

Revised: June 2015 (18th version) D15a

Standard Commodity Classification No. of Japan
87119

- Free radical scavenger -

RADICUT[®] Injection 30mg

< The Japanese Pharmacopoeia Edaravone injection >

Prescription drug*

Storage
Store at room temperature.

Expiration date
Do not use after the expiration date indicated on the package and the label.

Approval No.	21300AMZ00377000
Date of listing in the NHI reimbursement price	June 2001
Date of initial marketing in Japan	June 2001
International birth date	April 2001
Date of latest reexamination	March 2011
Date of latest additional indication	June 2015

*Caution - Use under the prescription of a physician etc.

CONTRAINDICATIONS (RADICUT is contraindicated in the following patients.)

- (1) Patients with severe renal impairment [The renal impairment may be aggravated. For use in patients with amyotrophic lateral sclerosis (ALS), see (3)-3),4) of "Important Precautions" section.]
- (2) Patients with a history of hypersensitivity to any of the ingredients of this product

2. The efficacy and safety of this product in patients with Japan ALS severity classification of grade 4 or above and patients with forced vital capacity less than 70% of theoretical normal value have not been established, since there is little clinical experience in such patients. Administration of this product in such patients should be judged carefully in consideration of risks and benefits.

DESCRIPTION

Active ingredient [in each ampoule (20 mL)]	Edaravone (JP)	30 mg
Inactive ingredients [in each ampoule (20 mL)]	Sodium bisulfite	20 mg
	L-cysteine hydrochloride hydrate	10 mg
	Sodium chloride	135 mg
	Sodium hydroxide	q.s.
	Phosphoric acid	q.s.
Description/ Dosage form	Clear and colorless / aqueous solution for injection	
pH	3.0 - 4.5	
Osmotic pressure ratio	ca. 1 (ratio to physiological saline)	

INDICATIONS

1. Improvement of neurological symptoms, disorder of activities of daily living, and functional disorder associated with acute ischaemic stroke
2. Inhibition on progression of functional disorder in patients with amyotrophic lateral sclerosis (ALS)

<Precautions related to INDICATIONS>

Use in patients with amyotrophic lateral sclerosis (ALS)

1. When this product is administered, the patient's eligibility should be assessed after investigating background such as Japan ALS severity classification, respiratory function of patients included in clinical trials and the result of each clinical trial and understanding the efficacy and safety of this product. (See "Clinical Studies" section.)

DOSAGE AND ADMINISTRATION

1. Improvement of neurological symptoms, disorder of activities of daily living, and functional disorder associated with acute ischaemic stroke
The usual adult dosage is one ampoule (30 mg of edaravone) diluted with an appropriate volume of physiological saline, etc., which is administered intravenously over 30 minutes twice a day in the morning and the evening.
Administration of this product should be initiated within 24 hours after the onset of the disease, and the duration of administration should be within 14 days.
2. Inhibition on progression of functional disorder in patients with amyotrophic lateral sclerosis (ALS)
The usual adult dosage is two ampoules (60 mg of edaravone) diluted with an appropriate volume of physiological saline, etc., which is administered intravenously over 60 minutes once a day.
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.

<Precautions related to DOSAGE AND ADMINISTRATION >**Use in patients with acute ischaemic stroke**

It should be considered that the duration of administration is

reduced according to the patient's clinical condition.

PRECAUTIONS

1. Careful Administration (RADICUT should be administered with care in the following patients)

- (1) Patients with renal impairment and/or dehydration [Acute renal failure or renal impairment may be aggravated. Especially in the patients with high BUN/creatinine ratio before administration, its fatal outcome has been reported. (See "Important Precautions" section.)]
- (2) Patients with infections [Acute renal failure or renal impairment may be aggravated due to the deterioration of systemic conditions. (See "Important Precautions" section.)]
- (3) Patients with hepatic impairment [Hepatic impairment may be aggravated. (See "Important Precautions" section.)]
- (4) Patients with cardiac diseases [Cardiac diseases may be aggravated. Renal impairment may occur as well.]
- (5) Patients with severe disturbance of consciousness (i.e. with Japan Coma Scale score of ≥ 100 , in which state patients do not awake to the external stimulation) [Fatal outcome has been reported in these patients. (See "Important Precautions" section.)]
- (6) Elderly patients [Fatal outcome has been reported in these patients. (See "Important Precautions" section.)]

2. Important Precautions

- (1) This product should be administered in liaison with a well-trained physician, who is well aware of this product and has enough experience treating for the disease indicated.
- (2) Prior to the administration of this product, enough explanation of the adverse reactions, etc. should be given to the patient or their appropriate proxy consentor on behalf of the patient.
- (3) After administration, aggravation of acute renal failure or renal impairment, severe liver disorder, and/or disseminated intravascular coagulation (DIC), which can be fatal, may be observed. Among these patients, serious cases concurrently developing renal impairment, hepatic impairment, and/or hematological disorders, etc., have been reported.
- 1) Laboratory tests for renal, hepatic function and blood cell counts should be performed in order to detect early changes in BUN, creatinine, AST (GOT), ALT (GPT), LDH, CK (CPK), red blood cell count and platelet count, before or immediately after administration, since the laboratory data may deteriorate at the early stage of administration in most cases. During administration, the laboratory tests should be performed frequently. If abnormal laboratory data and/or symptoms such as oliguria are found, this product should be immediately discontinued and appropriate therapeutic measures should be taken. Careful monitoring should be continued after the discontinuation of this product as well.
- 2) Patients with dehydration before administration, showing high BUN/creatinine ratio or other signs, should be care-

fully monitored systemically during administration, since fatal outcome has been reported in these patients.

- 3) Decreased serum creatinine due to muscle atrophy may occur in association with the disease progression in patients with ALS. Therefore, time course of serum creatinine level should be monitored to detect deteriorating tendency, instead of comparing serum creatinine value at single point in time with reference value. Since BUN level may fluctuate according to water amount in the body, time course of BUN level should be monitored to detect deteriorating tendency, instead of comparing BUN value at single point in time with reference value.
- 4) In patients with muscle atrophy, renal function evaluation unlikely to be affected by muscle mass should be performed periodically before and during the treatment such as estimated glomerular filtration rate (eGFR) based on serum cystatin C level, calculation of creatinine clearance by urine collection, in addition to measurement of serum creatinine and BUN.
- 5) It should be carefully considered whether to continue the administration of this product or not, when an antibiotic is coadministered for the treatment of infections during the administration of this product. If the administration is continued, laboratory data should be monitored more frequently. After the administration the patient should also be carefully monitored by the frequent laboratory data monitoring. (See "Drug Interactions" section.)
- 6) This product should be immediately discontinued and appropriate therapeutic measures should be taken, in liaison with a physician with enough knowledge and experience treating for renal failure, when renal impairment occurs during administration.
- 7) In the patients with infections or with severe disturbance of consciousness (i.e. with Japan Coma Scale score of ≥ 100) many fatal cases have been reported. Therefore the risk/benefit evaluation should be carefully carried out for these patients.
- 8) The elderly patients should be monitored carefully, since many fatal outcomes have been reported in the patients.

3. Drug Interactions

Precautions for coadministration (RADICUT should be administered with care when coadministered with the following drugs)

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Antibiotics (Cefazolin sodium, cefotiam hydrochloride, piperacillin sodium, etc.)	The patients should be carefully monitored and renal function tests should be performed frequently in the concomitant use of the antibiotics, since renal impairment may be aggravated. (See "Important Precautions" section.)	Mechanism is unknown. As this product is mainly excreted by the kidney, concomitant use of renally eliminated antibiotics may augment the loads of kidney.

4. Adverse Reactions

Acute ischaemic stroke

Clinical trials for NDA conducted in Japan (Data available at the time of approval)

Thirty adverse reactions due to this product were reported in 26 of 569 patients (4.57%). The main adverse reactions were 16 events of hepatic dysfunction (2.81%) and 4 events of rash (0.70%). Also, abnormal changes in laboratory test values were reported in 122 of 569 patients (21.4%). The major abnormal changes were abnormal liver function test with increased AST (GOT) in 43 of 558 patients (7.71%) and increased ALT (GPT) in 46 of 559 patients (8.23%).

Post-marketing surveys (Data available at the end of reexamination period)

In the drug use-result survey, 709 adverse reactions due to this product were reported in 431 of 3,882 patients (11.10%). The main adverse reactions were 160 events of liver disorder/abnormal hepatic function (4.12%), 79 events of increased AST (GOT) (2.04%), 59 events of increased ALT (GPT) (1.52%), 34 events of increased LDH (0.88%), 33 events of increased γ -GTP (0.85%), 24 events of increased ALP (0.62%), and 22 events of renal impairment (0.57%).

In the post-marketing clinical study, 30 adverse reactions due to this product were reported in 20 of 194 patients (10.31%). The main adverse reactions were 5 events of liver disorder/abnormal hepatic function (2.58%), 2 events of insomnia (1.03%), and 2 events of pyrexia (1.03%). Also, abnormal changes in laboratory test values were reported in 52 of 194 patients (26.8%). The major abnormal changes were 17 events of increased AST (GOT) (8.67%), 12 events of increased ALT (GPT) (6.19%), 10 events of increased serum uric acid (5.15%) and 9 events of increased creatinine (4.64%).

In the specified drug use survey in pediatric patients with ischaemic stroke, 6 adverse reactions due to this product were reported in 5 of 118 patients (4.24%). The main adverse reactions were 4 events of liver disorder/abnormal hepatic function (3.39%).

Amyotrophic lateral sclerosis (ALS)

Clinical trials for NDA conducted in Japan (Data available at the time of approval of additional indication)

Forty six adverse reactions due to this product were reported in 37 of 317 patients (11.7%). The main adverse reactions were 4 events of rash (1.3%), 4 events of liver disorder (1.3%), 3 events of hypertension (0.9%), 3 events of increased γ -GTP (0.9%), and 3 events of glucose urine present (0.9%).

(1) Clinically significant adverse reactions

1) **Acute renal failure (0.26%), nephrotic syndrome (0.02%)**: Renal function tests should be performed frequently and patients should be monitored carefully, since acute renal failure or nephrotic syndrome may occur. This product should be discontinued and appropriate therapeutic measures should be taken, when decreased renal function and/or the symptoms of oliguria, etc. are found. (See “Important Precautions” section.)

2) **Fulminant hepatitis (incidence unknown), hepatic dysfunction (0.24%), jaundice (incidence unknown)**:

Liver function tests should be performed frequently, and patients should be monitored carefully, since severe hepatitis including fulminant hepatitis, hepatic dysfunction or jaundice with significant increase in AST (GOT), ALT (GPT), ALP, γ -GTP, LDH, blood bilirubin, etc. may occur. This product should be discontinued and appropriate therapeutic measures should be taken when any abnormalities are found. (See “Important Precautions” section.)

3) **Thrombocytopenia (0.08%), granulocytopenia (incidence unknown)**: Hematological tests should be performed frequently and patients should be monitored carefully, since thrombocytopenia or granulocytopenia may occur. This product should be discontinued and appropriate therapeutic measures should be taken, when any abnormalities are found. (See “Important Precautions” section.)

4) **Disseminated intravascular coagulation (DIC) (0.08%)**: Hematological tests should be performed periodically, since DIC may occur. This product should be discontinued and appropriate therapeutic measures should be taken, when any abnormalities in hematological tests or symptoms suspicious of DIC are found.

5) **Acute lung injury (incidence unknown)**: Patients should be monitored carefully, since acute lung injury with pyrexia, cough, dyspnoea and chest X-ray abnormality may occur. This product should be discontinued and appropriate therapeutic measures, including administration of corticosteroids, should be taken, when any signs of acute lung injury are found.

6) **Rhabdomyolysis (incidence unknown)**: Patients should be monitored carefully, since rhabdomyolysis may occur. This product should be discontinued and appropriate therapeutic measures should be taken, when myalgia, weakness, increased CK (CPK) and increased blood and/or urine myoglobin are found.

7) **Shock, anaphylactoid reaction (incidence unknown, each)**: Patients should be monitored carefully, since shock and anaphylactoid reactions (urticaria, blood pressure decreased and dyspnoea, etc.) may occur. This product should be discontinued and appropriate therapeutic measures should be taken, when any abnormalities are found.

(2) Other adverse reactions

Incidence Type	5% > \geq 0.1%	0.1% >	Incidence unknown
Hypersensitivity ^{note)}	Rash	Redness, swelling, wheals, pruritus	Erythema (erythema multiforme exsudativum, etc.)
Hematologic	Decreased red blood cell count, increased white blood cell count, decreased white blood cell count, decreased haematocrit, decreased haemoglobin, increased platelet count, decreased platelet count		

Injection site		Injection site rash, injection site redness and swelling	
Hepatic	Increased total bilirubin, urobilinogen appeared, increased AST (GOT), increased ALT (GPT), increased LDH, increased Al-P, increased γ -GTP	Bilirubinuria	
Renal	Increased BUN, increased serum uric acid, proteinuria, haematuria, increased creatinine	Decreased serum uric acid	Polyuria
Gastrointestinal		Nausea, vomiting	
Others	Pyrexia, increased serum cholesterol, increased triglyceride, decreased serum total protein, increased CK (CPK), decreased CK (CPK), decreased serum potassium, increased serum potassium, glucose urine present	Feeling hot, increased blood pressure, decreased serum cholesterol, decreased serum calcium, headache	

The incidences were calculated based on the results of clinical studies in patients with acute ischaemic stroke conducted in Japan, post-marketing surveys, and clinical studies in patients with ALS conducted in Japan (at the time of approval of additional indication).

Note

Appropriate therapeutic measures such as discontinuation of this product should be taken, when these symptoms listed above occur.

5. Use in the Elderly

In elderly patients, this product should be discontinued and appropriate therapeutic measures taken when any adverse reactions are found, since they often have reduced physiological function. Special caution should be exercised in the elderly patients, since many fatal cases have been reported in these patients. (See "Important Precautions" section.)

6. Use during Pregnancy, Delivery or Lactation

- (1) RADICUT is not recommended to be administered to pregnant women or women who may possibly be pregnant. [The safety of the product in pregnant women has not been established.]
- (2) Lactation should be prohibited during administration of this product. [Animal studies in rats have shown that edaravone is excreted in breast milk.]

7. Pediatric Use

The safety of RADICUT in children has not been established (acute ischaemic stroke: little clinical experience, amyotrophic lateral sclerosis [ALS]: no clinical experience).

8. Precautions concerning Use

(1) Precautions when opening the ampoule:

This product 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.

(2) Precautions in preparation

- 1) As a general rule, this product 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).
- 2) This product 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).
- 3) This product should not be mixed with infusions of anticonvulsants including diazepam, phenytoin sodium, etc. (the solution may become cloudy).
- 4) This product should not be mixed with potassium canrenoate (the solution may become cloudy).

9. Other Precautions

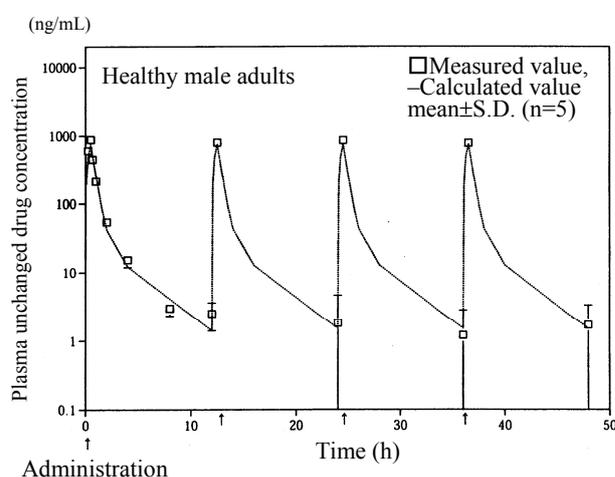
- (1) It has been reported that cerebral embolism reoccurred or cerebral haemorrhage occurred during or after administration of this product.
- (2) In a 28-days continuous intravenous infusion study in dogs, symptomatic changes, such as limited usage of limbs, abnormal gait, etc., and pathological nerve 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.

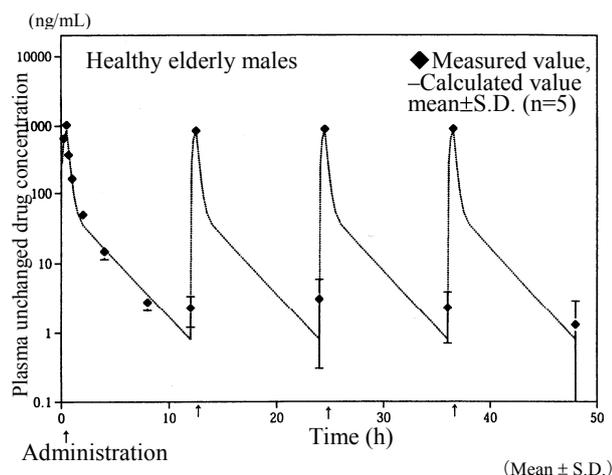
PHARMACOKINETICS

1. Plasma concentration¹⁾

The profiles of plasma unchanged drug concentration after multiple intravenous doses (0.5 mg/kg) over 30 minutes twice a day for 2 days to 5 healthy male adults and 5 healthy elderly males aged 65 years or more are illustrated in the following figures and pharmacokinetic parameters calculated from the profiles in plasma unchanged drug concentration after the initial dose are provided in the following table.

(Note) The approved dose of this product is 30 mg per one time for use in patients with acute ischaemic stroke and 60 mg per one time for use in patients with amyotrophic lateral sclerosis (ALS).





Pharmacokinetic parameter	Healthy male adults (n=5)	Healthy elderly males (n=5)
C_{max} (ng/mL)	888±171	1041±106
$t_{1/2\alpha}$ (h)	0.27±0.11	0.17±0.03
$t_{1/2\beta}$ (h)	2.27±0.80	1.84±0.17

The plasma unchanged drug concentration disappeared in both healthy adults and elderly males in the almost same way without any signs of accumulation.

2. Serum protein binding rates²⁾

The binding rates of edaravone (5 μ M and 10 μ M) to human serum protein and human serum albumin were 92% and 89-91%, respectively (*in vitro*).

3. Metabolism¹⁾

The major metabolite in healthy male adults and healthy elderly males was sulfate conjugate in plasma, and glucuronide conjugate was also detected in plasma. In urine, the major metabolite of the product was glucuronide conjugate and sulfate conjugate was also detected.

4. Excretion¹⁾

After repeated intravenous administration of this product to healthy male adults and healthy elderly males twice a day for 2 days (0.5 mg/kg/30 minutes X 2 times/day), 0.7-0.9% and 71.0-79.9% of the dose were recovered as unchanged drug and metabolites in urine, respectively, up to 12 hours after each dose.

(Note) The approved dose of this product is 30 mg per one time for use in patients with acute ischaemic stroke and 60 mg per one time for use in patients with amyotrophic lateral sclerosis (ALS).

CLINICAL STUDIES

1. Acute ischaemic stroke³⁻⁷⁾

In a placebo-controlled, double-blind study in patients with the acute ischaemic stroke within 72 hours after onset^{*1}, some improvement in neurological symptoms and impaired activities of daily living were reported in the edaravone group. A difference in the improvement rate for final global improvement rating was 32.8% (95% confidence interval: 20.3-45.3%), showing a significant difference between the

edaravone group and the placebo group by the rank-sum test.

In the subjects administered within 24 hours after onset, the difference in the improvement rate for final global improvement rating was 48.2% (95% confidence interval: 26.6-69.7%). Final global improvement rate (improved or higher) in all subjects and that in the group administered within 24 hours after onset are shown in Table 1.

Table 1: Proportion of subjects assessed as improved or higher in final global improvement rate

	Edaravone group	Placebo group
All subjects administered within 72 hours after onset	64.8% (81/125 subjects)	32.0% (40/125 subjects)
Subjects administered within 24 hours after onset	73.8% (31/42 subjects)	25.6% (10/39 subjects)

Furthermore, the rank-sum test showed a significant difference between the edaravone group and the placebo group, in functional prognosis (modified Rankin Scale) assessed in all subjects upon discharge from the hospital within 3 months (after 3 months if hospitalized for 3 months or more) and the edaravone group surpassed the placebo group in the rate of “no symptom” (edaravone group: 22.3% (27/121 subjects), placebo group: 10.0% (12/120 subjects)). In the subjects administered within 24 hours after onset, “no symptom” accounted for 34.1% (14/41 subjects) in the edaravone group and 2.9% (1/35 subjects) in the placebo group.

In both groups, concentrated glycerol and fructose were co-administered as basal therapy.

All clinical data generated before approval including the above results demonstrated more pronounced effect in subjects administered within 24 hours after onset. It was endorsed by the fact that the improvement rate (improved or higher) on global improvement rating in subjects administered 30 mg of edaravone within 24 hours after onset was 70.3% (71/101 subjects), but that in the subjects treated within 72 hours^{*1} was 65.9% (178/270 subjects).

*1 The clinical studies at the developmental stage were mainly conducted in patients with acute ischaemic stroke who were hospitalized within 72 hours after onset. Although the statistical analysis conducted in all the subjects showed efficacy, its stratified analysis revealed a more pronounced effect in patients treated within 24 hours after onset. Accordingly, the approved dosage and administration states “treatment should be initiated within 24 hours after onset”. (Note) Excerpts from the approved dosage and administration of this product:
Administration of this product should be initiated within 24 hours after the onset of the disease, and the duration of administration should be within 14 days.

2. Amyotrophic lateral sclerosis (ALS)

This product has not been evaluated in a study which can clarify the effect of the drug on survival.

(1) A placebo-controlled double-blind comparative study (the 2nd confirmatory study)⁸⁾

When edaravone or placebo was intravenously administered at 60 mg in patients with ALS (warranting “Definite” or “Probable” 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 80% and illness duration within 2 years) in 6 cycles of treatment^{*2}, 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 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	66	41.9±2.2	35.0±5.6	-7.50±0.66	2.49 [0.99, 3.98]	0.0013
Edaravone group	68	41.9±2.5	37.5±5.3	-5.01±0.64		

- The cases completed the 3rd cycle (reached Day 81 after treatment initiation) were evaluated.
- Mean ± SD
- At the time of 2 weeks after the 6th cycle completion or discontinuation of treatment (LOCF)
- Adjusted mean change ± SE
- Based on a model of analysis of variance with treatment groups, mean changes in ALSFRS-R scores in run-in period, the El Escorial and the revised Airlie House diagnostic criteria for ALS, and age as factors

(2) A placebo-controlled double-blind comparative study (the 1st confirmatory study)⁹⁾

When edaravone 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^{*2}, 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	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		

- The cases completed the 3rd cycle (reached Day 81 after treatment initiation) were evaluated.
- Mean ± SD
- At the time of 2 weeks after the 6th cycle completion or discontinuation of treatment (LOCF)
- Adjusted mean change ± SE
- 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) A placebo-controlled double-blind comparative study in patients with Japan ALS severity classification of grade 3¹⁰⁾

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^{*2}, mean changes from baseline in the revised ALS functional rating scale (ALSFRS-R) as primary endpoint were shown in Table 4 and statistically significant difference was not observed between the treatment groups.

Table 4: 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		

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

^{*2}: Once-daily consecutive administration for 14 days and subsequent cessation for 14 days of this product were combined in the 1st cycle of treatment. After completion of the 1st cycle, this product 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).

PHARMACOLOGY

1. Mechanism of action

There have been many reports describing that free radicals such as hydroxyl radical ($\cdot\text{OH}$) play a major causative role in the development of cerebral vascular disorder resulting from ischaemia. During ischaemia or ischaemic reperfusion, the hyperactivity of a metabolic system of arachidonic acid, etc. increases the production of free radicals. These free radicals peroxidize unsaturated fatty acid of cell membrane lipids, which leads to cell membrane injury and ultimately to cerebral dysfunction.

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.

This product scavenges free radicals and inhibits lipid peroxidation, and thereby prevents oxidative damage to brain cells (vascular endothelial cells/nerve cells).

In other words, this product protects the brain in case of acute ischaemic stroke by exerting its inhibitory effects against the development and progression (exacerbation) of ischaemic cerebral vascular disorder such as cerebral oedema, cerebral infarction, neurological deficits, and delayed neuronal death. In case of amyotrophic lateral sclerosis (ALS), this product suppresses the disease progression by exerting its inhibitory effects against the development of oxidative damage to nerve cells.

2. Effects against the acute ischaemic stroke

(1) Neuroprotective effect⁶⁾

NAA (N-acetyl aspartate) is a specific marker for viable neuronal cells that is reported to decrease immediately after the onset of ischaemic stroke and be scarcely detected in the injured tissues after 24 hours. When NAA was determined by ¹H-MRS (magnetic resonance spectroscopy) after administration of this product to patients with acute ischaemic stroke, NAA in the center of the infarct lesion was significantly retained on the 28th day after onset as compared to the control group.

(2) Inhibitory effect against a reduction in regional blood flow in the ischaemic penumbra⁷⁾

When regional cerebral blood flow was determined by ¹³⁵Xe-SPECT (single photon emission computerized tomography) after administration of this product to patients (n=8) with acute ischaemic stroke, the product exhibited its inhibitory effect against the reduction in regional cerebral blood flow in the ischaemic penumbra in 5 patients who improved in functional outcomes (modified Rankin Scale).

3. Cerebroprotecting effect in a cerebral ischaemia model¹¹⁻¹⁶⁾

(1) Effects of inhibiting cerebral oedema and ischaemic stroke and of alleviating neurological deficits

In an ischaemic cerebral vascular disorder model (rat), the intravenous administration of this product (3 mg/kg) after the occurrence of ischaemia or ischaemic reperfusion suppressed the progression of cerebral oedema and ischaemic stroke and remitted the following neurological deficits.

(2) Inhibitory effect against delayed neuronal death

In a forebrain ischaemic reperfused model (rat), the intravenous administration of this product (3 mg/kg) immediately after ischaemic reperfusion suppressed delayed neuronal death.

4. Free radical scavenging effect^{11,12,17-19)}

(1) Free radical scavenging effect and inhibitory effect against lipid peroxidation (*in vitro*)

Edaravone exhibited a hydroxyl radical scavenging effect. It also inhibited the peroxidation of linoleic acid and the lipid peroxidation in the brain homogenate caused by hydroxyl radical dose-dependently. Furthermore, it inhibited the lipid peroxidation of artificial phospholipid membrane liposome caused by water- and fat- soluble peroxy radicals.

(2) Free radical scavenging effect in a cerebral ischaemia model

The intravenous administration of this product at the dose (3 mg/kg) that exhibited a cerebroprotecting effect in a cerebral ischaemia model (rat) inhibited an increase in hydroxyl radical in the penumbra of the ischaemia and at the reperfused region of ischaemia.

(3) Inhibitory effect against vascular endothelial cell injury caused by free radical (*in vitro*)

1 μ M or more of this product inhibited cultured vascular endothelial cell injury *in vitro* caused by 15-HPETE (hydroperoxyeicosatetraenoic acid).

5. Non-clinical studies related to disease conditions of amyotrophic lateral sclerosis (ALS)²⁰⁾

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.

PHYSICOCHEMISTRY

Nonproprietary name: Edaravone

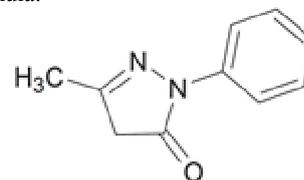
Chemical name:

5-Methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one

Molecular formula: C₁₀H₁₀N₂O

Molecular weight: 174.20

Structural formula:



Description:

Edaravone occurs as white to pale yellowish white crystals or crystalline powder. It is freely soluble in ethanol (99.5) and in acetic acid (100), and slightly soluble in water.

Melting point: 127-131 °C

CONDITIONS FOR APPROVAL

A risk management plan should be prepared and implemented appropriately.

PACKAGING

RADICUT Injection 30 mg:

20 mL × 10 ampoules

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REQUEST FOR LITERATURE SHOULD BE MADE TO:

Safety Information Department
Pharmacovigilance & Quality Assurance Division
Mitsubishi Tanabe Pharma Corporation
3-2-10, Dosho-machi, Chuo-ku, Osaka 541-8505, Japan

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