APPROVAL PACKAGE FOR:

APPLICATION NUMBER:
NDA 209176/S-007

Name: RADICAVA (edaravone) Injection, 30 mg/100 mL

Sponsor: Mitsubishi Tanabe Pharma Development America, Inc

Approval Date: November 15, 2018
<table>
<thead>
<tr>
<th>Reviews / Information Included in this Review</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Approval Letter</td>
<td>X</td>
</tr>
<tr>
<td>Tentative Approval Letter</td>
<td></td>
</tr>
<tr>
<td>Labeling</td>
<td>X</td>
</tr>
<tr>
<td>Medical Review(s)</td>
<td></td>
</tr>
<tr>
<td>Chemistry Review(s)</td>
<td>X</td>
</tr>
<tr>
<td>Pharm/Tox Review</td>
<td></td>
</tr>
<tr>
<td>Bioequivalence Review(s)</td>
<td></td>
</tr>
<tr>
<td>Statistical Review(s)</td>
<td></td>
</tr>
<tr>
<td>Microbiology Review(s)</td>
<td></td>
</tr>
<tr>
<td>Other Review(s)</td>
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</tr>
<tr>
<td>Administrative &amp; Correspondence Documents</td>
<td></td>
</tr>
</tbody>
</table>
APPLICATION NUMBER:
NDA 209176/S-007

APPROVAL LETTER
NDA 209176/S-007

APPROVAL LETTER

Mitsubishi Tanabe Pharma Development America, Inc.
U.S. Agent for Mitsubishi Tanabe Pharma Corporation
Attention: Douglas Dobak
Head of Regulatory Affairs
525 Washington Blvd, Suite 400
Jersey City, NJ 07310

Dear Mr. Dobak:

Please refer to your Supplemental New Drug Application (sNDA) dated and received July 19, 2018, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for RADICAVA (edaravone) Injection, 30 mg/100 mL (edaravone) injection.

This Prior Approval supplemental new drug application provides for the addition of a [ ] for the drug product Radicava (edaravone) Injection containing 60 mg of edaravone per 100 mL.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the prescribing information, text for the patient package insert, and Medication Guide) with the addition of any labeling changes in pending “Changes Being Effected” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.
The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes, and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton, bag, and blister film labels that are identical to enclosed bag, and blister film labels, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015, Revision 3). For administrative purposes, designate this submission “Product Correspondence – Final Printed Carton and Container Labels for approved NDA 209176/S-007.” Approval of this submission by FDA is not required before the labeling is used.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Avani Patel, Regulatory Business Process Manager, at (240) 402 - 1845.

Sincerely,

{See appended electronic signature page}

David Lewis, Ph.D.
Branch Chief, BII
Division of Post-Marketing Activities I
Office of Lifecycle Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Enclosures:
  Content of Labeling
  Carton, bag, and blister film Labeling
APPLICATION NUMBER:
NDA 209176/S-007

LABELING
FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

2.1 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-day drug-free period
- Subsequent treatment cycles with daily dosing for 10 days out of 14-day periods, followed by 14-day drug-free periods.
2.2 Preparation and Administration Information
RADICAVA is for intravenous infusion only.

Preparation
Do not use if the oxygen indicator has turned blue or purple before opening the package [see How Supplied/Storage and Handling (16.1, 16.2)]. Once the overwrap package is opened, use within 24 hours [see Storage and Handling (16.2)].

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

Administration
Administer a 60 mg dose of RADICAVA injection as an intravenous infusion bag over a total of 60 minutes (infusion rate approximately 1 mg per minute [3.33 mL per minute]).

Promptly discontinue the infusion upon the first observation of any signs or symptoms consistent with a hypersensitivity reaction [see Warnings and Precautions (5.1, 5.2)].

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

3 DOSAGE FORMS AND STRENGTHS
RADICAVA is supplied for intravenous infusion in a single-dose polypropylene bag containing 60 mg of edaravone in 100 mL of clear, colorless aqueous solution.

4 CONTRAINDICATIONS
RADICAVA is contraindicated in patients with a history of hypersensitivity to edaravone or any of the inactive ingredients of this product. Hypersensitivity reactions and anaphylactic reactions have occurred [see Warnings and Precautions (5.1, 5.2)]

5 WARNINGS AND PRECAUTIONS

5.1 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 (4)].

5.2 Sulfite Allergic Reactions
RADICAVA contains sodium bisulfite, a sulfite that may cause allergic type reactions, including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in susceptible people. The overall prevalence
of sulfite sensitivity in the general population is unknown. Sulfite sensitivity occurs more frequently in asthmatic people.

6 ADVERSE REACTIONS

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

- Hypersensitivity Reactions [see Warnings and Precautions (5.1)]
- Sulfite Allergic Reactions [see Warnings and Precautions (5.2)]

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

Most Common Adverse 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>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>RADICAVA (N=184) %</th>
<th>Placebo (N=184) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contusion</td>
<td>15</td>
<td>9</td>
</tr>
<tr>
<td>Gait disturbance</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>Headache</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Eczema</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Respiratory failure, respiratory disorder, hypoxia</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Glycosuria</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Tinea infection</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

*Pooled placebo-controlled studies include two additional studies with 231 additional patients, all using the same treatment regimen [see Clinical Studies (14)].
6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of RADICAVA outside of the United States. 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.

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 embryofetal developmental toxicity was not identified; the low dose is less than the recommended human dose of 60 mg, on a body surface area (mg/m²) basis.

In rabbits, intravenous administration of edaravone (0, 3, 20, or 100 mg/kg/day) throughout the period of organogenesis resulted in embryofetal death at the highest dose tested, which was associated with maternal toxicity. The higher no-effect dose for embryofetal developmental toxicity is approximately 6 times the recommended human dose (RHD) on a body surface area (mg/m²) 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/m² 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.

8.4 Pediatric Use

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

8.5 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.

8.6 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.

8.7 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.

11 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_{2}O and the molecular weight is 174.20.

The chemical structure is:

![Chemical structure of edaravone]

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

RADICAVA injection is supplied for intravenous infusion in a polypropylene bag containing 60 mg edaravone in 100 mL isotonic, sterile, aqueous solution, which is further overwrapped with polyvinyl alcohol (PVA) secondary packaging. The overwrapped package also contains an oxygen absorber and oxygen indicator to minimize oxidation. Each bag contains the following inactive ingredients: L-cysteine hydrochloride hydrate (20 mg), sodium bisulfite (40 mg). Sodium chloride is added for isotonicity and phosphoric acid and sodium hydroxide are added to adjust to pH 4.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
The mechanism by which RADICAVA exerts its therapeutic effect in patients with ALS is unknown.

12.3 Pharmacokinetics
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 Use in Specific Populations (8.5)].

**Patients with Renal and Hepatic Impairment**

No pharmacokinetic data are available in patients with renal impairment or hepatic impairment [see Use in Specific Populations (8.6, 8.7)].

**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.

**Drug Interaction Studies**

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

*In vitro* studies demonstrated that, at clinical dose, edaravone and its metabolites are not expected to significantly inhibit cytochrome P450 enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4), UGT1A1, UGT2B7, or transporters (P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, and OCT2) in humans. Edaravone and its metabolites are not expected to induce CYP1A2, CYP2B6, or CYP3A4 at the clinical dose level of RADICAVA.

**13 NONCLINICAL TOXICOLOGY**

**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

**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/m²) basis.

**14 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 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 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**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Change from Baseline LS Mean ± SE (95% CI)</th>
<th>Treatment Difference (RADICAVA – placebo [95% CI])</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td>RADICAVA 60mg</td>
<td>-5.01±0.64</td>
<td>2.49 (0.99, 3.98)</td>
<td>0.0013</td>
</tr>
<tr>
<td>Placebo</td>
<td>-7.50±0.66</td>
<td></td>
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</table>
16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

RADICAVA injection is supplied as a 60 mg/100 mL (0.6 mg/mL) clear, colorless, sterile solution for intravenous infusion in a single-dose polypropylene bag, overwrapped with polyvinyl alcohol (PVA) secondary packaging containing an oxygen absorber and oxygen indicator, which should be pink to reflect appropriate oxygen levels [see Dosage and Administration (2.2) and How Supplied/Storage and Handling (16.2)]. These are supplied in cartons as listed below.

NDC 70510-2172-0 60 mg/100 mL (0.6 mg/mL) single-dose bag
NDC 70510-2172-1 1 bag per carton

16.2 Storage and Handling

Store at up to 25°C (77°F). Excursions permitted from 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from light. Store in overwrapped package to protect from oxygen degradation until time of use. The oxygen indicator will turn blue or purple if the oxygen has exceeded acceptable levels. Once the overwrap package is opened, use within 24 hours.
17 PATIENT COUNSELING INFORMATION

Advise the patients to read the FDA-approved patient labeling (Patient Information).

Hypersensitivity Reactions

Advise patients to seek immediate medical care if they experience signs or symptoms of a hypersensitivity reaction [see Warnings and Precautions (5.1)].

Sulfite Allergic Reactions

Advise patients about potential for sulfite sensitivity. Inform patients that RADICAVA contains sodium bisulfite, which may cause allergic type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes, and to seek immediate medical care if they experience these signs or symptoms [see Warnings and Precautions (5.2)].

Pregnancy and Breastfeeding

Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during RADICAVA therapy [see Use in Specific Populations (8.1)].

Advise patients to notify their healthcare provider if they intend to breastfeed or are breastfeeding an infant [see Use in Specific Populations (8.2)].

Marketed and distributed by:
Mitsubishi Tanabe Pharma America, Inc., a US subsidiary of Mitsubishi Tanabe Pharma Corporation
525 Washington Blvd., Suite 400,
Jersey City, NJ 07310

RADICAVA is a registered trademark of Mitsubishi Tanabe Pharma Corporation
© Mitsubishi Tanabe Pharma Corporation [YYYY]
XXXXXX [MM/YYYY] Iss. MM/YY
PATIENT INFORMATION
RADICAVA (ra di kah vah)
(edaravone injection)
for intravenous infusion

What is RADICAVA?
RADICAVA is a prescription medicine used to treat people with Amyotrophic Lateral Sclerosis (ALS).
It is not known if RADICAVA is safe and effective in children.

Do not receive RADICAVA if you are allergic to edaravone or any of the ingredients in RADICAVA. See the end of this leaflet for a complete list of ingredients in RADICAVA.

Before you receive RADICAVA, tell your healthcare provider about all of your medical conditions, including if you:
- have asthma.
- are allergic to other medicines.
- are pregnant or plan to become pregnant. It is not known if RADICAVA will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if RADICAVA passes into your breastmilk. You and your healthcare provider should decide if you will receive RADICAVA or breastfeed.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive RADICAVA?
- You will be prescribed RADICAVA by a healthcare provider. RADICAVA will be given by intravenous (IV) infusion into your vein.
- It takes about 1 hour to receive the full dose of RADICAVA.
- Your healthcare provider will tell you how often you will receive RADICAVA.
- Your healthcare provider will monitor you closely during your treatment with RADICAVA.

What are the possible side effects of RADICAVA?
RADICAVA may cause serious side effects including:
1. Hypersensitivity (allergic) reactions. Hypersensitivity reactions have happened in people receiving RADICAVA and can happen after your infusion is finished. Tell your healthcare provider right away or go to the nearest emergency room if you have any of the following symptoms:
   - hives
   - breathing problems
   - itching
   - swelling of the lips, tongue, face
   - dizziness
   - fainting
   - wheezing
2. Sulfite allergic reactions. RADICAVA contains sodium bisulfite, a sulfite that may cause a type of allergic reaction that can be serious and life-threatening. Sodium bisulfite can also cause less severe allergic reactions, for example, asthma episodes, in certain people. Sulfite sensitivity can happen more often in people who have asthma than in people who do not have asthma. Tell your healthcare provider right away or go to the nearest emergency room if you have any of the following symptoms:
   - hives
   - trouble breathing or swallowing
   - itching
   - swelling of the lips, tongue, face
   - dizziness
   - asthma attack (in people with asthma)
   - wheezing
   - fainting

Your healthcare provider will monitor you during treatment to watch for signs and symptoms of all the serious side effects.

The most common side effects of RADICAVA include bruising (contusion), problems walking (gait disturbance), and headache. These are not all the possible side effects of RADICAVA. Call your healthcare provider for medical advice about side effects.

You may report side effects to Mitsubishi Tanabe Pharma America, Inc. at 1-888-292-0058 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

What are the ingredients in RADICAVA?
Active ingredient: edaravone
Inactive ingredients: L-cysteine hydrochloride hydrate, sodium bisulfite, sodium chloride, phosphoric acid, and sodium hydroxide.

Marketed and distributed by: Mitsubishi Tanabe Pharma America, Inc., a US subsidiary of Mitsubishi Tanabe Pharma Corporation, 525 Washington Blvd., Suite 400, Jersey City, NJ 07310

For more information, go to www.Radicava.com or call 1-888-292-0058.

This Patient Information or Medication Guide has been approved by the U.S. Food and Drug Administration

Revised or Issued: MM/YYYY
Radicava®
(edaravone) injection
60 mg/100 ml (0.6 mg/ml)
For Intravenous Infusion Only
Sterile Solution
Single Use - Discard unused portion
Rx only
100 mL X 1 bag
Each bag contains the following inactive ingredients:
L-cysteine hydrochloride hydrate (21 g), sodium bicarbonate (75 mg), sodium chloride (16 mg), 20 mg of hydrochloric acid and 30 mg of sodium hydroxide are added to adjust pH to 4

Mitsubishi Tanabe Pharma
Attention

- Do not use the product if the indicator has changed color to blue or purple before opening the outer package (Oxygen indicator: Normal color is pink)
- Do not eat the indicator
- Do not eat the oxygen absorber

Do not open until ready to use.

Once the overwrap package is opened, use within 24 hours and write "Discard after MM/DD/YYYY" on the top left of the bag.

Radicava 60mg Blister Film

2018.06.27
Office of Lifecycle Drug Products  
Division of Post-Marketing Activities II  
Review of Chemistry, Manufacturing, and Controls

1. **NDA Supplement Number:** NDA 209176 / S-007

2. **Submission(s) Being Reviewed:**

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</tbody>
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3. **Provides For from the Cover Letter:** the addition of (b)(4) for the drug product Radicava® (edaravone) Injection containing 60 mg of edaravone per 100 mL.

4. **Review #:** 1

5. **Clinical Review Division:** CDER/OEI/DNP

6. **Name and Address of Applicant:**
   Mitsubishi Tanabe Pharma Corporation  
   3-2-10 Doshomachi  
   Chuo-ku, Osaka  
   Japan 541-0045

7. **Drug Product:**

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosage Form</th>
<th>Strength</th>
<th>Route of Administration</th>
<th>Rx or OTC</th>
<th>Special Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radicava® (edaravone)</td>
<td>Injection</td>
<td>30 mg/100 mL</td>
<td>IV</td>
<td>Rx</td>
<td>No</td>
</tr>
</tbody>
</table>

8. **Chemical Name and Structure of Drug Substance:**

   ![Chemical Structure]
   
   USAN: Edaravone  
   CAS Number: 89-25-8  
   Chemical name: 3-Methyl-1-phenyl-2-pyrazolin-5-one  
   Molecular formula: C₁₀H₁₀N₂O  
   MW: 174.20

9. **Indication:** treatment of amyotrophic lateral sclerosis (ALS).

11. Consults:

<table>
<thead>
<tr>
<th>Consults</th>
<th>Recommendation</th>
<th>Date</th>
<th>Reviewer</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPF/Facility</td>
<td>Approve</td>
<td>09/12/2018</td>
<td>Cassandra Abellard</td>
</tr>
<tr>
<td>DMEPA</td>
<td></td>
<td>10/17/2018</td>
<td>Ebony Whaley, PharmD, BCPPS</td>
</tr>
<tr>
<td>DMEPA</td>
<td>Adequate*</td>
<td>11/06/2018</td>
<td>Ebony Whaley, PharmD, BCPPS</td>
</tr>
</tbody>
</table>

*DMEPA was consulted twice regarding the proposed changes to the drug product label.
DMEPA’s first review found the proposed drug product’s carton and container labeling to be inadequate. In response to an IR, the sponsor made most of the recommended changes. DMEPA’s subsequent review found the sponsor’s revised carton and container labeling to be adequate.

12. Executive Summary:

In this Prior Approval Supplemental submission, the sponsor proposes the addition of a new (b)(4) namely 60 mg of edaravone per 100 mL (60 mg/100 mL), for the drug product Radicava® (edaravone) Injection. The currently approved formulation is 30 mg of edaravone per 100 mL (30 mg/100 mL). Importantly, the daily recommended dose of edaravone remains unchanged at 60 mg and the proposed (b)(4) injection time remains unchanged at 60 minutes.

Two information requests (IRs) were sent to the sponsor regarding the proposed labeling for the Radicava IV bag:

- On 09/28/2018, requesting further information regarding the sponsor’s “summative interview” results included in a document entitled “Pro-Active Risk Assessment of Proposed Radicava® Bag Change – Human Factors and Potential Errors” (dated 06/22/2018).
- On 10/22/2018, requesting revisions to the draft carton and container labeling to address, most importantly, the possibility that patients and caregivers will not be able to easily discern that the new 60 mg/100 mL Radicava formulation is in fact a new strength.

The applicant’s responses to the two IRs, which communicated their agreement to make almost all the recommended corrections and changes to the prescribing information (PI), was
found to be adequate for a CMC point of view and from DMEPA’s perspective in a memorandum entitled “Review of Revised Label and Labeling” (dated 11/06/2018).

13. Conclusions & Recommendations:
This supplement is recommended for approval from the CMC perspective.

14. Comments/Deficiencies to be Conveyed to Applicant: None

15. Primary Reviewer:
Richard T. Matsuoka, CMC reviewer, Branch 2, Division of Post-Marketing Activities I, Office of Lifecycle Drug Products, Office of Pharmaceutical Quality (OPQ)

16. Secondary Reviewer:
David B. Lewis, Branch Chief, Branch 2, Division of Post-Marketing Activities I, Office of Lifecycle Drug Products, OPQ

17 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page
Comments: concur; recommend approval from the standpoint of CMC
APPLICATION NUMBER:
NDA 209176/S-007

OTHER REVIEW(S)
REGULATORY BUSINESS PROCESS MANAGER LABELING REVIEW

Office of Program and Regulatory Operations

Application: NDA-209176-SUPPL-7

Name of Drug: RADICAVA® (edaravone) Injection, 30 mg/100 mL

Applicant: Mitsubishi Tanabe Pharma Corporation

Contact information: Douglas N. Dobak Head of Regulatory Affairs

Material Reviewed:

<table>
<thead>
<tr>
<th>Material</th>
<th>Submitted Date</th>
<th>Receipt Date</th>
<th>Compared to</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bag and Carton Labels</td>
<td>October 31, 2018</td>
<td>October 31, 2018</td>
<td>Supplement 5 submitted on April 20, 2018 and approved on August 17, 2018</td>
</tr>
<tr>
<td>Blister film for 60 mg</td>
<td>July 19, 2018</td>
<td>July 19, 2018</td>
<td>Original approved on May 5, 2017 and Final Printed Labels submitted on May 12, 2017</td>
</tr>
</tbody>
</table>

Background and Summary Description:

Radicava is currently marketed as a 30 mg/100 mL intravenous infusion bag. To administer the 60 mg dose with the 30 mg/100 mL product, two intravenous infusion bags are infused over 30 minutes each for a total infusion time of 60 minutes. With this supplement, the sponsor proposes to introduce a 60 mg/100 mL intravenous infusion bag. To administer the 60 mg dose with the proposed 60 mg/mL product, only one intravenous infusion bag is infused over 60 minutes.

DMEPA was consulted on August 8, 2018. The revised carton labeling and container label for Radicava Injection are acceptable from a medication error perspective dated November 6, 2018 by NDA-209176-SUPPL-7.
Ebony Whaley and Lolita White. This supplement is recommended for approval from CMC perspective as of November 6, 2018 by Richard Matsuoka and David Lewis.

OND-RPM was notified because of the toxicity studies and human factory study. Per the email conversation, the human factor data are considered as risk assessment data. The submitted toxicity studies are not new to the submission. OND is okay with OPQ managing this supplement.

PATIENT INFORMATION:

1. Revised date:

Last Approved on May 5, 2017:

Revised or Issued: 05/2017

Proposed change submitted on July 19, 2018

Comment:
This is a minor editorial change to update the revised date upon approval of the supplement and it is acceptable.
PRESCRIBING INFORMATION:

1. **Update in the DOSAGE FORMS AND STRENGTHS and REVISED DATE under HIGHLIGHTS OF PRESCRIBING INFORMATION:**

Last Approval letter for Original dated May 5, 2017:

![Image](image-url)

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**CONTRAINDICATIONS**

Patients with a history of hypersensitivity to edaravone or any of the inactive ingredients in RADICAVA.

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Proposed change submitted on July 19, 2018:

Comments:

1. Addition of DOSAGE FORMS AND STRENGTHS reflects for the drug product Radicava® (edaravone) Injection containing 60 mg of edaravone per 100 mL. This change is acceptable from CMC perspective.
2. Update in the revised date is a minor editorial change and it is acceptable.

2. **Change in the Administration Section:**

Last Approval letter for Original dated May 5, 2017:

Administer each 60 mg dose of RADICAVA injection as two consecutive 30 mg intravenous infusion bags over a total of 60 minutes (infusion rate approximately 1 mg per minute [3.33 mL per minute]).
Proposed change submitted on July 19, 2018:

Comment:
This change reflects the proposed change as described in comment 1 and it is acceptable from CMC perspective.

3. Update in strength in the DOSAGE FORMS AND STRENGTHS:

Last Approval letter for Original dated May 5, 2017:

3 DOSAGE FORMS AND STRENGTHS

RADICAVA is supplied for intravenous infusion in a single-dose polypropylene bag containing 30 mg of edaravone in 100 mL of clear, colorless aqueous solution.

Proposed change submitted on July 19, 2018:

Comment:
This change reflects the proposed change as described in comment 1 and it is acceptable from CMC perspective.

4. Update in the Administration Section:

Last Approval letter for Original dated May 5, 2017:

RADICAVA injection is supplied for intravenous infusion in a polypropylene bag containing 30 mg edaravone in 100 mL isotonic, sterile, aqueous solution, which is further overwrapped with polyvinyl alcohol (PVA) secondary packaging. The overwrapped package also contains an oxygen absorber and oxygen indicator to minimize oxidation. Each bag contains the following inactive ingredients: L-cysteine hydrochloride hydrate (10 mg), sodium bisulfite (20 mg). Sodium chloride is added for isotonicity and phosphoric acid and sodium hydroxide are added to adjust to pH 4.

Proposed change submitted on July 19, 2018:
5. **Update in the How Supplied section:**

**Last Approval letter for Original dated May 5, 2017:**

16.1 How Supplied

RADICAVA injection is supplied as a 30 mg/100 mL (0.3 mg/mL) clear, colorless, sterile solution for intravenous infusion in single-dose polypropylene bags, each overwrapped with polyvinyl alcohol (PVA) secondary packaging containing an oxygen absorber and oxygen indicator, which should be pink to reflect appropriate oxygen levels [see Dosage and Administration (2.2) and How Supplied/Storage and Handling (16.2)]. These are supplied in cartons as listed below.

NDC 70510-2171-1  30 mg/100 mL (0.3 mg/mL) single-dose bag
NDC 70510-2171-2  2 bags per carton

**Proposed change submitted on July 19, 2018:**

**Comment:**
Addition of 60 mg/100 mL bag, This change is acceptable from CMC perspective.
6. **Update in the registered trademark and date:**

_Last Approval letter for Original dated May 5, 2017:_

Comment:

Update to and updated date upon the approval of this supplement reflects the proposed change. This minor editorial change is acceptable.

**BAG LABEL:**

Supplement-5 submitted on April 20, 2018 and approved on August 17, 2018:
Proposed changes submitted on October 31, 2018:

Comments:
1. Proposal to use the Expiration date in MM/YYYY format. The sponsor did not implement DMEPA’s recommendation regarding the expiration date format due to the sponsor’s contact manufacturer having a limitation on the equipment capability; however, DMEPA finds the sponsor’s proposal to use the format MM/YYYY acceptable.
2. Utilizing a different color labeling (green) along with updating and relocating the strength to 60 mg in order to differentiate them from the current 30 mg/100 mL strength IV bags (blue and gray) with the goal of minimizing the risk of the medication error.
3. Update in the NDC number. This change is acceptable per 21 CFR 201.2 & 21 CFR 207.35(b)(3)(i) and per DMEPA perspective.
4. Update in the Barcode. This change reflects the proposed change and it is acceptable from 21 CFR 201.25.
6. This change is acceptable from CMC perspective.

CARTON LABEL:

Supplement-5 submitted on April 20, 2018 and approved on August 17, 2018:
Proposed change submitted on October 31, 2018:

Comments:
1. Addition of New Strength under the principal display panel. This change is acceptable from DMEPA perspective.
2. Update in the NDC Number per 21 CFR 201.2 & 21 along with changes in the background color to yellow for the carton labels, gray background for the drug name Radicava, and green font with new strength 60 mg/100 mL. These changes are acceptable from DMEPA perspective to differentiate the new strength.
3. Addition of Intravenous Infusion Only Statement and discard the unused portion in the principal display panel. This change is acceptable per the approval of the original dated May 5, 2017: RADICAVA is supplied for intravenous infusion in a single-dose polypropylene bag containing 30 mg of edaravone in 100 mL of clear, colorless aqueous solution.
4. Relocation of the inactive ingredients (for 60 mg strength) with updated number of bag at the bottom of the display panel. This change is acceptable from DMEPA perspective.

5. Change in the expiration date format. This change is acceptable per DMEPA perspective.

6. Relocated the statement “For Intravenous Infusion” along with the statement “Infuse 60 mg/100 mL bag over a period of 60 minutes”\(^{(b)(d)}\). These changes are acceptable per DMEPA perspective.

7. Change the location of Radicava with updated strength and new NDC. This change is acceptable per DMEPA perspective.

8. Change the location of table and updated barcode on the side panel which reflect the new strength 60mg/100 mL. These changes are acceptable per DMEPA perspective.

9. Change the location of Rx only under the side panel. This change is acceptable per DMEPA perspective.

10. Addition of inactive ingredients to reflect the new strength under the side panel. This change is acceptable per DMEPA.

11. Addition of “Do not swallow” and “Discard unused IV Solution” under the cautions Section”. These changes are acceptable as described in comment 3.

12. Addition of statement under Usage section of the side panel “Once the overwrap package is opened, use within 24 hours.” This change was approved under Storage and handling in the original letter dated May 5, 2017 and it is acceptable.

13. Change in the storage temperature for the excursion permitted to 15°C- 30°C (59°F-86°F). This change was recommended by DMEPA and it is acceptable.

14. Updated 60 mg strength at the bottom of the side panel. This change is acceptable per DMEPA.

15. Change in the color and design of the bag icon to reflect the 60 mg strength under the side panel. This change is acceptable per DMEPA perspective.

16. Addition of NDC with 60 mg strength on the top of the carton label with gray background and green font. Removal of number of bags and Infuse each bag over a period of 30 minutes statement. These changes are acceptable per DMEPA perspective.

**BLISTER FILM:**

Original approved on May 5, 2017 and Final Printed Labels submitted on May 12, 2017:
Proposed changes submitted on July 19, 2018:
Comments: Updated NDC number and Barcode. These changes are acceptable per 21 CFR 201.2 & 21 CFR 207.35(b)(3)(i) and 21 CFR 201.25 respectively.

Recommendations

The changes to content of labeling, and bag, carton and blister film labels are acceptable. The supplement is recommended for approval.

{See appended electronic signature page}

Avani Patel, PharmD
Regulatory Business Process Manager
Office of Programs and Regulatory Operations
Office of Pharmaceutical Quality
Date 11/13/2018

{See appended electronic signature page}

Teicher Agosto, PharmD
Regulatory Business Process Manager
Office of Programs and Regulatory Operations
Office of Pharmaceutical Quality
Date 11/13/2018