

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

PrRADICAVA®

(edaravone injection)

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

Treatment for amyotrophic lateral sclerosis (ALS)

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

RADICAVA (edaravone) is indicated to slow the loss of function in patients with amyotrophic lateral sclerosis (ALS), as measured by the ALS Functional Rating Scale - Revised (ALSFRS-R).

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

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.

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. For a complete listing, see DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

3 DOSAGE AND ADMINISTRATION

RADICAVA is a ready to use sterile solution to be administered by intravenous infusion only.

3.1 Recommended Dose and Dosage Adjustment

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.

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

3.2 Administration

Preparation

Do not use if the oxygen indicator has turned blue or purple before opening the package (See SPECIAL HANDLING INSTRUCTIONS). Once the overwrap package is opened, use within 24 hours (See 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 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 WARNINGS AND PRECAUTIONS, General, Hypersensitivity Reactions).

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

4 OVERDOSAGE

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

5 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
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

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.

6 WARNINGS AND PRECAUTIONS

General

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).

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.

6.1 Special Populations

6.1.1 Pregnant Women

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 behaviour) at clinically relevant doses. Most of these effects occurred at doses that were also associated with maternal toxicity (see NON-CLINICAL TOXICOLOGY, Reproduction).

6.1.2 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. However, edaravone and its metabolites are excreted in the milk of lactating rats. Because many drugs are excreted in human milk, caution should be exercised. 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.

6.1.3 Pediatrics

Pediatrics (<18 years of age): Safety and effectiveness of RADICAVA in pediatric patients have not been established.

6.1.4 Geriatrics

Geriatrics (>65 years of age): 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.

7 ADVERSE REACTIONS

7.1 Adverse Reaction Overview

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

- Hypersensitivity Reactions (See WARNINGS AND PRECAUTIONS)
- Sulfite Allergic Reactions (See WARNINGS AND PRECAUTIONS)

7.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials 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 is useful for identifying drug-related adverse events and for approximating rates.

The safety profile of RADICAVA compared to placebo was assessed in 3 clinical trials:

- Two double-blind, randomized, placebo-controlled studies in patients with grade 1-2 ALS (Japanese severity classification) with a total 343 subjects
- One double-blind, randomized, placebo-controlled study in patients with grade 3 ALS with 25 subjects

In the double-blind randomized, placebo-controlled trials, 184 ALS patients were administered RADICAVA 60 mg or placebo 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.

Table 2 lists the adverse reactions that occurred in $\geq 2\%$ 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 $\geq 10\%$ of RADICAVA-treated patients were contusion, gait disturbance, and headache.

Table 2: Adverse Reactions from Pooled Placebo-Controlled Trials^a that Occurred in 2% of RADICAVA-Treated Patients and 2% More Frequently than in Placebo Patients

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

^a Pooled placebo-controlled studies include two additional studies with 231 additional patients, all using the same treatment regimen (See CLINICAL TRIALS).

7.3 Post-Market Adverse Reactions

The following adverse reactions have been identified during post-approval use of RADICAVA outside of Canada. 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 DRUG INTERACTIONS

8.1 Overview

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 the recommended 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 recommended clinical dose of RADICAVA.

9 ACTION AND CLINICAL PHARMACOLOGY

9.1 Mechanism of Action

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

9.2 Pharmacodynamics

Cardiac Electrophysiology: In a Japanese study in healthy male subjects, at a dose 5 times the recommended dose, RADICAVA did not prolong the QT interval to any clinically relevant extent.

9.3 Pharmacokinetics

Table 3: Summary of Edaravone Pharmacokinetic Parameters in ALS patients

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	Edaravone (69)	60.5 (30-75)	Male (55%) Female (45%)
			Placebo (68)	60.1 (38-75)	Male (60%) Female (40%)

	C _{max}	T _{max}	t _½ (h)	AUC _{0-∞}	CL	Vd
Single dose mean	1046.6 ng/mL	1[h]	6.34 [h]	1362.3 ng*h/mL	43.7 [L/h]	80.9 [L]

Absorption: 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 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.

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.

Elimination: 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 the sulfate conjugate, and only 1% of the dose or less 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 4.5 to 6 hours. The half-lives of its metabolites are 2 to 2.8 hours.

Special Populations and Conditions

Pediatrics: Safety and effectiveness of RADICAVA 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 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: Mild, moderate and severe hepatic impairment have no clinically significant effects on the pharmacokinetics of edaravone. No dose adjustment is needed in these patients.

Renal Insufficiency: Mild and moderate renal impairment have no clinically significant effects on the pharmacokinetics of edaravone. No dose adjustment is needed in these patients. No studies have been performed to characterize the pharmacokinetics of edaravone or establish its safety in patients with severe renal impairment.

10 STORAGE, STABILITY AND DISPOSAL

Store between 15 - 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 *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 and commercially available infusion set materials have been observed.

11 SPECIAL HANDLING INSTRUCTIONS

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

12 PHARMACEUTICAL INFORMATION

Drug Substance

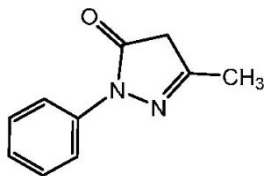
Proper name: RADICAVA

Common name: 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.

13 CLINICAL TRIALS

13.1 Trial Design and Study Demographics

Table 4: Summary of patient demographics for clinical trials in Amyotrophic Lateral Sclerosis

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	Edaravone (69) Placebo (68)	60.5 (30-75)	Male (55%) Female (45%)

13.2 Study Results

Study MCI186-19

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 in 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 $\geq 80\%$)
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:

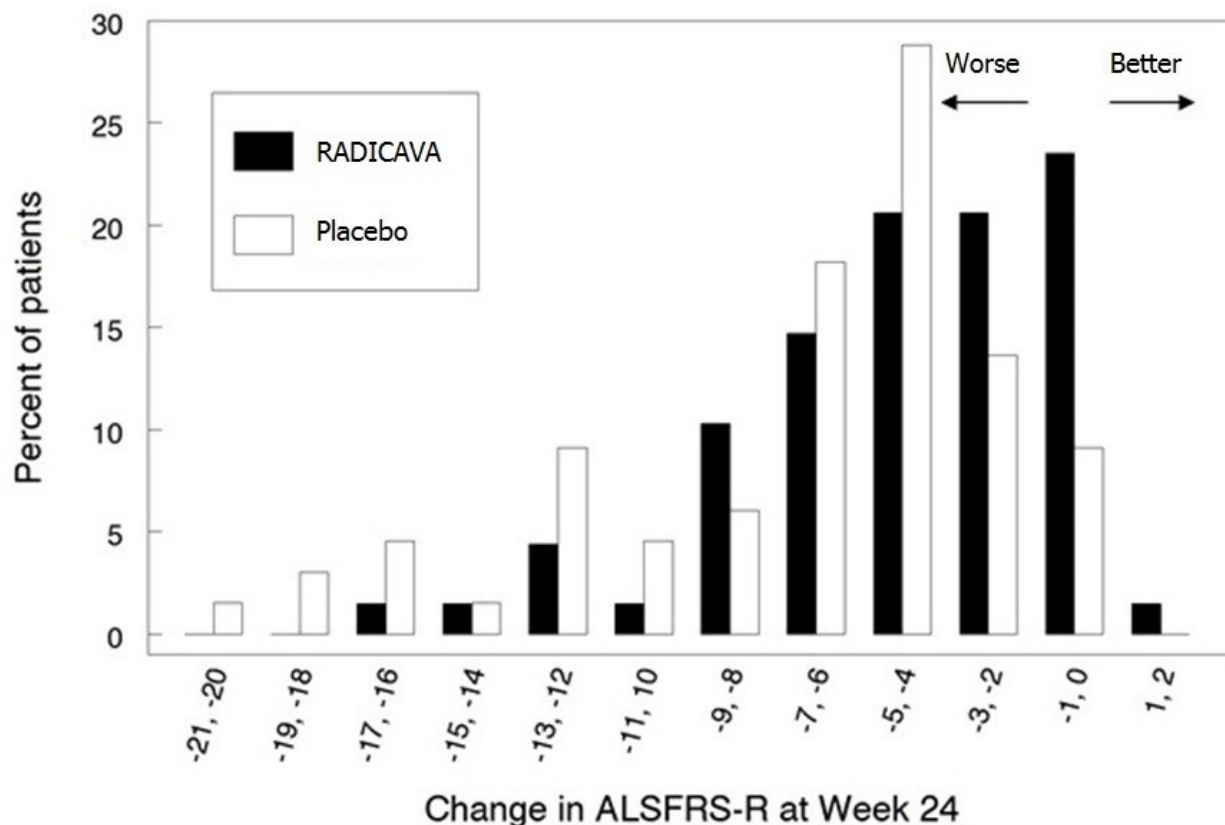
- An initial treatment cycle with daily dosing for 14 days, followed by a 14-day drug-free period (Cycle 1)
- Subsequent treatment cycles with daily dosing for 10 days out of 14-day periods, followed by 14-day drug-free periods (Cycles 2-6).

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

Table 5: Analysis of Change from Baseline to Week 24 in ALSFRS-R Scores

Treatment	Change from Baseline LS Mean \pm SE (95% CI)	Treatment Difference (RADICAVA – placebo [95% CI])	p-value
RADICAVA 60mg	-5.01 \pm 0.64	2.49 (0.99, 3.98)	0.0013
Placebo	-7.50 \pm 0.66		

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



14 NON-CLINICAL TOXICOLOGY

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 recommended human dose (RHD) of 60 mg, on a body surface area (mg/m²) 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 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 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 gestation day 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.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

RADICAVA (ra di ká vah)

edaravone injection

Read this carefully before you start taking **RADICAVA** 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 used for?

- RADICAVA is a prescription medicine used to slow the loss of function in patients with Amyotrophic Lateral Sclerosis (ALS).

How does RADICAVA work?

The exact way RADICAVA works in the body in patients with ALS is unknown. RADICAVA slows the loss of physical function including speech, swallowing, handwriting, cutting food and others.

What are the ingredients in RADICAVA?

Medicinal ingredient: edaravone

Non-medicinal ingredients: L-cysteine hydrochloride hydrate, sodium bisulfite, sodium chloride, phosphoric acid, and sodium hydroxide, water for injection.

RADICAVA comes in the following dosage forms:

Sterile solution, 30 mg/100 mL

Do not use RADICAVA if:

- You are allergic to edaravone or any of the ingredients in RADICAVA, including sulfites.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take RADICAVA. 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.

How to take RADICAVA:

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

Usual dose:

Your healthcare professional will determine your dose.

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

Overdose:

If you think you have taken too much RADICAVA, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using RADICAVA?

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

The most common side effects of RADICAVA include bruising, problems walking, 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: <ul style="list-style-type: none">• Hives• Breathing problems• Itching• Swelling of the lips, tongue, face• Dizziness• Wheezing• Fainting			X
Sulfite allergic reactions: <ul style="list-style-type: none">• Asthma attack (in people with asthma)• Hives• Breathing problems• Itching• Swelling of the lips, tongue, face• Dizziness• Wheezing			X

<ul style="list-style-type: none"> Fainting 			
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If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to 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.html>) 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 will be stored between 15 - 30°C and protected from light.

If you want more information about RADICAVA:

- 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://health-products.canada.ca/dpd-bdpp/index-eng.jsp>); the manufacturer's website www.RADICAVA.ca, or by calling 1-888-212-2253.

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