

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**209176Orig1s000**

**RISK ASSESSMENT and RISK MITIGATION  
REVIEW(S)**

**Division of Risk Management (DRISK)**  
**Office of Medication Error Prevention and Risk Management (OMEPRM)**  
**Office of Surveillance and Epidemiology (OSE)**  
**Center for Drug Evaluation and Research (CDER)**

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<b>Application Type</b>	NDA
<b>Application Number</b>	209176
<b>PDUFA Goal Date</b>	March 17, 2017
<b>OSE RCM #</b>	2016-1433
<b>Reviewer Name</b>	Bob Pratt, Pharm.D.
<b>Team Leader</b>	Donella Fitzgerald, Pharm.D.
<b>Deputy Division Director</b>	Jamie Wilkins Parker, Pharm.D.
<b>Review Completion Date</b>	March 1, 2017
<b>Subject</b>	Evaluation of Need for a REMS
<b>Established Name</b>	Edaravone
<b>Trade Name</b>	Radicava
<b>Name of applicant</b>	Mitsubishi Tanabe Pharma Corporation
<b>Therapeutic Class</b>	Free radical-scavenger
<b>Formulation(s)</b>	30 mg in 100 mL solution
<b>Dosing Regimen</b>	60 mg intravenous infusion daily for 14 consecutive days followed by a 2-week drug free period (Cycle 1), then administration of a 60 mg intravenous infusion daily for 10 days over a 14 day period followed by a 2-week drug free period (Cycle 2 and thereafter).

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## EXECUTIVE SUMMARY

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This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Radicava (edaravone) is necessary to ensure the benefits of this product outweigh its risks. Mitsubishi Tanabe Pharma Corporation (Mitsubishi) submitted a New Drug Application (NDA 209176) on June 16, 2016, for edaravone with the proposed indication of treatment of amyotrophic lateral sclerosis (ALS). There were no serious safety concerns associated with the use of edaravone in the supporting ALS clinical studies; however, post marketing analysis of the applicant's global safety database identified cases in Japan of possible hypersensitivity or anaphylactic reactions where there was a reasonable chance of causality. The applicant did not submit a REMS or other risk management plan with the application but proposes the use of a Medication Guide as part of the labeling.

ALS is a rare, serious, and devastating neurodegenerative disease that is invariably fatal. Edaravone showed substantial evidence of clinical efficacy and has a favorable benefit-risk profile. Therefore, this reviewer recommends that a REMS is not needed to ensure the benefits of edaravone outweigh its risks.

## 1 Introduction

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This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Radicava (edaravone) is necessary to ensure the benefits of this product outweigh its risks. Mitsubishi submitted a New Drug Application (NDA 209176) on June 16, 2016, for edaravone with the proposed indication of treatment of amyotrophic lateral sclerosis (ALS). This application is under review in the Division of Neurology Products. The applicant did not submit a REMS or other risk management plan with the application but proposes the use of a Medication Guide as part of the labeling.

## 2 Background

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### 2.1 PRODUCT INFORMATION

Radicava (edaravone), a new molecular entity<sup>a</sup>, is a free radical-scavenger developed as a neuro-protectant for oxidative stress. Edaravone was first approved in 2001 in Japan for the treatment of acute ischemic stroke and was also approved in Japan in June 2015 and in South Korea in December 2015 for the treatment of ALS. It has been suggested that oxidative stress plays a role in motor neuron degeneration and astrocyte dysfunction in ALS.<sup>1</sup> The mechanism of action of edaravone is based upon a free radical scavenging effect in body tissues.

Edaravone is supplied as a 30 mg in 100 mL solution. The applicant's proposal is to administer the drug using a 60 mg intravenous infusion over 60 minutes daily for 14 consecutive days followed by a 2-week drug free period (Cycle 1), then administration of a 60 mg intravenous infusion daily for 10 days over a 14 day period followed by a 2-week drug free period (Cycle 2 and thereafter) as ongoing therapy.<sup>b</sup> The

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<sup>a</sup> FDAAA factor (F): Whether the drug is a new molecular entity.

<sup>b</sup> FDAAA factor (D): The expected or actual duration of treatment with the drug.

drug will likely be administered in various settings that include physician practices, hospital-affiliated outpatient clinics, infusion centers, as well as at home via home infusion services. Edaravone received orphan product designation for the treatment of ALS in May 2015.

## **2.2 REGULATORY HISTORY**

The following is a summary of the regulatory history for NDA 209176 relevant to this review:

- 05/12/2015: Orphan product designation granted for the treatment of amyotrophic lateral sclerosis.
- 06/16/2016: NDA 209176, for the treatment of amyotrophic lateral sclerosis received.
- 12/05/2016: A post mid-cycle meeting was held between the Agency and the applicant via teleconference. There was no discussion regarding the need for a REMS. The meeting minutes, dated December 23, 2016, stated there are no major safety concerns at this time and there are currently no plans for a REMS.

## **3 Therapeutic Context and Treatment Options**

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### **3.1 DESCRIPTION OF THE MEDICAL CONDITION**

Amyotrophic lateral sclerosis (ALS) is a relentlessly progressive, devastating, rare neurodegenerative disorder of unknown etiology that causes muscle weakness, disability, and eventually death. The median survival from the time of diagnosis is three to five years. Incidence rates for ALS in Europe and North America are estimated to range between 1.5 and 2.7 per 100,000 persons per year, whereas prevalence rates range between 2.7 and 7.4 per 100,000 persons. The incidence of ALS increases with age, especially after 40 years of age, and peaks at age 74, decreasing thereafter.<sup>2,3</sup>

The clinical hallmark of ALS is the combination of upper motor neuron and lower motor neuron signs and symptoms. Upper motor neuron findings of weakness, hyperreflexia, and spasticity result from degeneration of frontal motor neurons and axons. Lower motor neuron findings of weakness, atrophy, and fasciculations are a consequence of degeneration of motor neurons in the brainstem and spinal cord. Cognitive and autonomic symptoms, among other symptoms, may also be present. The progressive course of ALS eventually produces one or both of the life-threatening aspects of the disease, which are neuromuscular respiratory failure and dysphagia. Dysphagia poses a risk for aspiration of food, liquids, or secretions with resultant pneumonia, and also increases the risk of dehydration and malnutrition.<sup>3</sup>

### **3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS**

Rilutek® (riluzole), approved in 1995, is the only approved treatment for ALS at this time. The drug is thought to reduce glutamate-induced excitotoxicity and consequent neuronal cell death, though the exact mechanism of action is unknown. In placebo-controlled studies, treatment with riluzole increased the time to a composite endpoint of tracheostomy or death, but measures of muscle strength and neurological function did not show a benefit.<sup>4</sup>

Respiratory symptoms as well as dysphagia, nutrition, fatigue, spasticity, sialorrhea, pseudobulbar affect, depression, sleep problems, and other symptoms may benefit from specific medical management, including ventilation-related interventions.<sup>5</sup>

## 4 Benefit Assessment

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The ALS clinical development program included three randomized, double-blind, placebo controlled Phase 3 studies that evaluated treatment with edaravone 60 mg.<sup>c</sup> All studies were conducted and completed in Japan.

- Study MCI186-16 enrolled 205 subjects with Grade 1 and 2 ALS<sup>d</sup> to edaravone (n=101) or placebo (n=104). The primary efficacy endpoint was the change in the revised ALS functional rating scale score<sup>e</sup> (ALSFRS-R) from baseline to Cycle 6.
- Study MCI186-17 was a placebo-controlled extension of study 186-16 in 180 subjects with Grade 1 and 2 ALS. Subjects who received edaravone in study 186-16 were reassigned to edaravone (E-E group) or placebo (E-P group). Any subject who received placebo in study 186-16 was switched to edaravone (P-E group). The primary efficacy endpoint was the change in ALSFRS-R from Cycle 7 to 12.
- Study MCI186-19 was a replication of study 186-16 in 137 subjects with Grade 1 and 2 ALS randomized to edaravone (n=69) or placebo (n=68). Inclusion criteria were defined based on subgroup analyses of study 186-16 and included subjects who had functionality retained in most activities of daily living (ADL) domains, as well as normal respiratory function and an onset of ALS within two years. The primary efficacy endpoint was the change in ALSFRS-R from baseline to Cycle 6. (The study included an open-label extension phase with an additional six treatment cycles.)

Several secondary endpoints throughout the trials were also evaluated including time to death or certain disease progression<sup>f</sup>, change in % forced vital capacity (FVC), and other measures. It is notable the applicant did not correct for multiple statistical testing of the secondary endpoints.

In study 186-16, the adjusted least squares mean change in ALSFRS-R score from baseline to Cycle 6 was -5.70 in the edaravone group compared with -6.35 in the placebo group, for a between-group-difference of 0.65 in favor of edaravone; however this finding was not significant (p=0.41). Secondary endpoints in the full analysis set did not show a significant difference. However, additional post-hoc exploratory analyses identified a beneficial trend favoring edaravone that was mainly driven by data from subjects

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<sup>c</sup> Cycle 1: IV administration of the study drug once each day for 14 consecutive days, followed by a 2-week drug-free period. Cycle 2 and thereafter: IV administration of the study drug once a day for any 10 days within a 2-week period, followed by a 2-week drug-free period.

<sup>d</sup> Classification of ALS was based on a Japanese severity scale that rated ALS function on a scale of increasing severity from Grade 1 to 5.

<sup>e</sup> The ALSFRS-R is a validated questionnaire-based 48-point scale that measures physical function in carrying out activities of daily living for patients with ALS.

<sup>f</sup> In addition to death, certain disease progression was defined as disability of independent ambulation, loss of upper limb function, tracheotomy, use of a respirator, and use of tube feeding. (Loss of useful speech was also included in the definition for study 186-19.)

who had functionality retained in most activities of daily living (ADL) domains with normal respiratory function. These analyses were used in defining the inclusion criteria for study 186-19.

Study 186-17 evaluated subjects who completed Cycle 6 of study 186-16. The adjusted least squares mean change in ALSFRS-R score from Cycle 7 to the end of Cycle 12 was -4.42 in the E-E group compared with -5.58 in the E-P group, for a between-group-difference of 1.16 in favor of edaravone; however this finding was not significant ( $p=0.22$ ). There was no difference in secondary endpoints.

In Study MCI186-19, the adjusted least squares mean change in ALSFRS-R score from baseline to Cycle 6 was -5.01 in the edaravone group compared with -7.50 in the placebo group, for a between-group-difference of 2.49 in favor of edaravone that was statistically significant ( $p=0.0013$ ). With regard to secondary endpoints, there were 2 events of certain disease progression in the edaravone group compared with 6 events in the placebo group ( $p=0.128$ ). The adjusted least squares mean change in %FVC from baseline to Cycle 6 was -15.61 in the edaravone group compared with -20.40 in the placebo group, for a between-group-difference of 4.79 in favor of edaravone ( $p=0.094$ ).

In his review, the clinical reviewer concluded that substantial evidence of efficacy of edaravone in the treatment of ALS has been demonstrated based on a positive single study, MCI186-019, which showed a very persuasive and statistically significant primary endpoint, as well as supportive evidence from some of the secondary endpoints.<sup>g</sup>

## 5 Risk Assessment & Safe-Use Conditions

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The primary safety analysis set is comprised of the placebo-controlled studies in ALS, Cycles 1 through 6, in which 184 subjects received edaravone and 184 subjects received placebo. A total of 349 subjects received edaravone during the ALS studies; 306 (87.7%) received 6 cycles of edaravone and 98 (28.1%) received 12 cycles of edaravone.

### 5.1 SERIOUS ADVERSE EVENTS<sup>h,i</sup>

There were 6 treatment-emergent deaths in the primary safety set, 4 in the edaravone group and 2 in the placebo group. All of the fatal events were respiratory-related, occurring in Cycles 3 through 6, and all were attributed to worsening ALS. During Cycles 7 through 12 in the study extensions, 2 subjects in the E-P group, 5 subjects in the P-E group, and 4 subjects in the E-E group died. All of the fatal events were related to respiratory failure, pneumonia, or cardiac arrest, and were attributed to worsening ALS.

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<sup>g</sup> FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.

<sup>h</sup> Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, in subject hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the subject or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

<sup>i</sup> FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.

The clinical reviewer agreed with the applicant that disease progression is most likely the cause of the cases of death.

In the primary safety set, treatment-emergent serious adverse events (SAEs) were reported in a smaller number of subjects [32 (17.4%)] in the edaravone group compared with the placebo group [41 (22.3%)]. The most common SAEs were reported in the MedDRA System Organ Class (SOC) gastrointestinal disorders (edaravone vs. placebo: 19 vs. 21) and the SOC respiratory disorders (11 vs. 12). The most frequently reported MedDRA Preferred Terms (PT) were dysphagia (edaravone vs. placebo: 18 vs. 19), respiratory disorder (6 vs. 2), and musculoskeletal disorder (4 vs. 5). There were 3 serious infections in the edaravone group compared with 2 in the placebo group. The clinical reviewer noted the incidence of SAEs was generally low on treatment, and most SAEs seemed related to disease progression.

## **5.2 SEVERE ADVERSE EVENTS**

The proportion of subjects reporting at least 1 severe treatment-emergent adverse event (TEAE) was lower in the edaravone group compared to the placebo group (12.0% vs. 15.2%). The most frequently reported severe TEAEs in both groups (by PT) were gait disturbance (edaravone vs. placebo: 5.4% vs. 2.7%); dysphagia (3.3% vs. 4.9%); and musculoskeletal disorder (2.2% vs. 2.7%). Although gait disturbance was reported at a higher incidence in the edaravone group, the clinical reviewer noted the small numbers of patients tested and the contribution of the underlying disease confounds accurate attribution of causality.

## **5.3 SKIN ADVERSE EVENTS**

Skin TEAEs were reported in 23.4% (43/184) of subjects in the edaravone group and 19.6% (36/184) of subjects in the placebo group. None of the adverse events were serious or severe. Preferred terms reported at a higher incidence in the edaravone group include eczema (edaravone vs. placebo: 12 vs. 4), dermatitis contact (11 vs. 6), rash (7 vs. 4), erythema (5 vs. 3), urticaria (2 vs. 1), dermatitis (1 vs. 0), and toxic skin eruption (1 vs. 0). The case of toxic skin eruption was considered by the investigator to be non-serious and not severe; the patient withdrew from the study and the event resolved with medical management (a detailed description of the toxic skin eruption was not provided).

## **5.4 HYPERSENSITIVITY EVENTS**

In analyses of postmarketing reports from Japan, hypersensitivity reactions (redness, wheals and erythema multiforme) and anaphylactic reactions (urticaria, blood pressure decreased and dyspnea) have been reported. The clinical reviewer believes there were 10 cases that could be attributable to or at least potentially exacerbated by edaravone.

## **6 Expected Postmarket Use**

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Edaravone is likely to be prescribed primarily by neurologists. It is expected that the drug will be administered in various settings that include physician practices, hospital-affiliated outpatient clinics, infusion centers, as well as at home via home infusion services.

## **7 Risk Management Activities Proposed by the applicant**

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The applicant did not submit a REMS or other risk management plan with the application but proposes the use of a Medication Guide as part of the labeling.

## **8 Discussion of Need for a REMS**

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ALS is a relentlessly progressive, devastating, rare neurodegenerative disorder of unknown etiology that causes muscle weakness, disability, and eventually death. Riluzole was approved for the treatment of ALS based upon increasing the time to tracheostomy or death, but the clinical studies that supported approval showed no improvement in muscle strength or neurological function. There continues to be a crucial unmet medical need for effective treatments for ALS.

Based on the positive effect on the ALSFRS-R score observed in study 186-19, the clinical reviewer concluded that significant evidence of the efficacy of edaravone for the treatment of ALS has been demonstrated and that there is a favorable benefit-risk profile. The safety profile as derived from the ALS development program did not have any serious safety concerns. The pivotal study demonstrated a highly significant effect on the primary efficacy endpoint, with edaravone-treated subjects showing a smaller decrease in the mean change in ALSFRS-R score from baseline to Cycle 6 compared with subjects in the placebo group. Although the time to progression and change in %FVC secondary endpoints did not show a significant difference from placebo, each showed a trend in favor of edaravone. It is noted that the proposed edaravone dosing regimen is somewhat atypical (in particular, drug administration on 10 of 14 days during Cycle 2 and subsequent cycles), which may be modified during ongoing labeling negotiations with the applicant.

Fatal events during the studies were attributed to worsening ALS. In the primary safety set, serious adverse events were reported in a smaller proportion of subjects in the edaravone group (17.4%) compared with the placebo group (22.3%). Severe adverse events were also reported in a smaller proportion of edaravone-treated subjects compared with placebo. Although there was an imbalance in skin TEAEs with a larger number reported in the edaravone group, the events were non-serious and not severe. Skin-related adverse events will be described in the Adverse Events section of the labeling. Hypersensitivity adverse events have been reported in the postmarket setting in other indications, and the proposed labeling includes addition of this information to the warnings section of the labeling.

At this time, this reviewer is not recommending a REMS for the management of the potential risks of edaravone therapy.

## **9 Conclusion & Recommendations**

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Amyotrophic lateral sclerosis is a devastating disorder that is invariably fatal and in need of additional effective treatments. Based on the clinical review, the benefit-risk profile is favorable; therefore, this reviewer is not recommending a REMS for edaravone to ensure the benefits outweigh the risks.

Should DNP have any concerns or questions or if new safety information becomes available, please send a consult to DRISK.

## 10 Materials Reviewed

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The following is a list of materials informing this review:

1. Mitsubishi. Draft labeling for edaravone, NDA 209176, September 13, 2016.
2. Mitsubishi. Clinical Overview for edaravone, NDA 209176, June 16, 2016.
3. Mitsubishi. Summary of Clinical Safety for edaravone, NDA 209176, June 16, 2016.
4. Mitsubishi. Summary of Clinical Efficacy for edaravone, NDA 209176, June 16, 2016
5. Breder C. Division of Neurologic Products. Clinical Review for edaravone, NDA 209176, February 2, 2017.

## 11 Appendices

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### 11.1 REFERENCES

<sup>1</sup> D'Amico E, et al. Clinical perspective on oxidative stress in sporadic amyotrophic lateral sclerosis. *Free Radic Biol Med* 2013;65:509-27.

<sup>2</sup> Elman LB and McCluskey L. Clinical features of amyotrophic lateral sclerosis and other forms of motor neuron disease. In:UpToDate, Shefner JM and Dashe JF (Eds), UpToDate, Waltham, MA 2016.

<sup>3</sup> Maragakis NJ, et al. Epidemiology and pathogenesis of amyotrophic lateral sclerosis. In:UpToDate, Shefner JM, Targoff IN and Dashe JF (Eds), UpToDate, Waltham, MA 2016.

<sup>4</sup> Choudry RB, et al. Disease modifying treatment of amyotrophic lateral sclerosis. In:UpToDate, Shefner JM, Targoff IN and Dashe JF (Eds), UpToDate, Waltham, MA 2016.

<sup>5</sup> Galvez-Jimenez N. Symptom-based management of amyotrophic lateral sclerosis. In:UpToDate, Shefner JM, Targoff IN, Morrison RS, and Dashe JF (Eds), UpToDate, Waltham, MA 2016.

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03/01/2017

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03/02/2017