▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – RADICAVA ® EDARAVONE

1 NAME OF THE MEDICINE

Edaravone.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each clear glass ampoule contains 30 mg of edaravone in 20 mL concentrated injection.

Excipient(s) with known effect: Each ampoule contains sodium bisulfite.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Concentrated solution for injection filled in a clear glass ampoule.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

RADICAVA is indicated in adults with a diagnosis of amyotrophic lateral sclerosis who are independent in activities of daily living with normal respiratory function and where treatment is initiated within two years of disease onset.

Efficacy has not been demonstrated in patients outside of this defined population.

4.2 DOSE AND METHOD OF ADMINISTRATION

RADICAVA concentrated injection must be diluted before use and is for intravenous infusion only. Promptly discontinue the infusion upon the first observation of any signs or symptoms consistent with a hypersensitivity reaction (see Section 4.4 Special warnings and precautions for use).

The recommended dosage of RADICAVA is 60 mg of edaravone (two ampoules) diluted with 100 mL of 0.9% sodium chloride for infusion and administered as an intravenous infusion 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.

Radicava is for single *use in one patient only. Discard any residue.*

To reduce microbiological hazard, use as soon as practicable after dilution. If storage is necessary, hold at 2°-8°C for not more than 24 hours.

Special populations

No dosage adjustment is required in patients with hepatic impairment and mild and moderate renal impairment (estimated glomerular filtration rate (eGFR) >30 mL/min/1.73m^2).

The effects of severe renal impairment on the pharmacokinetics of RADICAVA have not been studied, however exposure to edaravone is not expected to be significantly affected in patients with eGFR <30 mL/min/1.73m^2 who do not require renal replacement therapy. Pharmacokinetics of RADICAVA have not been studied in patients undergoing renal replacement therapy and use of RADICAVA in this population is not recommended.

4.3 CONTRAINDICATIONS

RADICAVA is contraindicated in patients with a history of hypersensitivity to edaravone or any of the excipients listed in Section 6.1 List of excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

HYPERSENSITIVITY REACTIONS

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

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 Section 4.3 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.

Sodium content

Each ampoule of RADICAVA contains 135 mg sodium chloride, 6.75 mg/mL. This should be taken into consideration by patients on a controlled sodium diet.

Use in the elderly

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.

Paediatric use

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

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

The pharmacokinetics of edaravone is not expected to be significantly affected by inhibitors of CYP enzymes, or UGTs. The major metabolite of edaravone, edaravone sulfate, is a substrate for OAT1 and OAT3. Inhibitors of these transporters may alter exposures to edaravone sulphate.

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), uridine diphosphate glucuronosyltransferase (UGT) isoforms UGT1A1, UGT2B7, or the following transporters, P-gp, BCRP, OATP1B1, OATP1B3, OAT1 and OCT2 in humans. The major metabolite of edaravone, edaravone sulfate, is an inhibitor of OAT3. The clinical relevance of this is unknown.

Edaravone and its metabolites are not expected to induce CYP1A2, CYP2B6, or CYP3A4 at the clinical dose level of edaravone.

No interaction studies have been performed *in vivo*.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There are no data on potential effects of RADICAVA on human fertility.

In rats, 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 oestrus cycle and mating behaviour 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 maximum recommended human dose (MRHD) of 60 mg, on a body surface area (mg/m^2) basis.

Use in pregnancy – Pregnancy Category B3

There are no adequate data on the developmental risk associated with the use of RADICAVA in pregnant women.

In rats, intravenous administration of edaravone throughout the period of organogenesis resulted in lower fetal weights at doses greater than or equal to 30 mg/kg/day. Maternal toxicity was also seen at these doses. A no effect dose for embryofetal developmental toxicity was less than the MRHD of 60 mg, on a body surface area (mg/m^2) basis.

In rabbits, intravenous administration of edaravone throughout the period of organogenesis resulted in embryofetal death at 100 mg/kg/day, which was associated with maternal toxicity. The no effect dose for embryofetal developmental toxicity is approximately 6 times the MRHD on a body surface area (mg/m^2) basis.

Women should avoid pregnancy while taking edaravone. If edaravone is used during pregnancy or if the patient becomes pregnant while taking edaravone, the patient should be apprised of the potential hazard to the fetus.

Use in lactation.

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 were excreted at high levels 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.

In rats, intravenous administration of edaravone from the end of gestation throughout lactation resulted in an increased incidence of stillbirths and offspring mortality at 200 mg/kg/day, a dose at which maternotoxicity was observed. Additional findings in offspring included: increased locomotor activity in a behavioural study at maternal doses greater than or equal to 20 mg/kg/day; delayed physical development in females; and an increase in embryonic deaths in the next generation. The no effect dose for developmental toxicity is less than the MRHD on a body surface area (mg/m^2) basis

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

RADICAVA has no influence on the ability to drive and use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The tabulated incidence of adverse drug reactions from 3 Phase III clinical studies in patients with amyotrophic lateral sclerosis (ALS) in Japan are provided.

Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: Incidence of adverse drug reactions from clinical studies

Organ system	Very common	Common
Infections and infestations		Tinea infection
Nervous system disorders		Headache
Respiratory, thoracic and mediastinal disorders		Respiratory failure Respiratory disorder Hypoxia
Skin and subcutaneous tissue disorders		Eczema Dermatitis
Renal and urinary disorders		Glycosuria
General disorders and administration siteconditions	Gait disturbance	
Injury, poisoning and procedural complications	Contusion	

Frequency for Tinea infection, Headache, Respiratory failure/disorder, Hypoxia, Eczema, Dermatitis, are based on group of similar PTs.

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 Events Observed During Clinical Studies

Table 2 summarizes the Adverse Events in randomised, placebo-controlled trials with an incidence ≥ 2% in the pooled edaravone group and at an incidence greater than placebo, by treatment group.

The most frequently reported Adverse Events with edavarone (≥ 3% and greater than placebo) were contusion (14.7% vs. 8.7%), gait disturbance (12.5% vs. 9.2%), headache (8.2% vs. 5.4%), eczema (6.5% vs. 2.2%), dermatitis contact (6.0% vs. 3.3%), respiratory disorder (4.3% vs. 1.1%), rash (3.8% vs. 2.2%), glucose urine present (3.8% vs. 1.6%), and upper respiratory tract inflammation (3.3% vs. 1.6%).

Table 2- Incidence of Adverse Events Occurring in at Least 2% of Subjects in the Pooled Edaravone Group and Greater than Placebo Pooled [Placebo-Controlled Studies.

SOC PT	Placebo (N=184) n	(%)	Edaravone (N=184) n	(%)
Any AE[a]	160	(87.0)	161	(87.5)
Infections and infestations[a]	57	(31.0)	63	(34.2)
Tinea pedis	2	(1.1)	4	(2.2)
Upper respiratory tract infection	3	(1.6)	5	(2.7)
Nervous system disorders[a]	23	(12.5)	26	(14.1)
Headache	10	(5.4)	15	(8.2)
Respiratory, thoracic and mediastinal disorders[a]	24	(13.0)	26	(14.1)
Respiratory disorder	2	(1.1)	8	(4.3)
Upper respiratory tract inflammation	3	(1.6)	6	(3.3)
Gastrointestinal disorders[a]	68	(37.0)	57	(31.0)
Nausea	1	(0.5)	4	(2.2)
Skin and subcutaneous tissue disorders[a]	37	(20.1)	47	(25.5)
Dermatitis contact	6	(3.3)	11	(6.0)
Eczema	4	(2.2)	12	(6.5)
Erythema	3	(1.6)	5	(2.7)
Rash	4	(2.2)	7	(3.8)
Musculoskeletal and connective tissue disorders[a]	39	(21.2)	36	(19.6)
Myalgia	2	(1.1)	4	(2.2)
General disorders and administration site conditions[a]	37	(20.1)	41	(22.3)
Gait disturbance	17	(9.2)	23	(12.5)
Investigations[a]	14	(7.6)	13	(7.1)
Glucose urine present	3	(1.6)	7	(3.8)
Injury, poisoning and procedural complications[a]	36	(19.6)	39	(21.2)
Ligament sprain	4	(2.2)	5	(2.7)
Excoriation	3	(1.6)	5	(2.7)
Contusion	16	(8.7)	27	(14.7)

MedDRA version 17.0. A subject reporting more than 1 TEAE for a particular PT or SOC is counted only once for that PT or SOC.
Includes TEAEs with an incidence ≥ 2% in the pooled edaravone group and greater than the pooled placebo group.
[a] Count for all subjects who had at least 1 TEAE.

Postmarketing Experience

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

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

The mechanism by which RADICAVA exerts its therapeutic effect in patients with ALS is unknown. Edaravone is a free radical scavenger to reduce oxidative stress.

Clinical trials

Study MCI186-19

The efficacy of RADICAVAfor the treatment of ALS was established in a 6-month, randomised, 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, dyspnoea, orthopnea, and respiratory insufficiency). Each item is scored from 0-4, with higher scores representing greater functional ability."

The decline in ALSFRS-R total scores from baseline was significantly less in the RADICAVA treated patients as compared to placebo (see Table 3). The distribution of change in ALSFRS-R scores from baseline to week 24 by percent of patients is shown in Figure 1.

Table 3: Analysis of Change from Baseline to Week 24 in ALSFRS-R Total Scores

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

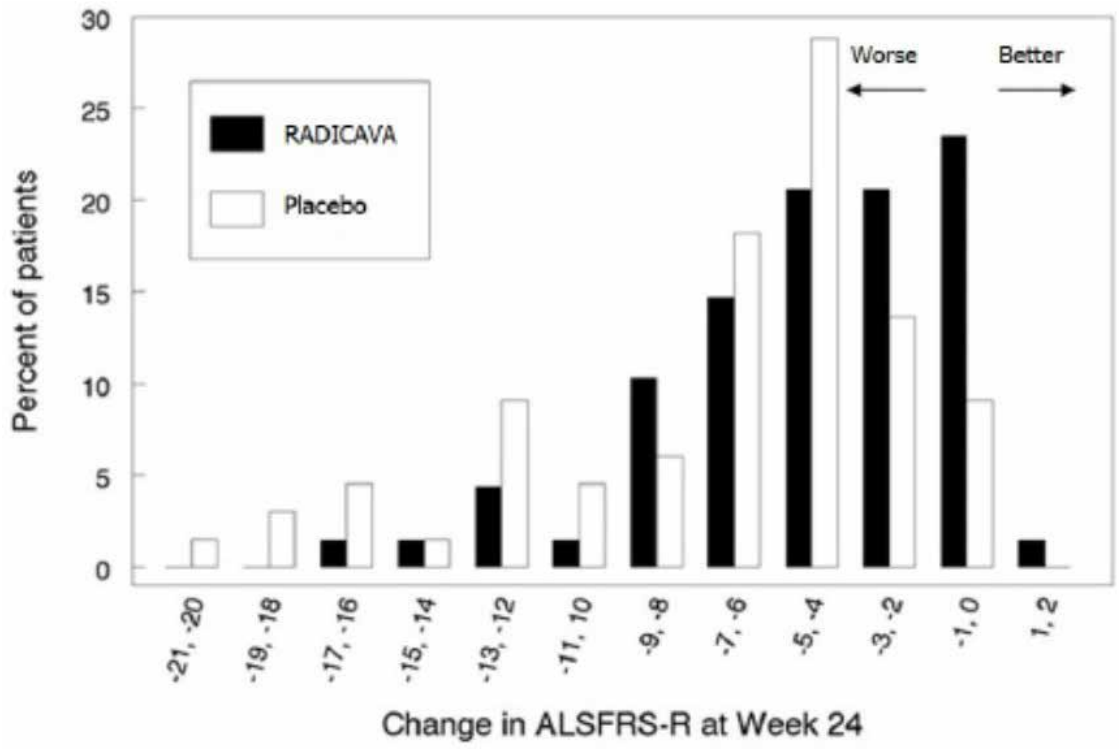


Figure 1: Distribution of change from baseline to week 24 in ALSFRS-R scores

No benefit on survival was demonstrated.

Study MCI186-16

Study MCI186-16 was a randomised, double-blind, parallel-group, placebo-controlled Phase III trial to evaluate the efficacy and safety of 60 mg/day edaravone. The dosing schedule was the same as described for Study MCI186-19.

The primary endpoint was ALSFRS-R score change from Baseline in Cycle 1 to the end of Cycle 6 (24 weeks) or at discontinuation.

The main analyses were performed in the Full Set Analysis (FAS), which consisted of 101 subjects in the edaravone (E) group and 104 subjects in the placebo (P) group, for a total of 205 subjects. Fourteen subjects in P group and 9 subjects in E group were discontinued before the end of Cycle 6. The results of the analysis of the primary efficacy endpoint of change from Baseline to the end of Cycle 6 in ALSFRS-R are shown in Table 4. While a beneficial trend favouring edaravone was observed in the FAS, the prespecified primary analyses did not statistically demonstrate the efficacy of edaravone in comparison to placebo.

In additional exploratory analyses to evaluate the beneficial trend observed with edaravone, the beneficial trend favouring edaravone was mainly driven by data from subjects who had functionality retained in most ADL domains with normal respiratory function and lived independently (refer to Table 4).

Table 4: Analysis of Change from Baseline to Week 24 in ALSFRS-R Total Scores

Study number	Group	Number of subjects in LOCF analyses	Adjusted mean	Between-group differences in the adjusted mean	p-value
			LS mean±SE	LS mean±SE (95% CI)	
MCI186-16 (FAS)	P group	99	-6.35±0.84	0.65±0.78 (-0.90 , 2.19)	p=0.4108
	E group	100	-5.70±0.85		
MCI186-16 (EESP)[a]	P group	46	-7.06±1.13	2.20±1.03 (0.15 , 4.26)	p=0.0360
	E group	53	-4.85±1.24		
MCI186-16 (Definite or Probable/EESP/2y)[a]	P group	29	-7.59±1.34	3.01±1.33 (0.35 , 5.67)	p=0.0270
	E group	39	-4.58±1.55		
MCI186-16 (non-"EESP")[a]	P group	53	-5.24±1.25	-1.42±1.16 (-3.73 , 0.89)	p=0.2251
	E group	47	-6.65±1.17		
MCI186-16 (non-"Definite or Probable/EESP/2y")[a]	P group	70	-5.54±1.08	-0.57±1.00 (-2.55 , 1.41)	p=0.5711
	E group	61	-6.11±1.03		

Note: LOCF was applied to subjects who completed Cycle 3 (subjects who reached 81 days after treatment initiation). Subjects who dropped out before Day 81 were excluded.

[a] EESP, Definite or Probable/EESP/2y, Non-EESP, and Non-Definite or Probable EESP/2y analyses were post-hoc.

**EESP = efficacy-expected subpopulation defined by scores of ≥2 points on all 12 items of the ALS functional Rating Scale-Revised (ALSFRS-R) and a percent predicted forced vital capacity (%FVC) ≥80% at baseline.*
**definite/probable EESP 2 years (dpEESP2y) = efficacy-expected subpopulation defined, in addition to EESP criteria, had definite or probable ALS diagnosed by revised El Escorial criteria, and disease duration of ≤2 years.*

No benefit on survival was demonstrated.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

RADICAVA is administered by intravenous injection with the maximum plasma concentration (C_{max}) of edaravone reached by the end of the infusion (60 mg edaravone for 60 min). No gender effect on edaravone pharmacokinetics has been found. There were no significant racial differences in C_{max} and the area under the concentration-time curve (AUC) of edaravone between Japanese and Caucasian subjects. There was a trend of more than dose-proportional increase in 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 metabolised 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 volunteers, 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 the sulfate conjugate of edaravone is hydrolysed 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

Paediatric Population

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

Elderly

No age effect on edaravone pharmacokinetics has been found.

Renal Impairment

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.

Hepatic Impairment

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

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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

Carcinogenicity

Edaravone was not carcinogenic at oral doses up to 350 mg/kg/day in transgenic mice and oral doses up to 250 mg/kg/day in rats. Exposures or estimated exposures (AUC) at the highest tested doses were 22 and 133 times in mice and rats, respectively, the AUC at the MRHD of 60 mg.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sodium bisulfite, cysteine hydrochloride monohydrate, sodium chloride, sodium hydroxide, phosphoric acid and water for injections.

6.2 INCOMPATIBILITIES

No incompatibilities between RADICAVA and commercially available infusion set materials have been observed.

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

It is not recommended that the RADICAVA solution for infusion be mixed with total parenteral nutrition preparations and/or with amino-acid infusions before administration and should not be administered through the same intravenous line as those preparations.

It is not recommended that the RADICAVA solution for infusion be mixed with infusions of potassium canrenoate, or anticonvulsants including diazepam, phenytoin sodium because the solution may become cloudy.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25 °C.

6.5 NATURE AND CONTENTS OF CONTAINER

RADICAVA 30 mg/20 mL concentrated solution for injection is supplied as a clear, colourless, sterile solution in Type I clear glass ampoules and supplied in cartons containing 10 ampoules.

Pack size – 10 ampoules x 20 mL

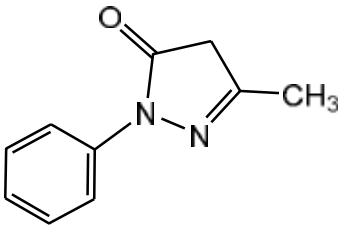
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 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.

Chemical structure



Chemical Names - 3-Methyl-1-phenyl-2-pyrazolin-5-one
Molecular formula - $C_{10}H_{10}N_2O$
Molecular weight - 174.20

CAS number

89-25-8

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription only Medicine

8 SPONSOR

Teva Pharma Australia Pty Ltd
Level 1, 37 Epping Road,
Macquarie Park,
NSW 2113, Australia
Ph: 1800 288 382
www.tevapharma.com.au

9 DATE OF FIRST APPROVAL

DD/MM/YYYY

10 DATE OF REVISION

N/A

RADICAVA® is a registered trademark of Mitsubishi Tanabe Pharma Corporation.

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.1 THERAPEUTIC INDICATIONS	Indication revised as recommended by the TGA
4.2 DOSE AND METHOD OF ADMINISTRATION	Section revised as requested by the Delegate
4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)	Section revised as requested by the Delegate
5.1 Clinical Trials	Section revised as requested by the Delegate