DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209176

NDA APPROVAL

Mitsubishi Tanabe Pharma Development America, Inc.
Attention: Douglas N. Dobak
US Agent for Mitsubishi Tanabe Pharma Corporation
Vice President, Head of Regulatory Affairs and Quality Assurance
525 Washington Blvd, Suite 400
Jersey City, NJ 07310

Dear Mr. Dobak:

Please refer to your New Drug Application (NDA) dated and received June 16, 2016, 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.

This new drug application provides for the use of Radicava (edaravone) injection 30 mg/100 mL for the treatment of amyotrophic lateral sclerosis (ALS).

We have completed our review of this 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 package insert and patient package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton labels that are identical to the carton labels submitted on June 16, 2016, and container labels that are identical to the container labels submitted on April 21, 2017, 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 — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015, Revision 3)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 209176**" Approval of this submission by FDA is not required before the labeling is used.

In addition, we refer to your submission dated January 20, 2017, containing a proposal for submitting revised carton and container labels and to our agreement provided in a letter dated January 30, 2017. We note your January 20, 2017, agreement to implement the following revisions to the June 16, 2016, Radicava carton and container labels within 9 to 13 months. Please report the date of implementation of these revisions in your first NDA annual report.

A. Carton label:

1. Revise the strength statement to display the strength per total followed by strength per mL enclosed by parentheses, as depicted below.

30 mg/100 mL (0.3 mg/mL)	OR	30 mg/100 mL (0.3 mg/mL)

2. Delete the statement [redacted (b) (4)] and change to "Injection" to correctly display the dosage form.
3. The carton label must be revised to include quantitative inactive ingredient information to comply with 21 CFR 201.100(b)(5) for injectables.
4. Each dose of Radicava requires two infusion bags for a total infusion time of 60 minutes, and the carton labeling lists the infusion time as [redacted (b) (4)] minutes. This information may be misinterpreted [redacted (b) (4)] Therefore, the statement [redacted (b) (4)] should be revised to "Infuse each 30 mg/100 mL bag over a period of 30 minutes."
5. Relocate the "Rx Only" statement to the principal display panel (PDP) and ensure that it appears less prominent than other important information (e.g., proprietary name, established name, strength, route of administration) on the PDP.

B. Container label:

1. See recommendation A.3. and revise accordingly.

ADVISORY COMMITTEE

Your application for edaravone was not referred to an FDA advisory committee because the safety profile of edaravone is acceptable for the proposed indication and the clinical trial design is acceptable.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indications in pediatric patients unless this requirement is waived, deferred, or inapplicable. Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of carcinogenicity due to administration of edaravone.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

3208-1 A carcinogenicity study of edaravone, administered by a clinically relevant route, in mouse.

The timetable you submitted on March 10, 2017, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	06/2017
Final Protocol Submission:	10/2017
Study Completion:	11/2020
Final Report Submission:	03/2021

3208-2 A two-year carcinogenicity study of edaravone, administered by a clinically relevant route, in rat.

The timetable you submitted on March 10, 2017, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	06/2017
Final Protocol Submission:	10/2017
Study Completion:	11/2020
Final Report Submission:	03/2021

Finally, we have determined that only clinical trials (rather than nonclinical or observational studies) will be sufficient to identify unexpected serious risks resulting from altered pharmacokinetics of edaravone in patients with severe hepatic impairment or an unexpected serious risk of QT prolongation after administration of edaravone.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following trials:

3208-3 Conduct a clinical trial to evaluate the effects of hepatic impairment on the pharmacokinetics of edaravone in patients with severe hepatic impairment and demographic-matched (e.g., age, gender, race, weight) healthy subjects who receive a single-dose treatment of edaravone. Please refer to the Guidance for Industry Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072123.pdf).

The timetable you submitted on March 10, 2017, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	10/2017
Final Protocol Submission:	12/2017
Trial Completion:	12/2019
Final Report Submission:	06/2020

3208-4 A clinical trial to assess the risk of QT prolongation with edaravone to exclude mean QTc effects greater than 20 ms.

The timetable you submitted on March 10, 2017, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	10/2017
Final Protocol Submission:	03/2018
Trial Completion:	03/2019
Final Report Submission:	11/2019

You should allow sufficient time for the Agency to review, provide feedback, and come to concurrence on these protocols prior to beginning the studies and trials.

Submit clinical protocols to your IND with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)," "Required Postmarketing Final Report Under 505(o)," "Required Postmarketing Correspondence Under 505(o)."**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii), requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

3208-5 Conduct a randomized, double-blind, controlled trial of edaravone in patients with ALS (definite or probable, according to ALS El Escorial Revised Airlie House criteria). Patients should be randomized (1:1:1) to the approved dosing regimen and dosage of edaravone (60 mg), the approved dosage of edaravone (60mg) with a daily or near-daily dosing regimen, or to a dosage of 120 mg of edaravone (a dosage even higher would be desirable if supported by safety data), with a daily or near-daily dosing regimen. The primary efficacy endpoint will be the change in the revised ALS functional rating scale score (ALSFRS-R) from baseline to the end of the study. The study duration will be at least 24 weeks.

The timetable you submitted on May 4, 2017, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	04/2018
Final Protocol Submission:	10/2018
Study/Trial Completion:	04/2022
Final Report Submission:	10/2022

You should allow sufficient time for the Agency to review, provide feedback, and come to concurrence on the protocol prior to initiation of the trial.

Submit clinical protocols to your IND 126396 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary

should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled **"Postmarketing Commitment Protocol," "Postmarketing Commitment Final Report," or "Postmarketing Commitment Correspondence."**

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert, Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

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

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive

copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Jack Dan, RPh, Regulatory Project Manager, at (240) 402-6940.

Sincerely,

{See appended electronic signature page}

Ellis F. Unger, MD
Director
Office of Drug Evaluation I
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure:
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ELLIS F UNGER
05/05/2017