SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCTS, DOSAGE FORM AND STRENGTH

RADICAVA®

Solution for IV infusion

Each 1ml contains 1.5mg Edaravone (20ml ampoule contains 30mg Edaravone)

In addition to the active ingredient, the medicine also contains:
Sodium chloride, sodium bisulfite, L-cysteine hydrochloride hydrate, phosphoric acid, sodium hydroxide, water for injection

2 INDICATIONS AND USAGE

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

3 DOSAGE AND ADMINISTRATION

General Information

Treatment with RADICAVA should be initiated and monitored in specialized centers, by physicians experienced in the management of patients with ALS.
Treatment with RADICAVA may only be initiated if the patient has clinically definite, clinically probable or "probable laboratory/EMG-supported ALS".

The efficacy of RADICAVA has so far only been shown when therapy is initiated in early stage disease (patients are either capable of working or at least can independently perform activities of daily living). Whilst there is evidence in support of the efficacy of RADICAVA when initiated in patients with a more advanced stage of the disease, this data is very limited overall. There is no adequate data supporting continuation of RADICAVA therapy in patients with pronounced impairment of respiratory function (rule of thumb: %FVC $\leq$ 50%) or in patients with pronounced functional worsening. In patients with significant worsening of overall and/or pulmonary symptoms/function, consideration should therefore be given to discontinuing RADICAVA.

3.1 Dosage Information

The recommended dosage of RADICAVA is an intravenous infusion of 60 mg administered over a 60-minute period, according to the following schedule:

- An initial treatment cycle with daily dosing for 14 days, followed by a 14-days drug-free period
- Subsequent treatment cycles with daily dosing for 10 days out of 14-days periods, followed by 14-days drug-free periods

3.2 Preparation and Administration Information for RADICAVA

RADICAVA is for intravenous infusion only.

Preparation

Dilute two ampoules (60mg in total) with an appropriate volume of physiological saline for intravenously administration over 60 minutes period, once a day.

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

Administration

Administer the diluted 60 mg dose of RADICAVA over a total of 60 minutes IV infusion.

Promptly discontinue the infusion upon the first observation of any signs or symptoms consistent with a hypersensitivity reaction *[see Warnings and Precautions (6.1, 6.2)]*.

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

4 DOSAGE FORM AND STRENGTH

RADICAVA is supplied for intravenous infusion in a single-dose ampoule containing 30 mg of edaravone in 20 mL clear and colorless aqueous solution.

5 CONTRAINDICATIONS

RADICAVA is contraindicated in patients with a history of hypersensitivity to edaravone or to any of the inactive ingredients in this product. Hypersensitivity reactions and anaphylactic reactions have occurred *[see Warnings and Precautions (6.1, 6.2)]*.

Hypersensitivity to the active substance or to any of the excipients listed in section 9.

6 WARNINGS AND PRECAUTIONS

6.1 Hypersensitivity Reactions

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

Patients should be monitored carefully for hypersensitivity reactions. If hypersensitivity reactions occur, discontinue RADICAVA, treat per standard of care, and monitor until the condition resolves *[see Contraindications (5)]*.

6.2 Sulfite Allergic Reactions

RADICAVA contains sodium bisulfite (E-222), a sulfite that may rarely cause severe hypersensitivity reactions and bronchospasm, 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 than non-asthmatic people.

6.3 Effects on ability to drive and use machines

Patients should be advised not to drive or operate machinery until they know how this medicine affects them.

6.4 Excipients with known effects

This medicine contains 57.5 mg sodium in each 20ml ampoule, equivalent to 2.9% of the WHO recommended maximum daily intake of 2g sodium for an adult.

This medicine contains sodium bisulfite (E-222) *[see Sulfite Allergic Reactions (6.2).]*

7 ADVERSE REACTIONS

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

- Hypersensitivity Reactions *[see Warnings and Precautions (6.1)]*
- Sulfite Allergic Reactions *[see Warnings and Precautions (6.2)]*

7.1 Clinical Trials Experience

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

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

Most Common Adverse Reactions Observed During Clinical Studies

Table 1 lists the adverse reactions that occurred in > 2% of patients in the RADICAVA- treated group and that occurred at least 2% more frequently than in the placebo-treated group in randomized placebo-controlled ALS trials. The most common adverse reactions that occurred in >10% of RADICAVA-treated patients were contusion, gait disturbance, and headache.

Table 1: Adverse Reactions from Pooled Placebo-Controlled Trials[a] that Occurred in >2% of RADICAVA -Treated Patients and >2% More Frequently than in Placebo Patients

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

[a] Pooled placebo-controlled studies include two additional studies with 231 additional patients, all using the same treatment regimen *[see Clinical Studies (12)]*.

7.2 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 [see Warnings and Precautions (6.1, 6.2)].

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

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

Data

Animal Data

In rats, intravenous administration of edaravone (0, 3, 30, or 300 mg/kg/day) throughout the period of organogenesis resulted in reduced fetal weight at all doses. In dams allowed to deliver naturally, offspring weight was reduced at the highest dose tested. Maternal toxicity was also observed at the highest dose tested. There were no adverse effects on reproductive function in the offspring. A no-effect dose for embryo fetal developmental toxicity was not identified; the low dose is less than the recommended human dose of 60 mg for RADICAVA 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 embryo fetal death at the highest dose tested, which was associated with maternal toxicity. The higher no-effect dose for embryo fetal developmental toxicity is approximately 6 times the recommended human dose (RHD) for on a body surface area (mg/m^2) basis.

The effects on offspring of edaravone (0, 3, 20, or 200 mg/kg/day), administered by intravenous injection to rats from GD 17 throughout lactation, were assessed in two studies. In the first study, offspring mortality was observed at the high dose and increased activity was observed at

the mid and high doses. In the second study, there was an increase in stillbirths, offspring mortality, and delayed physical development (vaginal opening) at the highest dose tested. Reproduction function in offspring was not affected in either study. Maternal toxicity was evident in both studies at all but the lowest dose tested. The no-effect dose for developmental toxicity (3 mg/kg/day) is less than the RHD on a mg/m^2 basis.

8.2 Lactation

Risk Summary

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

8.3 Pediatric Use

Safety and effectiveness of RADICAVA in children and adolescents under the age of 18 years have not been established.

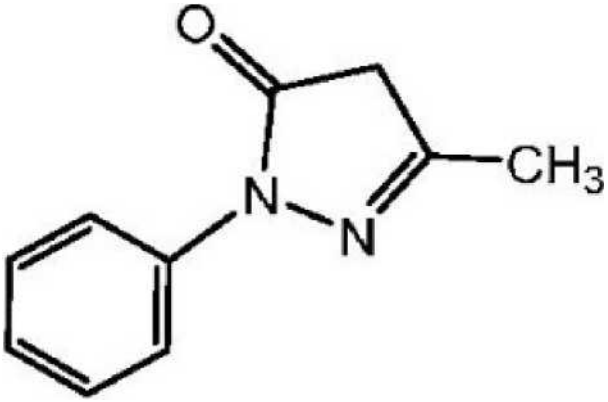
8.4 Geriatric Use

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.

9 DESCRIPTION

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

The chemical structure is:



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

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

RADICAVA is supplied for intravenous infusion in an ampoule containing 30 mg edaravone in 20 mL isotonic, sterile, aqueous solution. Each ampoule contains the following inactive ingredients: sodium bisulfite (20 mg), L-cysteine hydrochloride hydrate (10 mg). Sodium chloride is added for isotonicity and phosphoric acid and sodium hydroxide are added to adjust to pH 4.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

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

10.2 Pharmacodynamics

Cardiac Electrophysiology

At exposures at least 5 times higher than that of the recommended doses of RADICAVA, edaravone does not prolong the QT interval to any clinically relevant extent.

10.3 Pharmacokinetics

RADICAVA is administered by IV infusion. The maximum plasma concentration (C_{max}) of edaravone was reached by the end of infusion. There was a trend of more than dose proportional increase in area under the concentration-time curve (AUC) and 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 after intravenous administration of 63.1 L.

Elimination

The mean terminal elimination half-life of edaravone is approximately 4.5 to 9 hours. The half-lives of its metabolites are 3 to 6 hours. Following intravenous administration, the total clearance of edaravone is estimated to be 35.9 L/h.

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 (UGT1A1, UGT1A6, UGT1A7, UGT1A8, UGT1A9, UGT1A10, UGT2B7, and UGT2B17). 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 (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 kidney before excretion into the urine.

Specific Populations

Geriatric Patients

No age effect on edaravone pharmacokinetics has been found *[see Use in Specific Populations (8.4)]*.

Patients with Renal Impairment

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

Patients with Hepatic Impairment

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

Male and Female Patients

No gender effect on edaravone pharmacokinetics has been found.

Racial or Ethnic Groups

There were no significant racial differences in C_{max} and AUC of edaravone between Japanese and Caucasian subjects.

Drug Interaction Studies

The pharmacokinetics of edaravone is not expected to be significantly affected by inhibitors of cytochrome P450 (CYP) enzymes, UGTs or major transporters.

In vitro studies demonstrated that, at the recommended dosage, 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 other 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 dosage of edaravone.

In vitro data indicated that edaravone was not a substrate of OATP1B1 or OATP1B3.

11 NONCLINICAL TOXICOLOGY

11.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In a 26-week carcinogenicity study in male and female transgenic (Tg rasH2) mice, oral administration of edaravone (0 [water control], 0 [vehicle control], 100, 150, or 350 mg/kg) resulted in no increase in tumors.

In a 2-year carcinogenicity study in rats, oral administration of edaravone (0, 50, 100, or 200 mg/kg in males; 0, 50, 100, or 250 mg/kg in females) resulted in no increase in tumors.

Carcinogenicity studies of edaravone using the intravenous route have not been conducted.

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 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 are up to approximately 3 times the RHD for RADICAVA (60 mg) on a body surface area (mg/m^2) basis.

11.2 Animal Toxicology and/or Pharmacology

Oral administration of edaravone (0, 10, 30, 100, or 300 mg/kg/day) in dogs for 39 weeks resulted in neurotoxicity, characterized by white matter vacuolation in the spinal cord and vacuolation and nerve fiber atrophy in the sciatic nerve, at the two highest doses tested. The microscopic findings were accompanied by gait abnormalities, loss of patellar reflex, and inability to rise.

12 CLINICAL STUDIES

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

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

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

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

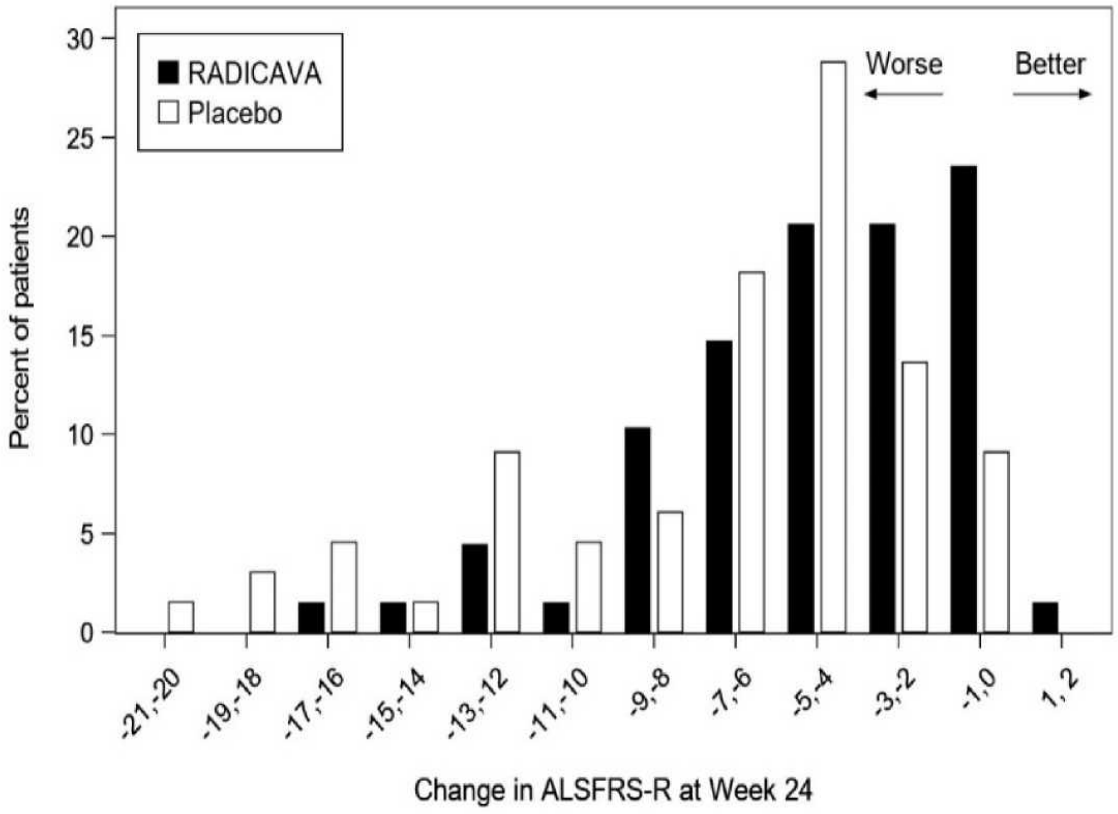
- An initial treatment cycle with daily dosing for 14 days, followed by a 14-day drug-free period (Cycle 1)
- Subsequent treatment cycles with daily dosing for 10 days out of 14-day periods, followed by 14-day drug-free periods (Cycles 2-6).

The primary efficacy endpoint was a comparison of the change between treatment arms in the ALSFRS-R total scores from baseline to Week 24. The ALSFRS-R scale consists of 12 questions that evaluate the fine motor, gross motor, bulbar, and respiratory function of patients with ALS (speech, salivation, swallowing, handwriting, cutting food, dressing/hygiene, turning in bed, walking, climbing stairs, dyspnea, orthopnea, and respiratory insufficiency). Each item is scored from 0-4, with higher scores representing greater functional ability. The decline in ALSFRS-R scores from baseline was significantly less in the RADICAVA-treated patients as compared to placebo (see Table 2). The distribution of change in ALSFRS-R scores from baseline to Week 24 by percent of patients is shown in Figure 1.

Table 2: Analysis of Change from Baseline to Week 24 in ALSFRS-R Scores

Treatment	**Change from Baseline LS Mean ± SE(95% CI)**	**Treatment Difference (RADICAVA - placebo [95% CI])**	***P*- value**
RADICAVA	-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



13 HOW SUPPLIED/STORAGE AND HANDLING

13.1 How Supplied

RADICAVA is supplied as a 30 mg/20 mL (1.5 mg/mL) clear, colorless, sterile solution for intravenous infusion in single-dose ampoules. Every carton box contains ten ampoules.

13.2 Storage and Handling

RADICAVA

Store RADICAVA at up to 25°C.

Chemical and physical in-use stability of the diluted solution for infusion was demonstrated for 24 hours at 30°C .

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

Shelf life
The expiry date of the product is indicated on the packaging materials.

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