RADICAVA™

edaravone

1. NAME OF THE MEDICINAL PRODUCT

RADICAVA™ 30mg/20ml Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

(INN: Edaravone)

Each ampoule contains 30mg of edaravone in 20mL. After dilution, 1mL of solution contains approximately 0.43mg of edaravone.

RADICAVA contains sodium bisulfite, a sulphite that may cause allergic type reactions. For the full list of excipients, see *List of excipients (section 6.1).*

3. PHARMACEUTICAL FORM

Injection
A clear and colourless aqueous solution for injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

Delaying progression of functional disorder in patients with amyotrophic lateral sclerosis (ALS) not more than grade 2[1] with normal lung function

4.2 Posology and mode of administration

Posology
The usual adult dosage is two ampoules (60 mg of edaravone) diluted with 100mL of physiological saline, etc., which is administered intravenously over 60 minutes once a day.

Special population
Paediatric Use
Safety and effectiveness of RADICAVA in paediatric patients have not been established.

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

Renal Impairment
The effect of renal impairment on the pharmacokinetics of RADICAVA has not been studied. However, renal impairment is not expected to significantly affect the exposure to edaravone. No dose adjustment is needed in these patients.

[1] the patients who are able to work or perform housework or independent living but unable to work.

Hepatic Impairment
The effect of hepatic impairment on the pharmacokinetics of RADICAVA has not been studied. No dose adjustment is needed for patients with mild or moderate hepatic impairment. No specific dosing recommendation can be provided for patients with severe hepatic impairment.

Mode of Administration
Administer two ampoules (60mg of edaravone) diluted in 100 mL of physiological saline, over a total of 60 minutes (infusion rate approximately 1 mg per minute [2.33 mL per minute]).

Usually, the duration of administration and cessation of this product are combined in one cycle of treatment for 28 days and the cycle should be repeated. This product is consecutively infused for 14 days in the duration of administration followed by cessation for 14 days in the 1st cycle, and from the 2nd cycle, this product is infused for 10 of 14 days in the duration of administration followed by cessation for 14 days.

Promptly discontinue the infusion upon the first observation of any signs or symptoms consistent with a hypersensitivity reaction *[see Special warnings and precautions for use (4.4)]*

Other medications should not be mixed with RADICAVA.

4.3 Contraindications

RADICAVA is contraindicated in patients with a history of hypersensitivity to any of the ingredients of RADICAVA

4.4 Special warnings and precautions for use

RADICAVA should be carefully administered to the following patients:

Elderly patients:
RADICAVA should be administered with care. The elderly patients should be monitored carefully, since many fatal outcomes have been reported in the patients.

Anaphylactoid reaction:
– Patients should be monitored carefully, since anaphylactoid reaction (e.g., urticaria, blood pressure decreased and dyspnoea) may occur.
– If anaphylactoid reaction occurs, RADICAVA should be discontinued and appropriate therapeutic measures should be taken.

Precautions when opening the ampoule
RADICAVA is supplied in a “one-point-cut ampoule”. Break the ampoule while pulling its neck downward with the round mark frontal. To avoid contamination with foreign substances upon cutting ampoule, the cut point of the ampoule should be wiped with an alcohol swab before opening.

Other precaution
In a 28-days continuous intravenous infusion study in dogs, symptomatic changes, such as limited usage of limbs, abnormal gait, etc., and pathological nerve fibre degeneration in the peripheral nerves and spinal cord (dorsal funiculus) were observed at the doses of edaravone of 60 mg/kg/day and above.

4.5 Interaction with other medicinal products and other forms of interactions

The concomitant use of RADICAVA with antibiotics such as cefazolin sodium, cefotiam hydrochloride, and piperacillin sodium may aggravate renal impairment. If these antibiotics are used concomitantly, the patients should be closely monitored and renal function tests should be performed

frequently.

The mechanism is unknown. The concomitant use of RADICAVA with renally eliminated antibiotics may compromise renal function, because RADICAVA is mainly excreted by the kidney.

4.6 Fertility, pregnancy and lactation

The use of RADICAVA during pregnancy is not recommended. The safety of RADICAVA in pregnant women has not been established.

Lactation should be prohibited during administration of RADICAVA. No information on the excretion of RADICAVA into human breast milk is available.

Studies in rats showed that RADICAVA was excreted into breast milk.

4.7 Effects on ability to drive and use machines

No studies on the effect of RADICAVA on the ability to drive and use machines have been performed.

4.8 Undesirable effects

The incidence of adverse drug reactions is provided using the following standard categories. The adverse events are coded using MedDRA version 18.1 and are presented as preferred terms by System Organ Class.

Very common	≧10%
Common	≧1% and <10%
Uncommon	≧0.1% and <1%
Rare	≧0.01% and < 0.1%
Very rare	< 0.01%

Undesirable effects in acute ischaemic stroke[2] patients from clinical studies and post-marketing experience in Japan

Blood and lymphatic system disorders
Uncommon: Anaemia
Rare: Disseminated intravascular coagulation, thrombocytopenia

Metabolism and nutrition disorders
Rare: Hypokalaemia, hyperkalaemia, hyperuricaemia, hypoproteinaemia

Nervous system disorders
Rare: Headache

Respiratory, thoracic and mediastinal disorders
Rare: Interstitial lung disease

Gastrointestinal disorders
Rare: Nausea, vomiting

Hepatobiliary disorders
Common: Hepatic function abnormal
Uncommon: Liver disorder
Rare: Jaundice, hepatitis

[2] Acute ischaemic stroke (AIS) was approved in Japan.

Skin and subcutaneous tissue disorders
Uncommon: Rash
Rare: Pruritus, urticaria, drug eruption, erythema, eczema, rash pruritic

Renal and urinary disorders
Uncommon: Renal impairment
Rare: Renal failure, acute kidney injury, nephrotic syndrome, renal disorder, haematuria, proteinuria

General disorders and administration site conditions
Uncommon: Pyrexia
Rare: Feeling hot, hyperthermia, injection site erythema, injection site rash, swelling, infusion site erythema

Investigations
Common: Aspartate aminotransferase increased, alanine aminotransferase increased, blood lactate dehydrogenase increased, gamma-glutamyl transferase increased, blood alkaline phosphatase increased
Uncommon: blood bilirubin increased, blood cholesterol increased, blood creatine phosphokinase increased, blood creatinine increased, blood triglyceride increased, blood urea increased, blood uric acid increased, haematocrit decreased, blood urine present, haemoglobin decreased, platelet count decreased, protein total decreased, red blood cell count decreased, white blood cell count decreased, white blood cell count increased, platelet count increased, protein urine present, urine urobilin present, blood creatine phosphokinase decreased
Rare: Blood uric acid decreased, blood calcium decreased, blood pressure increased, blood cholesterol decreased, urine bilirubin increased, liver function test abnormal, blood potassium decreased, blood potassium increased, body temperature increased, protein urine

Undesirable effects in acute ischaemic stroke patients from post-marketing experience in Japan (frequency not known)

Hepatobiliary disorders
Fulminant hepatitis

Blood and lymphatic system disorders
Granulocytopenia

Respiratory, thoracic and mediastinal disorders
Interstitial lung disease

Musculoskeletal and connective tissue disease
Rhabdomyolysis

Immune system disorders
Shock, anaphylactoid reaction

Skin and subcutaneous tissue disorders
Erythema

Renal and urinary disorders
Polyuria

Undesirable effects from clinical studies for amyotrophic lateral sclerosis (ALS) in Japan
Skin and subcutaneous tissue disorders
Common: Rash
Uncommon: Eczema

Investigations
Uncommon: Glucose urine present

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

5.1.1 Mechanism of action
Although the etiology of development and disease progress of amyotrophic lateral sclerosis (ALS) are unknown, a possible involvement of oxidative stress caused by free radicals is suggested. RADICAVA scavenges free radicals and inhibits lipid peroxidation, and thereby prevents oxidative damage to brain cells (vascular endothelial cells/nerve cells) and suppresses the disease progression by exerting its inhibitory effects against the development of oxidative damage to nerve cells.

Non clinical studies
In an animal study using transgenic rats in which mutant superoxide dismutase (known as a responsible gene for familial ALS), edaravone was intravenously administered at 3 mg/kg/hr over 1 hour for 2 days followed by cessation for 2 days as one-cycle and the cycle was repeated until loss of righting reflex. The result showed a significant inhibitory effect on reduction of angle in female rats in an inclined plane test to evaluate motor function in extremities globally.

5.1.2 Efficacy/Clinical studies

1) Placebo-controlled double-blind comparative study (second confirmatory study)
The efficacy of RADICAVA for the treatment of ALS was established in a 6-month, randomized, placebo-controlled, double-blind study conducted in Japanese patients with ALS who were living independently and met the following criteria at screening:

1. Functionality retained most activities of daily living (defined as scores of 2 points or better on each individual item of the ALS Functional Rating Scale – Revised [ALSFRS-R; described below])
2. Normal respiratory function (defined as percent-predicted forced vital capacity values of [%FVC] ≥80%)
3. Definite or Probable ALS based on El Escorial revised criteria
4. Disease duration of 2 years or less

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

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

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

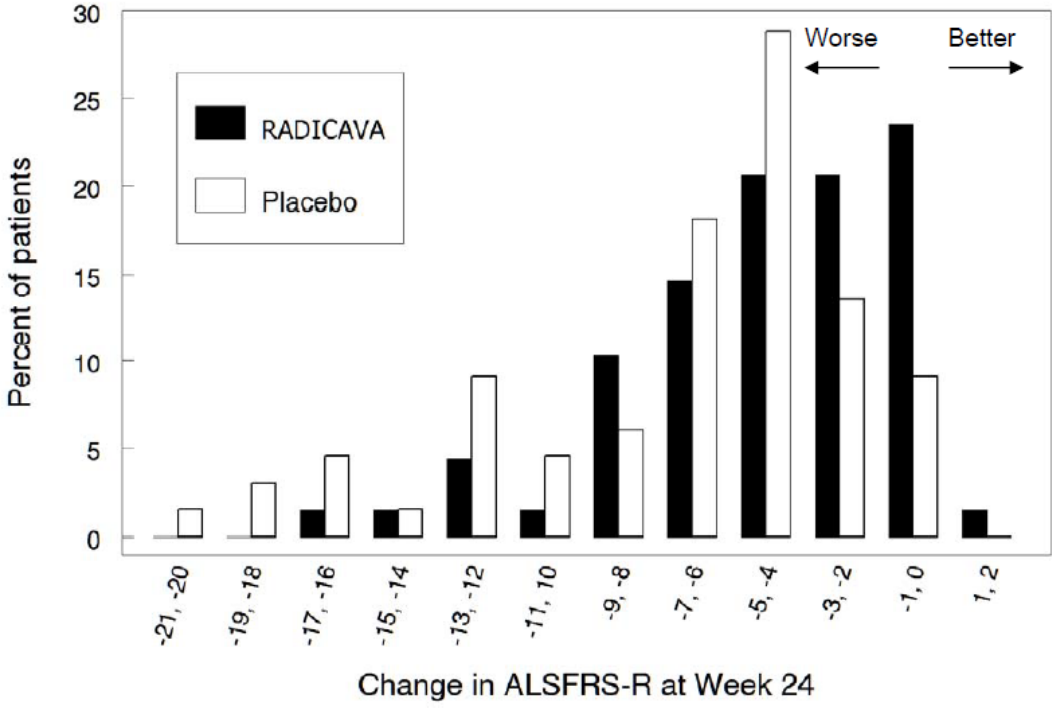
The primary efficacy endpoint was a comparison of the change between treatment arms in the ALSFRS-R total scores from baseline to Week 24. The ALSFRS-R scale consists of 12 questions that evaluate the fine motor, gross motor, bulbar, and respiratory function of patients with ALS (speech,

salivation, swallowing, handwriting, cutting food, dressing/hygiene, turning in bed, walking, climbing stairs, dyspnea, orthopnea, and respiratory insufficiency). Each item is scored from 0-4, with higher scores representing greater functional ability. The decline in ALSFRS-R scores from baseline was significantly less in the RADICAVA-treated patients as compared to placebo (see Table 1). The distribution of change in ALSFRS-R scores from baseline to Week 24 by percent of patients is shown in Figure 1.

Table 1: Analysis of Change from Baseline to Week 24 in ALSFRS-R Scores

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

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



2) Placebo-controlled double-blind comparative study (first confirmatory study)

When RADICAVA or placebo was intravenously administered at 60 mg in patients with ALS (warranting “Definite”, “Probable” or “Probable-laboratory-supported” according to the El Escorial and the revised Airlie House diagnostic criteria for ALS, rated as grade 1 or 2 in Japan ALS severity classification, having forced vital capacity (%FVC) not less than 70%, and illness duration within 3 years) in 6 cycles of treatment*, mean changes from baseline in the revised ALS functional rating scale (ALSFRS-R) as primary endpoint were shown in Table 2 and statistically significant difference was not observed between the treatment groups.

Table 2: Mean changes from baseline in ALSFRS-R score

	No. of cases evaluated [a]	ALSFRS-R scores [b]		Mean change from baseline [d], [e]	Comparison with placebo group [e]	
		Before the 1st cycle	At the final Evaluation [c]		Difference between groups [95% CI]	P value
Placebo group	99	41.1±2.9	35.1±7.4	-6.35±0.84	0.65 [-0.90, 2.19]	0.4108
Edaravone group	100	40.5±3.5	35.3±7.1	-5.70±0.85		

a) The cases completed the 3rd cycle (reached Day 81 after treatment initiation) were evaluated.
b) Mean ± SD
c) At the time of 2 weeks after the 6th cycle completion or discontinuation of treatment (LOCF)
d) Adjusted mean change ± SE
e) Based on a model of analysis of variance with treatment groups, mean changes in ALSFRS-R scores in run-in period, initial symptoms (bulbar/limb symptom) and concurrent treatment with Riluzole as factors

3) Placebo-controlled double-blind comparative study in patients with Japan ALS severity classification of grade 3

When edaravone or placebo was intravenously administered at 60 mg in patients with Japan ALS severity classification of grade 3 ALS in 6 cycles of treatment*, mean changes from baseline in the revised ALS functional rating scale (ALSFRS-R) as primary endpoint were shown in Table 3 and statistically significant difference was not observed between the treatment groups.

Table 3: Mean changes from baseline in ALSFRS-R score

	No. of cases evaluated [a]	ALSFRS-R scores [b]		Mean change from baseline [d], [e]	Comparison with placebo group [e]	
		Before the 1st cycle	At the final Evaluation [c]		Difference between groups [95% CI]	P value
Placebo group	12	34.6±3.3	29.2±4.9	-6.00±1.83	-0.52 [-5.62, 4.58]	0.8347
Edaravone group	13	32.5±5.5	26.6±9.9	-6.52±1.78		

a) The cases completed the 3rd cycle (reached Day 81 after treatment initiation) were evaluated.
b) Mean ± SD
c) At the time of 2 weeks after the 6th cycle completion or discontinuation of treatment (LOCF)
d) Adjusted mean change ± SE
e) Based on a model of analysis of variance with treatment groups and mean changes in ALSFRS-R scores in run-in period as factors

*Once-daily consecutive administration for 14 days and subsequent cessation for 14 days of RADICAVA were combined in the 1st cycle of treatment. After completion of the 1st cycle, RADICAVA was administered for 10 of 14 days followed by cessation for 14 days from the second to sixth cycle (the treatment cycle was repeated 5 times).

5.2 Pharmacokinetic properties

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

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

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

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

Excretion
In Japanese and Caucasian healthy volunteer studies, edaravone was excreted mainly in the urine as its glucuronide conjugate form (70-90% of the dose). Approximately 5-10% of the dose was recovered in the urine as sulfate conjugate, and only 1% of the dose or less was recovered in the urine as unchanged form. *In vitro* studies suggest that sulfate conjugate of edaravone is hydrolyzed back to edaravone, which is then converted to the glucuronide conjugate in the human kidney before excretion into the urine.

Specific Populations
Geriatric Patients
No age effect on edaravone pharmacokinetics has been found *[see Posology and method of administration (4.2)]*.

Patients with Renal and Hepatic Impairment
No pharmacokinetic data are available in patients with renal impairment or hepatic impairment *[see Posology and method of administration (4.2)]*.

Male and Female Patients
No gender effect on edaravone pharmacokinetics has been found.

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

5.3 Preclinical safety data

Carcinogenesis
The carcinogenic potential of edaravone has not been adequately assessed.

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium bisulfite, L-cysteine hydrochloride hydrate, sodium chloride, sodium hydroxide, phosphoric acid

6.2 Incompatibilities

RADICAVA should be diluted with physiological saline (if the product is mixed with any infusion fluids including various saccharides, the concentration of edaravone may decrease with time).

RADICAVA should not be mixed with total parenteral nutrition preparations and/or amino-acid infusions before administration and should not be administered through the same intravenous line as those preparations (if the product is mixed with them, the concentration of edaravone may decrease with time).

RADICAVA should not be mixed with infusions of anticonvulsants including diazepam, phenytoin sodium, etc. (the solution may become cloudy).

RADICAVA should not be mixed with potassium canrenoate (the solution may become cloudy).

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Clear glass ampoule
Pack size: 10 x 20mL in a paper carton.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER

Mitsubishi Tanabe Pharma (Thailand) Co., Ltd.
Bangkok, Thailand.

Manufactured by:
Nipro Pharma Corporation Ise Plant,
Mie, Japan

8. MARKETING AUTHORIZATION NUMBERS

9. DATE OF AUTHORIZATION

10. DATE OF REVISION OF THE TEXT[3]

[3] Apr 2021