a] that Occurred in ≥2% of patients treated with RADICAVA (injection) and ≥2% More Frequently than in Placebo Patients

Adverse Reaction	**RADICAVA (injection) (N=184) n (%)**	**Placebo (N=184) n (%)**
Contusion	27 (15%)	16 (9%)
Gait disturbance	23 (13%)	17 (9%)
Headache	18 (10%)	11 (6%)
Dermatitis	14 (8%)	10 (5%)
Eczema	12 (7%)	7 (4%)
Respiratory failure, respiratory disorder, hypoxia	11 (6%)	7 (4%)
Glycosuria	7 (4%)	3 (2%)
Tinea infection	7 (4%)	4 (2%)

[a] Pooled placebo-controlled studies include two additional studies [MCI186-16 (102 RADICAVA patients and 104 placebo patients) and MCI186-18 (13 RADICAVA patients and 12 placebo patients)], all using the same treatment regimen (see **14 CLINICAL TRIALS**).

Table 4: Adverse Reactions from an Open-Label Safety Study that Occurred in ≥2% of patients treated with RADICAVA (oral suspension)

Adverse Reaction	RADICAVA (oral suspension) (N=185) n (%)
Fall, Contusion, Ligament sprain, Skin abrasion, Skin laceration	40 (22%)
Muscular weakness	30 (16%)
Musculoskeletal pain	24 (13%)
Fatigue, Asthenia	18 (10%)
Constipation	13 (7%)
Headache	11 (6%)
Dyspnoea	10 (5%)
Insomnia	9 (5%)
Salivary hypersecretion	9 (5%)
Upper respiratory tract infection	9 (5%)
Abdominal pain	8 (4%)
Dysphagia	8 (4%)
Depression	7 (4%)
Dizziness	7 (4%)
Muscle spasms	7 (4%)
Cough	6 (3%)
Nausea	6 (3%)
Peripheral swelling	6 (3%)
Weight decreased	6 (3%)
Amyotrophic lateral sclerosis	5 (3%)
Anxiety	5 (3%)
Arthralgia	5 (3%)
Balance disorder	5 (3%)
COVID-19	5 (3%)

Decreased appetite	5 (3%)
Hypertension	5 (3%)
Musculoskeletal stiffness	5 (3%)
Rash	5 (3%)
Diarrhoea	4 (2%)
Dry skin	4 (2%)
Respiratory failure	4 (2%)

8.3 Less Common Clinical Trial Adverse Reactions

List of less common adverse reactions reported in ≤ 2% of RADICAVA patients and that occurred at least 1% more frequently than in placebo patients, in pooled placebo-controlled trials.

- **Gastrointestinal disorders:** Abdominal pain, Abdominal pain upper, Gastritis
- **General disorders and administration site conditions:** Gait inability, Chest pain
- **Hepatobiliary disorders:** Hepatic steatosis, Liver disorder
- **Infections and infestations:** Tinea infection
- **Injury, poisoning and procedural complications:** Procedural pain
- **Musculoskeletal and connective tissue disorders:** Neck pain

Abnormal Laboratory Findings
In an open-label safety trial, CK elevation >3x ULN was noted in 16 (10%) RADICAVA oral suspension patients.

8.5 Post-Market Adverse Reactions – RADICAVA (injection)

The following adverse reactions have been identified during post-approval use of RADICAVA (injection). 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.

- *Hypersensitivity reactions and anaphylaxis*
- *Skin and subcutaneous tissue disorders*

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

The pharmacokinetics of edaravone are not expected to be significantly affected by inhibitors of cytochrome P450 (CYP) enzymes, UGT conjugating enzymes, or major transporters. There is little potential for clinically significant interactions with drugs cleared by either CYP3A4 or the drug transporters BCRP or OAT3 at the recommended clinical dose of edaravone (see Table 5).

9.4 Drug-Drug Interactions

The drugs listed in this table are based on drug interaction studies.

Table 5: Established Drug-Drug Interactions

Edaravone	Source of Evidence	Effect	Clinical Comment
Sildenafil (CYP3A4 substrate)	CT	Simultaneous oral administration of edaravone did not result in clinically significant changes in the Cmax and AUC of sildenafil.	None
Rosuvastatin (BCRP substrate)	CT	Simultaneous oral administration of edaravone did not result in clinically significant changes in the Cmax and AUC of rosuvastatin.	None
Furosemide (OAT3 substrate)	CT	Simultaneous oral administration of edaravone did not result in clinically significant changes in the Cmax and AUC of furosemide.	None
Legend: CT = Clinical Trial			

In vitro studies demonstrated that, at the approved clinical dose, edaravone and its metabolites are not expected to significantly inhibit CYP enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A), conjugating enzymes UGT1A1 and UGT2B7, or transporters (p-gp, OATP1B1, OATP1B3, OAT1, OCT2, MATE1 and MATE2-K) in humans. Edaravone and its metabolites are not expected to induce CYP1A2 or CYP2B6, at the recommended clinical dose of edaravone.

9.5 Drug-Food Interactions

In order to maximize exposure, RADICAVA (oral suspension) should be taken in the morning after fasting overnight for at least 8 hours and waiting at least 1 hour after administration before eating or drinking anything except water. For patients who are unable to fast overnight, the required fasting interval can be shortened depending on the type of meal.
Please refer to 4 **DOSAGE AND ADMINISTRATION, 10 CLINICAL PHARMACOLOGY, Pharmacokinetics,** and the **PATIENT MEDICATION INFORMATION** for dosing details for oral administration.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

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

10.2 Pharmacodynamics

Cardiac Electrophysiology
At exposures approximately 5 times higher than that of the recommended dose of RADICAVA (injection) and RADICAVA (oral suspension), edaravone did not prolong the QT interval to any clinically relevant extent in healthy Japanese male subjects.

10.3 Pharmacokinetics

A pharmacokinetic single-dose study of RADICAVA (injection) and RADICAVA (oral suspension) was performed in healthy adult subjects under fasting conditions.

Table 6 provides a description of this study, along with the comparative pharmacokinetic parameters for both oral and intravenous administration. RADICAVA (oral suspension) administered at the dose of 105 mg demonstrated an equivalent AUC compared to RADICAVA (injection) at a dose of 60 mg i.v. for 60 minutes, and a Cmax not less than that of RADICAVA (injection). RADICAVA (oral suspension) demonstrated similar pharmacokinetics following administration via feeding tubes and oral administration.

Table 6: Study Description and Summary of Pharmacokinetic Parameters of Unchanged Edaravone for Single Doses of 105 mg/mL Oral Suspension and 60 mg/60 min IV Formulation in Healthy Adult Subjects

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (yrs) (Range)	Sex (%)
MCI186-J03	Single-dose, randomized, open-label, crossover study	Oral suspension: 105 mg IV: 60 mg/60 min.	42	33.1 (20 – 45)	Male (66.7%) Female (33.3%)

Single dose Treatment	Plasma PK Parameters	C_{max} ng/mL	T_{max}[a] (h)	AUC_{0-t} ng*h/mL	$AUC_{0-\infty}$ ng*h/mL	$T_{1/2}$ (h)	CL (L/h)	F (%)
Oral (N=42)	Mean CV%	1656 44.3	0.50 0.25, 0.75	1743 30.7	1762 30.6	9.75 86.9	67.9[b] 44.4	57.3 21.9
IV (N=42)	Mean CV%	1253 18.3	1.00 0.98, 1.02	1720 18.9	1736 19.1	8.82 94.4	35.9 20.9	- -

[a] Median and range [b] CL/F CV: Coefficient of variation

Absorption:

RADICAVA (oral suspension):

RADICAVA (oral suspension) is administered orally or via feeding tube. Edaravone is absorbed rapidly, with median peak concentrations occurring at approximately 0.5 hour (range: 0.25 to 0.75 hours) after fasted oral administration. The absolute bioavailability is about 57% because of a first pass effect when comparing 105 mg edaravone oral suspension and 60 mg edaravone intravenous formulation.

The maximum plasma concentration (C_{max}) and area under the concentration-time curve (AUC) of edaravone increases more than dose-proportional over the dose range of 30 to 300 mg. Edaravone does not accumulate in plasma with once-daily administration.

Effect of Food on Absorption:

Following oral administration of a developmental edaravone oral suspension to healthy subjects, the

C_{max} decreased by 83% and the AUC_T decreased by 61% with a high-fat meal (800 – 1000 calories, 50% fat) compared to fasted conditions. Following oral administration of edaravone 4 hours after a high-fat meal, the C_{max} and AUC_T decreased by 48% and 26%, respectively. Following oral administration of edaravone 2 hours after low-fat meal (400 – 500 calories, 25% fat), the C_{max} and AUC_T decreased by 46% and 20%, respectively.

Oral administration of an edaravone oral suspension to healthy subjects 8 hours after a high-fat meal, 4 hours after a low-fat meal or 2 hours after caloric supplement (250 calories, e.g., a protein drink), did not significantly impact the rate (C_{max}) and extent (AUC_T) of edaravone exposure. Administration of an oral suspension of edaravone 1 hour before a high-fat, high-calorie meal resulted in 34% and 16% decreases in the C_{max} and AUC_T, respectively; however, the decrease in exposure is not considered to be clinically significant.

In order to maximize exposure, RADICAVA (oral suspension) should be taken in the morning after fasting overnight for at least 8 hours and waiting at least 1 hour after administration before eating or drinking anything except water. For patients who are unable to fast overnight, the required fasting interval can be shortened depending on the type of meal (see **4 DOSAGE AND ADMINISTRATION** and the **PATIENT MEDICATION INFORMATION** for dosing details).

RADICAVA (injection)

Following i.v. administration, the maximum plasma concentration (C_{max}) of edaravone was reached by the end of infusion. There was a trend of a more than dose-proportional increase in area under the concentration-time curve (AUC) and C_{max} 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. Edaravone has a mean volume of distribution of 63.1 L following intravenous administration, suggesting substantial tissue distribution. Edaravone has an apparent volume of distribution of 164 L following oral administration.

Metabolism:

Edaravone is metabolized to a sulfate conjugate and a glucuronide conjugate, which are not pharmacologically active. Multiple uridine diphosphate glucuronosyltransferase (UGT) isoforms (UGT1A1, UGT1A6, UGT1A7, UGT1A8, UGT1A9, UGT1A10, UGT2B7, and UGT2B17) are involved in the glucuronidation of edaravone. In human plasma, edaravone is mainly detected as the sulfate conjugate, which is presumed to be formed by sulfotransferases. RADICAVA (oral suspension) results in 1.3- and 1.7-fold higher exposures for both sulfate and glucuronide metabolites, respectively, when compared to RADICAVA (injection) because of first pass metabolism.

Elimination:

Edaravone was excreted mainly in the urine as its glucuronide conjugate form (60-80% of the dose up to 48 hours). Approximately 6-8% of the dose was recovered in the urine as the sulfate conjugate, and <1% of the dose was recovered in the urine as the unchanged drug. In vitro studies suggest that the

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. The mean terminal elimination half-life of edaravone is approximately 9 hours. The half-lives of its metabolites are 3 to 6 hours. The total clearance of edaravone is estimated to be 35.9 L/h following intravenous administration, and the apparent total clearance of edaravone is estimated to be 67.9L/h following oral administration.

Special Populations and Conditions

- **Pediatrics:** Safety and effectiveness of RADICAVA (injection) and RADICAVA (oral suspension) in pediatric patients have not been established.
- **Geriatrics:** No age effect on edaravone pharmacokinetics has been found.
- **Sex:** No gender effect on edaravone pharmacokinetics has been found.
- **Pregnancy and Breast-feeding:** There are no adequate data on the developmental risk associated with the use of RADICAVA (oral suspension) and RADICAVA (injection) in pregnant women. 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.
- **Ethnic Origin:** There were no significant racial differences in C_{max} and AUC of edaravone between Japanese and Caucasian subjects.
- **Hepatic Insufficiency:** Following a single IV infusion of 30 mg edaravone (half the recommended dose of RADICAVA (injection)) over 60 minutes, the mean C_{max} and $AUC_{0-\infty}$ of unchanged edaravone were 1.20 and 1.17-fold greater in the subjects with mild hepatic impairment (Child-Pugh score of 5 or 6), 1.24 and 1.25-fold greater in the subjects with moderate hepatic impairment (Child-Pugh score of 7 to 9), and 1.20 and 1.19-fold greater in the subjects severe hepatic impairment (Child-Pugh score of 10 to 14) when compared to subjects with normal hepatic function, respectively. These changes in exposures are not considered to be clinically significant. No dosage adjustments are necessary in patients with hepatic impairment.
- **Renal Insufficiency:** Following a single IV infusion of 30 mg edaravone (half the recommended dosage of RADICAVA (injection)) over 60 minutes, the 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 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. 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.

11 STORAGE, STABILITY AND DISPOSAL

RADICAVA (oral suspension)

Pharmacy

Store RADICAVA (oral suspension) refrigerated between 2°C – 8°C and protect from light. Do not freeze. Store upright.

Patient
Store RADICAVA (oral suspension) upright at room temperature between 20°C–25°C. Protect from light.

Dispose of any RADICAVA (oral suspension) that is not used within 15 days after opening the bottle or within the 30 days (if unopened) from the date of shipment indicated on the carton label, which ever happens first.

RADICAVA (oral suspension) is supplied in cartons as listed below.

- RADICAVA (oral suspension) Starter Kit (14-day treatment cycle), including two (2) inner cartons, each containing one (1) bottle of 735 mg/35mL (105 mg/5 mL dose), two oral dosing syringes and one bottle adapter.
- RADICAVA (oral suspension) Kit (10-day treatment cycle), including one (1) bottle of 1050 mg/50 mL (105 mg/5 ml dose) with two oral dosing syringes and one bottle adapter.

RADICAVA (injection)

Store between 15°C - 30°C. Protect from light. Keep out of the reach and sight of children.
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 (See **12 SPECIAL HANDLING INSTRUCTIONS**). These are supplied in cartons as listed below.

02475472 30 mg/100 mL (0.3 mg/mL) single-dose bag
02475472 2 bags per carton

Incompatibilities
No incompatibilities between RADICAVA (injection) and commercially available infusion set materials have been observed.

12 SPECIAL HANDLING INSTRUCTIONS

RADICAVA (oral suspension)
Keep out of the sight and reach of children.
Discard 15 days after opening bottle or if unopened 30 days from date of shipment indicated on the carton pharmacy label.

RADICAVA (injection)
Store in overwrapped package to protect from oxygen degradation until time of use. The oxygen indicator in the secondary packaging should remain pink; if oxygen levels have exceeded acceptable levels, the indicator will turn blue or purple. Once the overwrap package is opened, use within 24 hours.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

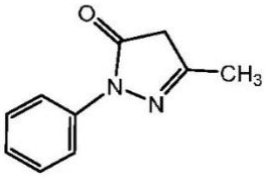
Drug Substance

Proper/Common names: Edaravone

Chemical name: edaravone

Molecular formula and molecular mass: The molecular formula is $C_{10}H_{10}N_2O$ and the molecular mass is 174.20.

Structural formula:



Physicochemical properties: 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.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

The efficacy of RADICAVA (oral suspension) is based on the comparative bioavailability study of RADICAVA (injection) and RADICAVA (oral suspension) in healthy subjects, demonstrating comparable exposure with both formulations (see **10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics**).

The efficacy of RADICAVA (injection) was established in a 6-month, randomized, placebo-controlled, double-blind study of intravenous RADICAVA (injection) (see **Table 7**).

Table 7: Summary of patient demographics for clinical trial of RADICAVA (injection) in Amyotrophic Lateral Sclerosis (ALS)

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
MCI186-19	Randomized, placebo-controlled, double-blind study	Intravenous infusion of 60 mg over 60 minutes 6 months (6 cycles) treatment	RADICAVA (69) Placebo (68)	60.5 (30-75)	Male (55%) Female (45%)

14.2 Study Results

- Study MCI186-19

Study MCT1186-19 was 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 (injection) 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 (injection) was administered as an intravenous infusion of 60 mg given over a 60-minute period according to the following schedule:

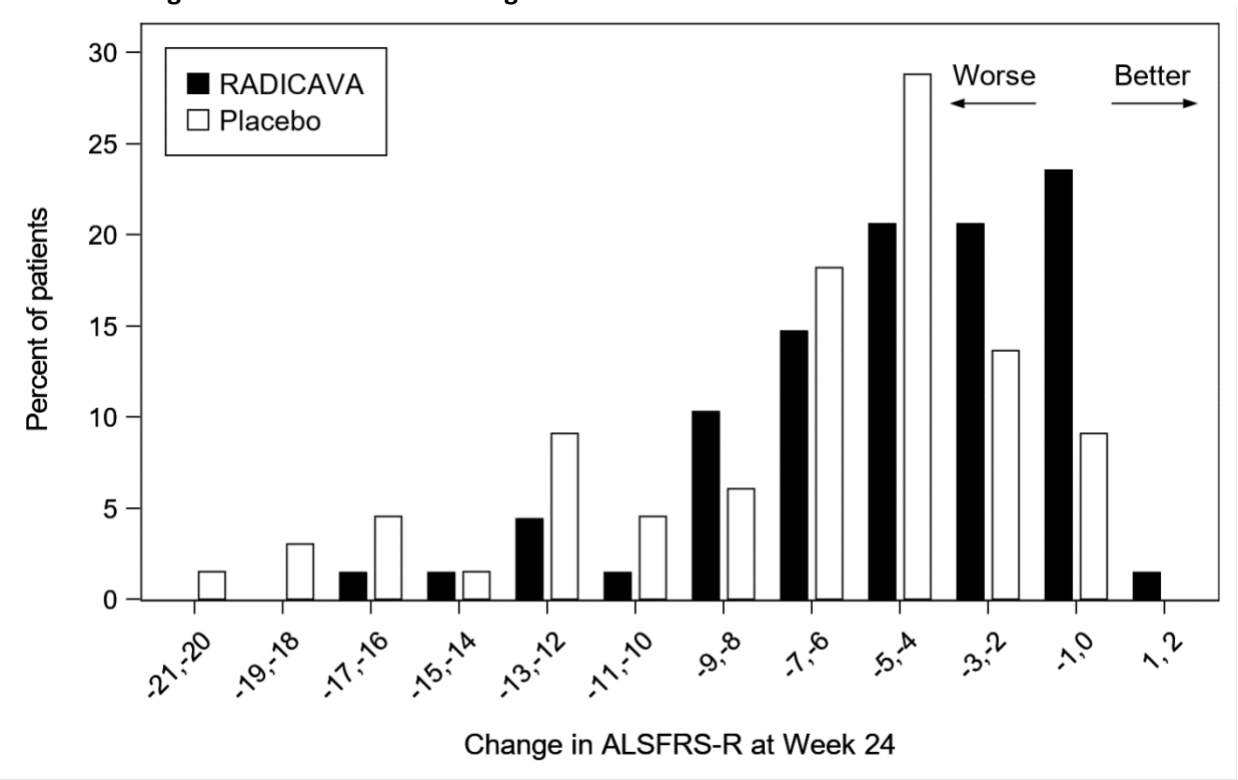
- An initial treatment cycle with daily dosing for 14 days, followed by a 14-day drug-free period (Cycle 1)
- Subsequent treatment cycles with daily dosing for 10 days out of 14-day periods, followed by 14-day drug-free periods (Cycles 2-6).

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

Table 8: 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 (injection) 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



15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

Neurotoxicity:

Neurotoxic changes following 24-hour continuous IV infusion (60-1000 mg/kg/day) in monkeys and dogs for 14-28 days and following oral administration of edaravone (100-300 mg/kg/day) in dogs for 39 weeks were characterized by white matter vacuolation in the spinal cord and vacuolation and nerve fiber atrophy in the sciatic nerve. The microscopic findings were accompanied by gait abnormalities, loss of patellar reflex, and inability to rise. Plasma edaravone exposure (AUC) at the no observed adverse effect level (NOAEL) for neurotoxicity (oral 30 mg/kg/day) was approximately 2 times greater than the exposure in humans at the recommended human dose (RHD) of RADICAVA (oral suspension) (105 mg/day).

Genotoxicity:

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

Carcinogenicity:

In a 26-week carcinogenicity study, in male and female CB6F1-Tg rasH2 mice, edaravone showed no indication of carcinogenic potential following repeated daily oral dosing of up to 350 mg/kg/day. In SD rats, edaravone showed no indication of carcinogenic potential following repeated daily oral dosing up to 200 mg/kg/day in males for 104 weeks and up to 250 mg/kg/day in females for 92 weeks.

Reproductive and Developmental Toxicology:

Impairment of Fertility

Intravenous administration of edaravone (0, 3, 20, or 200 mg/kg) prior to and throughout mating in male and female rats 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 were approximately 2 to 3 times the RHD for RADICAVA (injection) 60 mg or RADICAVA (oral suspension) 105 mg, on a body surface area (mg/m^2) basis.

Reproduction

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 was less than the RHD for RADICAVA (injection) 60 mg and RADICAVA (oral suspension) 105 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 was approximately 4 to 6 times the RHD for RADICAVA (injection) 60 mg or RADICAVA (oral suspension) 105 mg 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 highest 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) was less than the RHD for RADICAVA (injection) 60 mg and RADICAVA (oral suspension) 105 mg on a mg/m^2 basis.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
RADICAVA® (ra di ká vah)
(edaravone)
for intravenous infusion

Read this carefully before you start taking **Radicava (injection)** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Radicava**.

What is Radicava (injection) used for?

- RADICAVA (injection) is a prescription medicine used to treat patients with amyotrophic lateral sclerosis (ALS).

How does Radicava (injection) work?
The exact way RADICAVA (injection) works in the body in patients with ALS is unknown. RADICAVA (injection) slows the loss of physical function including speech, swallowing, handwriting, cutting food and others.

What are the ingredients in Radicava (injection)?
Medicinal ingredient: edaravone
Non-medicinal ingredients: L-cysteine hydrochloride hydrate, sodium bisulfite, sodium chloride, phosphoric acid, and sodium hydroxide, water for injection.

Radicava (injection) comes in the following dosage forms:
Sterile solution, 30 mg/100 mL

Do not use Radicava (injection) if:

- You are allergic to edaravone or any of the ingredients in RADICAVA, including sulfites. See **What are the ingredients in RADICAVA (injection)?** for a complete list of ingredients in RADICAVA (injection).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Radicava (injection). Talk about any health conditions or problems you may have, including if you:

- have asthma
- are allergic to other medicines or sulfites.
- 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 will pass into your breastmilk. You and your healthcare professional should decide if you will receive RADICAVA or breastfeed.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Radicava (injection):

Interactions with other drugs have not been established.

How to take Radicava (injection):

- RADICAVA (injection) will be given by intravenous (IV) infusion into your vein.
- It takes about 1 hour to receive the full dose of RADICAVA (injection).
- You will be closely monitored during your treatment with RADICAVA (injection).

Usual dose:

Your healthcare professional will determine your dose.

- The usual dose for RADICAVA (injection) is:
    - an initial treatment cycle with a daily dose of RADICAVA (injection) for 14 days, followed by a 14-day drug-free period.
    - follow-up treatment cycles where you will receive RADICAVA (injection) for 10 out of 14 days followed by a 14-day drug-free period.

Overdose:

If you think you, or a person you are caring for, have taken too much Radicava, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

N/A

What are possible side effects from using Radicava (injection)?

These are not all the possible side effects you may feel when taking RADICAVA (injection). If you experience any side effects not listed here, contact your healthcare professional.

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

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
UNKNOWN			

Hypersensitivity (allergic) reactions: • Hives • Breathing problems • Itching • Swelling of the lips, tongue, face • Dizziness • Wheezing • Fainting			X
Sulfite allergic reactions: • Asthma attack (in people with asthma) • Any of the above			X

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.htm) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

RADICAVA (injection) will be stored between 15 - 30°C and protected from light.

Keep out of reach and sight of children.

If you want more information about Radicava (injection):

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website [www.radicava.ca], or by calling 1-888-212-2253.

This leaflet was prepared by Mitsubishi Tanabe Pharma America, Inc., a US subsidiary of Mitsubishi Tanabe Pharma Corporation.

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Last Revised: NOV 08, 2022

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

RADICAVA® (ra di ká vah)

(edaravone oral suspension)

Read this carefully before you start taking **RADICAVA (oral suspension)** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **RADICAVA (oral suspension)**.

What is Radicava (oral suspension) used for?

RADICAVA (oral suspension) is a prescription medicine used to treat patients with amyotrophic lateral sclerosis (ALS).

It is not known if RADICAVA (oral suspension) is safe and effective in children.

How does Radicava (oral suspension) work?

The exact way RADICAVA (oral suspension) works in the body of patients with ALS is unknown. It slows the loss of physical function including speech, swallowing, handwriting, cutting food and other functions.

What are the ingredients in Radicava (oral suspension)?

Medicinal ingredient: edaravone

Non-medicinal ingredients: L-cysteine hydrochloride hydrate, phosphoric acid, polyvinyl alcohol, simethicone emulsion, sodium bisulfite, sodium hydroxide, sorbitol, water, xanthan gum

Radicava (oral suspension) comes in the following dosage forms:

Oral suspension 105 mg/5 mL

Do not use Radicava (oral suspension) if:

- You are allergic to edaravone or any of the ingredients in RADICAVA (oral suspension), including sulfites. See **What are the ingredients in RADICAVA (oral suspension)** for a complete list of ingredients in RADICAVA (oral suspension).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Radicava (oral suspension). Talk about any health conditions or problems you may have, including if you:

- have asthma
- are allergic to other medicines or sulfites.
- are pregnant or plan to become pregnant. It is not known if RADICAVA (oral suspension) will harm your unborn baby.

- are breastfeeding or plan to breastfeed. It is not known if RADICAVA (oral suspension) passes into your breastmilk. You and your healthcare professional should decide if you will receive RADICAVA (oral suspension) or breastfeed.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Radicava (oral suspension):

Interactions with other drugs have not been established.

How to take Radicava (oral suspension):

- Before using the RADICAVA (oral suspension) suspension, read the detailed Instructions for Use on how to take it at the end of the Patient Medication Information for Radicava (oral suspension).
- Take RADICAVA (oral suspension)
    - as prescribed by your healthcare professional
    - by mouth or using a feeding tube
    - in the morning on an empty stomach after not eating overnight for at least 8 hours.
        - If you are unable to fast overnight for 8 hours before your morning dose, you can reduce the fasting time to:
            - 4 hours if you eat a low-fat meal (400-500 calories, 25% fat)

            or
            - 2 hours if you take a calorie supplement (250 calories, e.g. Protein Drink).
        - wait at least 1 hour after taking RADICAVA (oral suspension) before eating or drinking anything except water.

Usual dose:
Adults: Take 105 mg (5 mL) by mouth or via a feeding tube according to the following schedule:

- For the first treatment cycle of 14 days with the Starter Kit, you will take RADICAVA (oral suspension) every day for 14 days, followed by 14 days without the medicine.
- For the cycles after the first treatment cycle, you will take RADICAVA (oral suspension) daily for 10 out of 14 days, followed by 14 days without the medicine

Overdose:

If you think you, or a person you are caring for, have taken too much Radicava (oral suspension), contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

- If you miss a dose of RADICAVA (oral suspension), take it as soon as possible if it is the same day

- Never take two doses of RADICAVA (oral suspension) on the same day to make up for a missed dose.

What are possible side effects from using Radicava (oral suspension)?

These are not all the possible side effects you may feel when taking RADICAVA (oral suspension). If you experience any side effects not listed here, contact your healthcare professional.

The most common side effects reported with RADICAVA (oral suspension) were fatigue, dizziness and headache.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
RARE			
Hypersensitivity (allergic) reactions: • Hives • Breathing problems • Itching • Swelling of the lips, tongue, face • Dizziness • Wheezing • Fainting			X
Sulfite allergic reactions: • Asthma attack (in people with asthma) • Any of the above			X

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.htm) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- **Pharmacy**: Store RADICAVA (oral suspension) refrigerated between 2 – 8°C and protect from light. Do not freeze. Store upright.

- **Patients**:
  - Store upright at room temperature between 20 – 25°C. Protect from light.
  - Discard 15 days after opening bottle or if unopened 30 days from date of shipment indicated on the carton pharmacy label

See detailed storage information on How to store RADICAVA (oral suspension) in the Instructions for Use at the end of the Patient Medication Information

Keep RADICAVA (oral suspension) and all medicines out of the reach and sight of children.

If you want more information about Radicava (oral suspension):

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website [www.radicava.ca], or by calling 1-888-212-2253.

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Last Revised <NOV-08-2022>

INSTRUCTIONS FOR USE

RADICAVA® (ra di ká vah)

oral suspension

Read this "Instructions for Use" before you take RADICAVA (oral suspension) for the first time and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare professional about your medical condition or treatment.

Important information about measuring RADICAVA (oral suspension): Always measure your prescribed dose of RADICAVA (oral suspension) using the oral syringe provided. Ask your healthcare professional who provided the medicine any question you have about how to measure your prescribed dose. **If you miss a dose of RADICAVA (oral suspension), take it as soon as possible if it is the same day. Never take two doses of RADICAVA (oral suspension) on the same day to make up for a missed dose. Do not take a dose of RADICAVA (oral suspension) on days 15 through day 28.**

How to prepare RADICAVA (oral suspension): Keep this "Instructions for Use" handy when preparing the treatment.

- If your healthcare provider prescribes Starter Kit, you will receive 2 bottles of RADICAVA (oral suspension). Each bottle will contain 35 mL of RADICAVA (oral suspension) for a total of 70 mL to be used for your first treatment cycle of 14 days. **Only open the second bottle when you have finished the first bottle.**
- If you were not prescribed the Starter Kit, for each treatment cycle you will receive 1 bottle of RADICAVA (oral suspension) that contains a total of 50 mL of RADICAVA (oral suspension) to be used for 10 days out of 14 day periods.
- Only use the bottle adapter and the two reusable 5mL oral syringes provided with the bottle.

How to store RADICAVA (oral suspension):

- Store upright at room temperature between 20 - 25°C. Protect from light.
- Discard 15 days after opening bottle or if unopened 30 days from date of shipment indicated on the carton pharmacy label.
- **Opening the bottle:**
    - When you open the bottle of RADICAVA (oral suspension) for the first use, write the date you open the bottle on the bottle label.
    - After opening the bottle of RADICAVA (oral suspension), use within 15 days.

- Once a bottle of RADICAVA (oral suspension) has been opened and used, a white crust may form on the neck or on the side of the bottle. This is due to normal use and you can continue to use RADICAVA (oral suspension) as prescribed.
- **Keep bottle tightly closed between each use. Protect from light.**

- **Throw away (discard) any RADICAVA (oral suspension) that is not used within 15 days after opening the bottle or if unopened within the 30 days from the date of shipment shown on the carton pharmacy label, whichever happens first.** Ask your healthcare professional how to properly throw away (discard) RADICAVA (oral suspension) you are no longer able to use.
- **Keep RADICAVA (oral suspension) and all medicines out of the reach of children.**

Each RADICAVA (oral suspension) carton contains:

- 1 RADICAVA (oral suspension) bottle
- 1 bottle adapter
- 2 (5 mL) reusable oral syringes

Use a new 5 mL oral syringe and bottle adapter when using a new bottle of RADICAVA (oral suspension) (see Figure A).

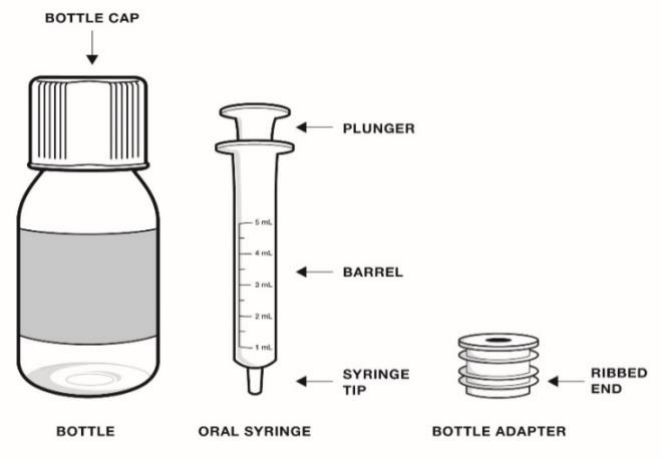

Figure A

Important information:

- Keep these instructions for future use.
- Do not share RADICAVA (oral suspension) with anyone else.
- Call your healthcare professional for medical advice about side effects. You may report any suspected side effects to Health Canada (see the Reporting Side Effects section in the **Patient Medication Information** for RADICAVA (oral suspension)).
- People who have problems using their hands may need assistance to draw up and give the correct dose of RADICAVA (oral suspension).

How to take RADICAVA (oral suspension)**:**

Take RADICAVA (oral suspension) as prescribed by your healthcare professional.

Dosing Information:

RADICAVA (oral suspension) has 2 different dosing schedules:

- For the first treatment cycle of 14 days with the Starter Kit, you will take RADICAVA (oral suspension) every day for 14 days, followed by 14 days without the medicine.
- For the cycles after the first treatment cycle, you will take RADICAVA (oral suspension) daily for 10 out of 14 days, followed by 14 days without the medicine

How RADICAVA (oral suspension) will be provided:

- If your healthcare professional prescribes the Starter Kit, you will receive two (2) bottles of RADICAVA (oral suspension). Each bottle contains 35 mL of RADICAVA (oral suspension) for a total of 70 mL to deliver 14 doses. There may be some medicine that remains in each bottle after the dose on day 7 and day 14 of the first treatment cycle. Throw away (discard) any medicine that remains.
- If your healthcare professional prescribes treatment cycles after the first treatment cycle with the starter kit, for each treatment cycle, you will receive one (1) bottle of RADICAVA (oral suspension) that contains a total of 50 mL of RADICAVA (oral suspension) to deliver 10 doses. There may be some medicine that remains in each bottle after 10 doses. Throw away (discard) any medicine that remains.

Fasting Information:

- Take RADICAVA (oral suspension) in the morning on an empty stomach after not eating overnight for at least 8 hours. If you are unable to fast overnight for 8 hours before your morning dose, you can reduce the fasting time to:
  - 4 hours if you eat a low-fat meal (400-500 calories, 25% fat)
    or
  - 2 hours if you take a calorie supplement (250 calories, e.g. Protein Drink).
- Wait at least 1 hour after taking RADICAVA (oral suspension) before eating or drinking anything except water.

Step 1 – Before each use of RADICAVA (oral suspension): Prior to opening the bottle, turn it upside down (invert) and shake vigorously up and down for at least **30 seconds** (see Figure B). Look at the liquid medicine to make sure it is mixed well. If you see any small pieces at the bottom of the bottle, invert the bottle and shake it up and down for another **30 seconds** or until you can no longer see the pieces at the bottom of the bottle (see Figure B). If the liquid medicine all looks the same, you can proceed to Step 2.

Shake up and down for at least 30 seconds

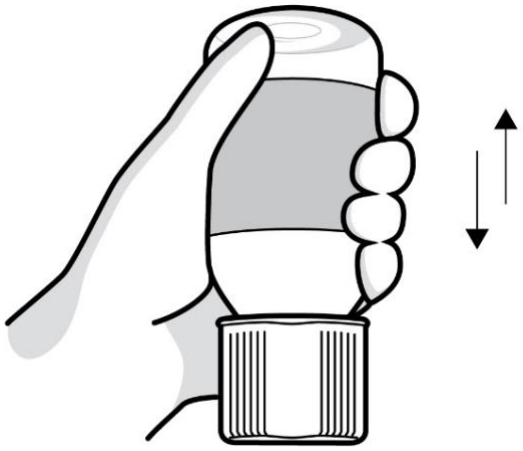

Figure B

Step 2: Open the bottle by **firmly pressing down** on the bottle cap and turning it counterclockwise (to the left). Place the open bottle upright on a flat surface. **Do not** throw away the bottle cap, you will need to replace it after taking each dose.

First time use of a bottle only. This must only be done 1 time for each bottle. Insert the ribbed end of the bottle adapter into the bottle by firmly pressing it in as far as it will go (see Figure C). **Do not** remove the bottle adapter.

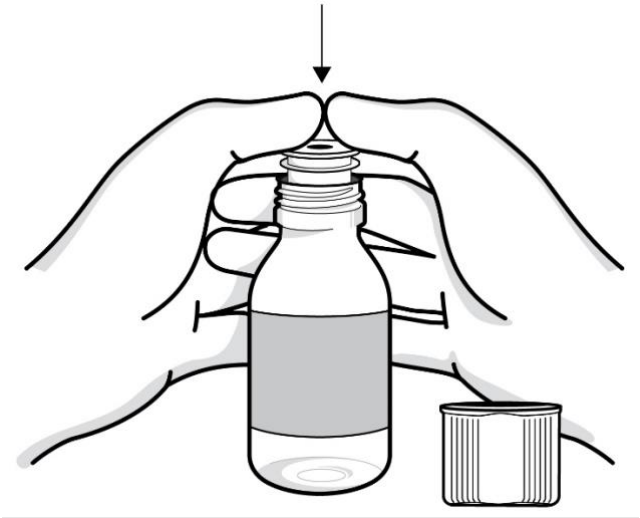

Figure C

Step 3: Remove the oral syringe from plastic wrap and make sure the plunger is inserted all the way into the barrel. Push the oral syringe plunger toward its tip to remove excess air (see Figure D). Insert the oral syringe into the opening of the bottle adapter until it is firmly in place (see Figure E). Turn the bottle upside down and slowly pull the plunger to remove a small amount of liquid (see Figure F).

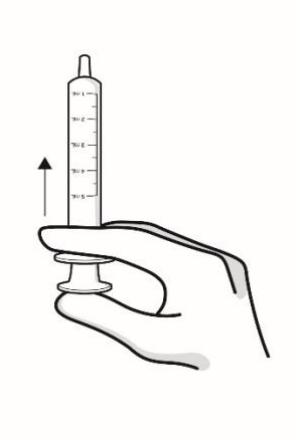

Figure D

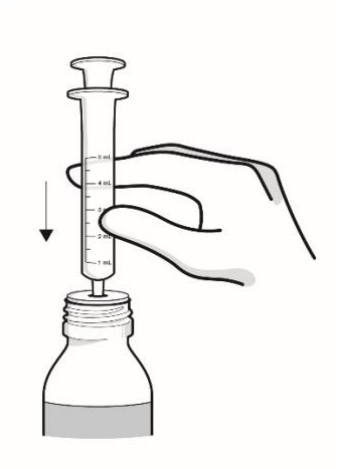

Figure E

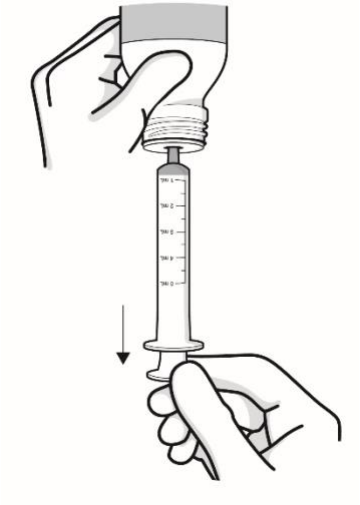

Figure F

Step 4: Keep the bottle upside down and pull the plunger until it goes up to the last line (5 mL) (see Figure G). While keeping the plunger in the same position, turn the bottle upright, and place it carefully on a flat surface. Remove the oral syringe by gently twisting or pulling it out from the bottle (see Figure H). Double check the amount of medicine before moving on to the next step (see Figure I).

Note: **Do not** remove the oral syringe while the bottle is upside down (medicine may leak out through the adapter).

Note: If the dose is not correct, insert the oral syringe tip firmly into the bottle adapter. Push the plunger all the way in so that the medicine flows back into the bottle. Turn the bottle upside down. Repeat Step 4.

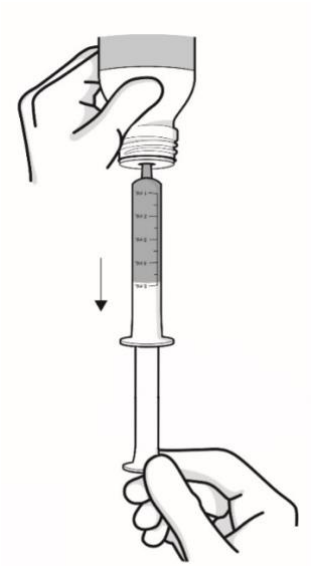

Figure G

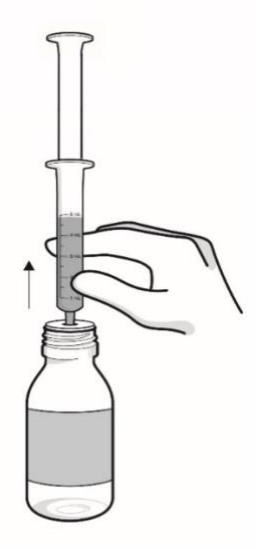

Figure H

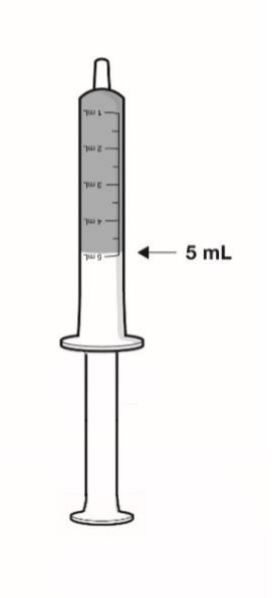

Figure I

Step 5: Place the tip of the oral syringe in the mouth and aim towards the inside of the cheek. Slowly press down on the plunger until the oral syringe is empty. Swallow all of the medicine (see Figure J). If needed, you can use up to 8 ounces or 1 cup of water to help swallow the medicine.

Note: It is normal for a small amount of medicine to remain in the tip of the syringe after taking.

Figure J

Step 6: Leave the bottle adapter inside the bottle. Place the bottle cap on the bottle and turn the cap clockwise (to the right). Keep bottle tightly closed between each use (see Figure K).

Figure K

Step 7: Remove the plunger from the oral syringe barrel by pulling the plunger and the barrel away from each other. **Rinse the oral syringe (plunger and barrel) with water only**. Allow it to air dry.

Figure L

Step 8: When the oral syringe (plunger and barrel) are dry, put the plunger back into the oral syringe barrel. **Do not throw away the oral syringe**. Store the syringe in a clean, dry place.

You must complete Steps 1 through 4 under "How to take RADICAVA (oral suspension)" before starting Step 9 under "How to take a dose of RADICAVA (oral suspension) through a feeding tube."

How to take a dose of RADICAVA (oral suspension) through a feeding tube:

Step 9. Using a catheter-tip syringe, flush the feeding tube with 1 ounce (30 mL) of water (see Figure M).

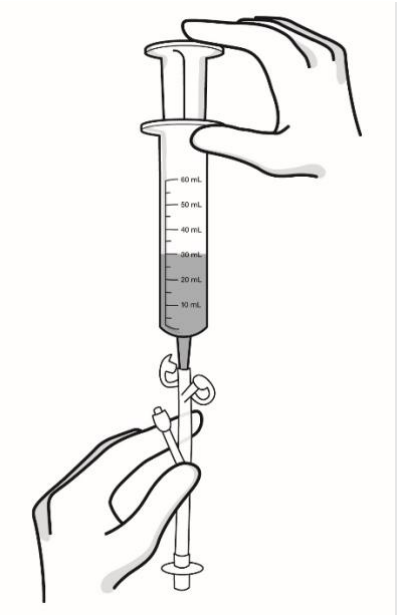

Figure M

Step 10. Place the oral syringe provided (containing the 5 mL of RADICAVA (oral suspension) into the feeding tube. Slowly push down the plunger until the oral syringe is empty (see Figure N).

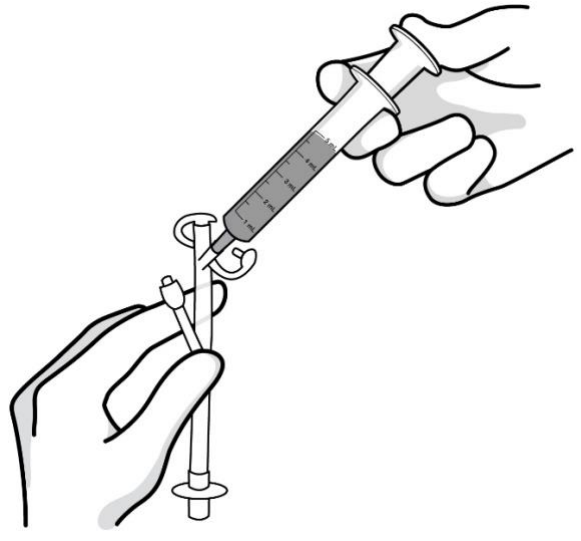

Figure N

Step 11. Using a catheter-tip syringe, flush the feeding tube with 1 ounce (30 mL) of water after taking dose of RADICAVA (oral suspension) (see Figure O).

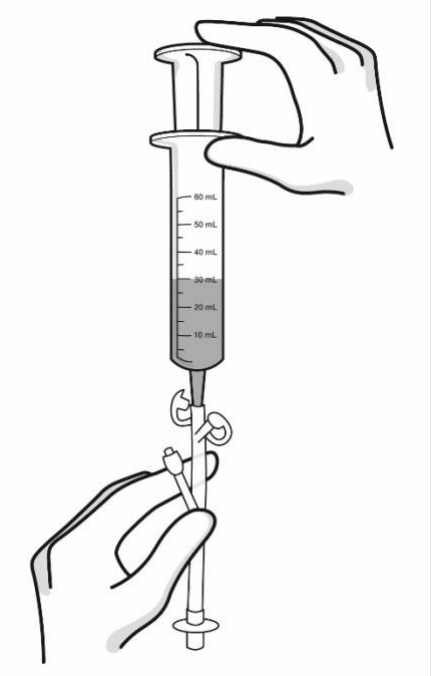

Figure O

Step 12. Leave the adapter in the bottle. Place the bottle cap on the bottle and turn it clockwise (to the right) to close the bottle. Keep the bottle tightly closed between each use (see Figure P).

Figure P

Step 13. Remove the plunger from the oral syringe barrel by pulling the plunger and barrel away from each other. Rinse the oral syringe (plunger and barrel) with water only (see Figure Q). Allow it to air dry.

Figure Q

Step 14. When the oral syringe (plunger and barrel) are dry, put the plunger back into the oral syringe barrel. **Do not throw away the oral syringe.** Store the oral syringe in a clean, dry place.

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