CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215446Orig1s000

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	April 25, 2022
To:	Susan Daugherty Senior Regulatory Project Manager **Division of Neurology I (DN I)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon Williams, MSN, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Sapna Shah, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	RADICAVA ORS (edaravone)
Dosage Form and Route:	oral solution
Application Type/Number:	NDA 215446
Applicant:	Mitsubishi Tanabe Pharma Development America, Inc. (MTDA)

1 INTRODUCTION

On November 12, 2021, Mitsubishi Tanabe Pharma Development America, Inc. (MTDA) submitted for the Agency's review an Original New Drug Application (NDA) for RADICAVA ORS (edaravone) oral suspension. The RADICAVA ORS (edaravone) oral supsenison is proposed to be indicated for the treatment of Amyotrophic Lateral Sclerosis (ALS). Edaravone was approved in the US for the treatment of ALS in May 2017 under the brand name of RADICAVA. This oral formulation allows RADICAVA ORS (edaravone) oral solution to be self-administered at home. It can also be administered through a PEG or feeding tube and allows patients with swallowing difficulty to benefit from the oral formulation.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology I (DN I) on January 6, 2022 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for RADICAVA ORS (edaravone) oral solution.

2 MATERIAL REVIEWED

- Draft RADICAVA ORS (edaravone) oral solution PPI and IFU received on November 12, 2021, revised by the Review Division throughout the review cycle and received by DMPP and OPDP on April 14, 2022.
- Draft RADICAVA ORS (edaravone) Prescribing Information (PI) received on November 12, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 14, 2022.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

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/s/

SHARON W WILLIAMS
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SAPNA SHAH
04/25/2022 11:48:19 AM

LASHAWN M GRIFFITHS
04/25/2022 11:51:17 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: April 22, 2022

To: John Troiani, Medical Officer,
Division of Neurology 1 (DN 1)

Susan Daugherty, Regulatory Project Manager (DN 1)

Tracy Peters, Associate Director for Labeling, (DN 1)

From: Sapna Shah, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, Team Leader, OPDP

Subject: OPDP Labeling Comments for RADICAVA ORS® (edaravone) oral suspension

NDA: 215446

In response to DN1's consult request dated January 6, 2022, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), instructions for use (IFU), and carton and container labeling for the original NDA submission for RADICAVA ORS® (edaravone) oral suspension (Radicava ORS).

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DN1 (Susan Daugherty) on April 14, 2022, and are provided below.

PPI/IFU: A combined OPDP and The Division of Medical Policy Programs (DMPP) review will be completed and comments on the proposed patient package insert and instructions for use will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on April 14, 2022, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Sapna Shah at (240) 402-6068 or Sapna.Shah@fda.hhs.gov.

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SAPNA SHAH
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	April 22, 2022
Requesting Office or Division:	Division of Neurology 1 (DN 1)
Application Type and Number:	NDA 215446
Product Name and Strength:	Radicava ORS (edaravone) oral suspension, 105 mg/5 mL
Applicant/Sponsor Name:	Mitsubishi Tanabe Pharma Corporation (MTDA)
OSE RCM #:	2021-2228-1
DMEPA 2 Safety Evaluator:	Chad Morris, PharmD, MPH
DMEPA 2 Acting Team Leader:	Stephanie DeGraw, PharmD

1 PURPOSE OF MEMORANDUM

MTDA submitted revised container labels and carton labeling received on April 14, 2022 for Radicava ORS. The Division of Neurology 1 (DN 1) requested that we review the revised container labels and carton labeling for Radicava ORS (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

MTDA implemented all of our recommendations, and we have no additional recommendations at this time.

[a] Morris, C. Label and Labeling Review for Radicava ORS (NDA 215446). Silver Spring (MD): FDA, CDER, OSE, DMEPA2 (US); 2022 MAR 11. RCM No.: 2021-2228.

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/s/

JOHN C MORRIS
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STEPHANIE L DEGRAW
04/22/2022 04:45:44 PM

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 14, 2022

TO: Teresa Buracchio, M.D.
Director (Acting)
Division of Neurology I
Office of Neuroscience
Office of New Drugs

FROM: Makini Cobourne-Duval, Ph.D., Pharmacologist
Stanley Au, Pharm.D., BCPS, Lead Pharmacologist
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Seongeun (Julia) Cho, Ph.D.
Director
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Remote regulatory assessment (RRA) of P-One Clinic, Tokyo, Japan.

1. Remote Regulatory Assessment Summary

The Office of Study Integrity and Surveillance (OSIS) arranged a remote regulatory assessment (RRA) of the clinical portion of study MT-1186-J03 (NDA 215446) conducted at P-One Clinic, Tokyo, Japan. An onsite inspection was not possible due to the disruption of inspectional activities by COVID-19 global pandemic.

Based on my review of the RRA observations and the firm's response to the RRA observations, I conclude the RRA observations did not impact the integrity of data with the exception of the subjects listed below. For these subjects, I recommend that the review division further evaluate the following edaravone data:

- (b) (6) – (b) (6): concentration data for period 1 at 10 hours
- (b) (6): period 2 PK and safety data

Furthermore, in reference to the discussion item, I recommend that the review division follow up with the applicant for details on the changes made to the informed consent document and determine whether the revisions impacted subject safety.

2. Reviewed Study:

Study MT-1186-J03 (NDA 215446)
"Bioequivalence Study of Oral Suspension and Intravenous Formulation of Edaravone in Healthy Adults Subjects"

Dates of conduct: 3/22/2019 (first subject screened) – 5/9/2019 (last follow-up assessment)

Clinical site: P-One Clinic
View Tower Hachioji 4F, 8-1 Yoka-Machi Hachioji
Tokyo, 192-0071, Japan

3. Scope of RRA

ORA investigators Jennifer C. Adams and Marilyn S. Babu reviewed the clinical portion of the above study conducted at P-One Clinic, Tokyo, Japan from 2/27/2022 to 3/13/2022.

The current assessment included auditing the following items:

- Inclusion/exclusion criteria
- Protocol compliance
- Test article accountability
- Investigational product administration
- Plasma PK sample collection, processing, storage, and transfer/shipping to the bioanalytical facility
- Randomization
- Adverse events reporting

4. RRA Observations

At the conclusion of the RRA, investigators Jennifer C. Adams and Marilyn S. Babu observed objectionable conditions and one discussion item was addressed with the firm's management during the close-out meeting.

The observations and discussion item, the firm's response dated 3/29/2022 (**Attachment 1**), and my evaluation are presented below.

4.1 Observations discussed at the close-out of RRA

4.1.1. Observation 1:
You did not prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation.

A. Study "Timetable." You used the Study "Timetable" as your only source document for a number of study tasks, including:

- Blood collection times for drug concentration measurements
- Blood collection times for hematology, biochemistry, and coagulation testing for subject safety
- Meal start times, including meals prior to and after the required fast
- Posture and water restriction start and end times
- Hospital admission and discharge date/time

The Study "Timetable" has pre-filled values for the activities above that are not completed contemporaneously with the performance of these activities. Furthermore, where two or more people have signed off as performing an activity for a group of subjects in the "Timetable," the documentation does not show specifically which of these staff performed the activity for each subject.

You stated that your process is to alter the pre-filled "Timetable" entries if deviations from the set schedule occur. This can also lead to discrepant study documentation, for example Subject (b) (6) dosing end time changed from scheduled end time 10:53 to actual end time 10:52. This value was changed in the source worksheets, but not revised in the "Timetable."

B. Source Documentation. You did not maintain source documentation for study activities, including:

- IV Pump usage showing which IV pumps were used on which subjects on which dates, including a log of all pump alarms and responses/actions taken.
- Storage of blood samples for drug concentration analysis on ice between sample collection and centrifugation
- Urine drug screen, pregnancy test, and alcohol breath test equipment/reagents used
- Mealtime endings, including meals prior to the required fast

Firm's Response:

Regarding
A. Study "Timetable". (Observation 1)

The firm had no specific response regarding using the timetable as a source document to record the completion of pertinent study activities for the audited study.

The firm proposed to develop a computerized system for their study timetable with a professional vendor to simultaneously record who performed a task, when the task was performed, and the result. They stated that they hope that such a computerized system would be available for use sometime in 2023.

The firm's currently uses a pre-filled study "timetable" which has the planned times for recording information such as blood collection times for PK measurement and subject safety. In response to the observation, the firm stated that they will update the timetable by adding a square within the same field of the pre-filled time for a tick mark (✓). The tick mark would be entered in the square by the user to confirm blood collection was conducted at the planned time and the user would add their signature. The name and signature of the person who performed the blood collection would also be included on the timetable. The firm provided an example of how the study timetable would be amended (within **Attachment 1**).

Regarding the other times of study activities such as the end of a fasting period and date/time of admission and discharge, the site will record who checked/confirmed the pre-filled date/time in the timetable. For other study activities (consumption of water and change in posture), the firm stated that the current timetable has a check box and signature box to indicate that tasks were performed at pre-filled planned time. However, they will provide additional explanation in the procedure or within the timetable.

The firm stated that moving forward, for times related to medication administration, a note will be added on the timetable to explain the pre-filled times are the planned times and that the actual times would be noted on the administration record.

OSIS Evaluation (Part A of Observation 1):

If the performance of a study activity deviates from the pre-filled scheduled time, then the staff member would strike through the scheduled time and document the actual time that study activity was conducted. However, it was noted that the practice of crossing out the pre-filled time and documenting the actual time was not performed for all study activities in which a time was noted on the timetable.

Specifically, for Subject (b) (6) the scheduled time of the end of edaravone IV dosing was pre-filled within the timetable as 10:53. However, in the administration record for that subject the end time for the edaravone intravenous formulation was recorded as 10:52. In this case the scheduled, pre-filled time in the timetable was not crossed out. However, the firm stated that for medication administration, the actual times were not noted in the study timetable but rather the actual times were documented on the separate administration record.

I reviewed a subset of the timetable records for a few subjects in Groups A, B, and C (including those with corrected clock times) and compared the blood collection times within the timetables to that in the PK listing in the study report. I confirmed that the times noted in the timetables (pre-filled or crossed out and handwritten) matched the times documented in the PK listing. There was no evidence identified to indicate that this finding impacted the integrity of the data.

The addition of checkboxes next to the pre-filled information for scheduled activities would indicate that each pre-filled entry was reviewed when a study activity was performed. Furthermore, the addition of a note on the timetable to explain that the actual times of the study activity are noted in the another named source record would indicate when there are additional source documents for specific study activities (medication administration). I find these proposed corrective actions are acceptable for part A of Observation.

Firm's Response:

Regarding
B. Source Documentation. (Observation 1)
The firm had no specific response to discuss the inadequate maintenance of source documents to record the completion of the study activities mention in the observation.

Regarding the usage of IV pumps for future studies, the firm stated that they will record the following in their source documents:

- A listing of pumps used organized by day and by subject
- IV pump alarm information and the staff's response to the alarm including the name of the person responsible for the action

Regarding the source documentation for the storage (handling of biological specimens) prior to centrifugation, the firm stated that they will record that the information was reviewed, as well

as the name of the person checking the sample storage conditions.

The firm also stated that they will record the devices and reagents including lot numbers used in subject screening tests such as urine drug tests, pregnancy tests, and breath alcohol tests.

Additionally, when a protocol requires fasting, the firm stated that they will record time of the start of the fast (end time of a meal).

OSIS Evaluation (Part B of Observation 1):

I reviewed the firm's response to part B of this observation and found the corrective actions acceptable.

1) Infusion pump documentation

The study report stated that the infusion pump stopped at 59 minutes after the start of the infusion, instead of the 60 minutes designated in the protocol, for 4 subjects (Subjects (b) (6)). Additionally, the infusion pump stopped twice for another subject (Subject (b) (6) infusion was completed 61 minutes after the start of the infusion.

However, the clinical study report also stated that subjects received the entire edaravone dose. There was no evidence to indicate that there were any dosing issues or subject safety issues related to the IV administration. Therefore, I find that this finding does not impact data integrity.

2) Subject sample handling documentation

For processing of subject samples, the MT-1186-J03 protocol states that subject samples should be maintained on ice. Based on discussions with ORA, this was not documented. While the observation states that an issue exists from sample collection to centrifugation, the observation also impacts the subsequent steps: plasma aliquoting and storage.

Stability data was generated as part of the analytical method validation for edaravone(validation report reference: MCI-186-E04). Based on the stability data for edaravone and edaravone metabolites in whole blood and plasma generated at room temperature, it is not expected that the potential processing of

subject samples without ice, if any, would impact the stability of the MT-1186-J03 pharmacokinetic samples.

I also observed an additional issue in reviewing the MT-1186-J03 subject sample processing source documents. For the period 1, 10 hour time point for subjects (b) (6) documenting the transfer of whole blood samples to centrifuge tubes containing stabilizer was missing. I recommend that the review division further evaluate the pharmacokinetic profiles of these subjects to determine if the possible omission of this sample processing step affected the reported edaravone concentration data for period 1 at 10 hours.

3) Documentation for reagents and equipment

I reviewed the findings regarding the lack of source documentation to record the reagents' lot numbers and the equipment used in the subject screenings (urine drug screen, pregnancy test, and alcohol breath test). Although documentation of this information is important for trackability and traceability in study conduct, the ORA investigators reported no issues with subject eligibility for the audited study. This finding does not impact the integrity of the data.

4) Documentation on fasting start times

I reviewed the findings regarding the lack of documentation for the start time of subject fasting periods. It was confirmed that although the start times for the fasting periods were not recorded, the start of mealtimes were recorded, and based on discussions with the ORA investigators, food consumption was not allowed outside of these designated mealtimes. Examination of the time difference between the start of mealtimes to the start time of medication administration indicates that the required minimum 10-hour fasting period was predicted to be maintained throughout the study. Therefore, the lack of documentation for the start of the fasting period did not impact the integrity of the study data.

4.1.2. OBSERVATION 2:

You did not ensure that an investigation is conducted according to the investigational plan. The study protocol specifies that the duration of hospitalization will be 7 days/6 nights and that intake of drugs, alcohol, nicotine, caffeine, and grapefruit are prohibited during the study period.

You discharged Subject (b) (6) from the inpatient facility for approximately 5 hours on Day 3 (8:50 – 13:50). You stated that

you obtained approval from the sponsor for this subject's discharge, but you didn't maintain documentation of who specifically provided this approval. You performed no re-entry physical exam, vital signs collection, or drug/alcohol screening on the subject's return.

Firm's Response:
The firm stated that they updated their procedures to address cases in which a subject is allowed to temporarily discharge and later be readmitted into a clinical study. Per their response, these procedures include the following:

- Documentation of any correspondence with the sponsor and whom from the sponsor authorized the temporary discharge
- Upon the return of the subject(s) to the site for readmittance in the clinical study, tests will be performed to ensure subject safety and protocol compliance after discussing with the sponsor. However, in cases which it is difficult to ensure subject safety, the site will consider discontinuing the subject from the study prior to a temporary discharge.

OSIS Evaluation:
Subject (b) (6) was temporarily discharged between period 1 and period 2 prior to the administration of the oral formulation of the drug product.

Because the subject's activities during the temporary discharge cannot be verified, it is not known whether Subject (b) (6) refrained from using prohibited substances including drugs, alcohol, nicotine, caffeine, and grapefruit before returning for period 2 dosing.

I recommend that the review division further evaluate whether the period 2 data for subject (b) (6) should be excluded from the study PK and safety assessments.

I found the corrective action proposed by the firm are acceptable to address the issue identified in this observation.

4.1.3 Additional Item Discussed at the close-out of RRA
The Clinical Investigator, Dr. Furihata, made minor changes to the informed consent document at the request of the sponsor mid-study and re-consented ongoing subjects without informing the ethics committee of the revisions or the re-consenting of subjects.

Firm's Response:
The firm did not respond to the discussion item.

OSIS Evaluation:

ORA did not specify what were the minor changes to the informed consent. I recommend that the review division follow up with the applicant for details on the changes made in the informed consent document and determine whether the revisions impacted subject safety.

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Edit: SA 03/31/22,4/7/22, 4/8/22, 4/12/22, 4/13/22,4/14/22 JC 4/8/22 4/13/2022

ECMS: Cabinets/CDER OTS/Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/CLINICAL/P-One Clinic, Keikokai Medical Corp. Hachioji, Tokyo, Japan

OSIS File #: BE 9313

Attachments

Attachment 1 – P-One Clinic's Response to Observations

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/s/

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Team Lead. Also signing for M.Cobourne-Duval, OSIS primary reviewer.

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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 4, 2022

TO: Billy Dunn, MD
Director
Office of Neuroscience
Office of New Drugs

FROM: Kara A. Scheibner, Ph.D.
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

Sarmistha Sanyal, Ph.D.
(DGDSI)
(OSIS)

THROUGH: Kimberly A. Benson, Ph.D.
Deputy Director
(DGDSI)
(OSIS)

SUBJECT: Remote record review (RRR) of (b) (4) (b) (4)

1. RRR Summary

The Office of Study Integrity and Surveillance (OSIS) conducted a remote record review (RRR) of the analytical portion of Study MT-1186-J03 (NDA 215446, Radaicava [edaravone] oral solution) conducted at (b) (4) onsite inspection was not possible due to the disruption of inspectional activities by the COVID-19 global pandemic.

We observed the following objectionable condition during the RRR: (b) (4) (b) (4)

Based on the evaluation of the observation, the objectionable condition had no impact on the integrity of the data or subject safety. Therefore, we conclude that data from the audited studies are reliable.

2. Reviewed Study

Study MT-1186-J03 (NDA 215446)
"Bioequivalence Study of Oral Suspension and Intravenous Formulation of Edaravone in Healthy Adult Subjects"

Two bioanalytical studies were reviewed under Study MT-1186-J03:

Study GB19001D: "Determination of MCI-186 and its Sulfate and Glucuronide Concentrations in Human Plasma"
Sample Analysis Period: (b) (4)

Study GB19002D: "Determination of MCI-186 and its Sulfate and Glucuronide Concentrations in Human Urine"
Sample Analysis Period: (b) (4)

3. Scope of RRR

OSIS scientists Kara A. Scheibner, Ph.D. and Sarmistha Sanyal, Ph.D. reviewed the analytical portion of the above studies conducted at (b) (4) (b) (4) (b) (4) The RRR included an examination of study records, method validations, and sample analyses. The RRR also included interviews with the firm's management and staff via a translator, and a review of SOPs, operations, and electronic systems.

4. RRR Observations

At the conclusion of the RRR, we observed one objectionable condition. We discussed the following item with the firm's management during the RRR close-out meeting.

Our evaluation of the observation, and the firm's response dated (b) (4) (**Attachment 1**) is presented below.

(b) (4) servation discussed at the close-out of RRR:

(b) (4)

(b) (4)

Firm's Response:

(b) (4)

OSIS Evaluation:

(b) (4)

(b) (4)
After our review of , we concluded that study data were not affected by this observation, and that the data for study MT-1186-J03 are reliable.

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Edit: MFS 04/04/2022; KAB 04/04/2022

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OSIS File #: (b) (4)

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MICHAEL F SKELLY
04/04/2022 03:44:39 PM

KIMBERLY A BENSON
04/04/2022 03:53:06 PM

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: March 14, 2022

From: Interdisciplinary Review Team for Cardiac Safety Studies

Through: Christine Garnett, PharmD
Clinical Analyst, DCN

To: Susan Daugherty
Division of Neurology 1

Subject: QT Consult to NDA215446 (SDN 0001)

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 2/28/2022 regarding the sponsor's QT/QTc assessments. We reviewed the following materials:

- Summary of clinical pharmacology studies (NDA215446 / SDN0001; link).
- Summary of clinical pharmacology studies (NDA209176/SND0001; link)
- Previous IRT review(s) for NDA209176 dated 01/17/2020 in DARRTS (link); and
- Proposed RADICAVA ORS label (NDA216951 / SDN 0001; link).

1 Responses for the review division

Question from the review division: The applicant is relying on a 2-period, 2-sequence, cross-over study (MT-1186-J03) to establish bioequivalence between Radicava and Radicava ORS. The study results demonstrated that, Radicava ORS has an equivalent AUC0-∞ to the approved Radicava (geometric mean ratio [90% CI]: 0.977 [0.917, 1.041]). The geometric mean ratio and its lower limit of 90% CI for Cmax of the 105 mg oral suspension compared to 60 mg/60 min IV was also within the bioequivalence range, while the upper limit of 90% CI exceeded 1.25 as anticipated (geometric mean ratio [90% CI]: 1.217 [1.090, 1.359]). Plasma concentrations of both sulfate and glucuronide conjugates were 1.3- to 2.2-fold higher following the oral dose of 105 mg than after IV dosing. In addition, the applicant relying on a Phase 3, open-label, long-term safety study (MT-1186-A01) to demonstrate safety of edaravone oral suspension.

According to Radicava (NDA 209176) and IRT-QT report DARRTS dated 01/21/2020, effects of QT/QTC interval were evaluated in study MCI-186-J25 using edaravone at therapeutic (60

mg/60 min IV) and supra-therapeutic (300 mg/60 min IV) doses. The Applicant concluded that, "at a dose 5 times the recommended dose, edaravone does not prolong the QT interval to any clinical relevant extent".

Does the QTIRT agree with the Applicant's conclusion?

IRT's response: We have previously reviewed the results from Study MCI-186-J25 (DARRTS 01/17/2020), a three-way cross-over study assessing the potential for QTc prolongation for edavarone, which did not show significant QTc prolongation at doses up to 300 mg IV. The highest dose provides 7.3-fold and 4.6-fold exposure coverage over the maximum recommended IV (60 mg/h) and oral (105 mg) therapeutic doses, respectively, and is 3.6-times higher than the high clinical exposure scenario (oral dosage in subjects with moderate renal impairment) supporting waiving the requirement for a positive control (ICH E14 Q&A (R3) 5.1). Furthermore, the mean C_{max} of the sulfate conjugate (the predominant circulating moiety) after 300 mg IV is estimated to be about 3-fold higher than the observed mean C_{max} after oral 105 mg dose and the increase in concentration with the new formulation is therefore not expected to be associated with QT prolongation. We therefore agree with the QT labeling proposed by the sponsor.

2 BACKGROUND

Edaravone is a free radical scavenger that exhibits lipid peroxidation inhibitory effects and inhibits cell damage by lipid peroxides. The aqueous solution of edaravone (RADICAVA) was reviewed under NDA209176 and approved for treatment of Amyotropic Lateral Sclerosis (AML) at the daily dose of 60 mg infused intravenously (IV) for 1 hour for 14 days. In the current NDA215446, the sponsor is proposing an oral suspension of edaravone for treatment of AML at daily dose of 105 mg for 14 days followed by 14-day drug holiday.

Edaravone has oral bioavailability of >77% and T_{max} of 0.5 hour (range, 0.25 to 0.75 hours). Its terminal elimination half-life ($t_{1/2}$) is about 9 hours, and the proposed dosing is associated with minimal systemic accumulation, consistent with its $t_{1/2}$. It is primarily metabolized by sulfotransferase and UGT enzymes to sulfate and glucuronide conjugates, respectively. The half-lives of its metabolites are 3 to 6 hours and are therefore expected to have minimal accumulation after once daily dosing. The sulfate conjugate is the main circulating metabolite, and its concentration is 3-times and 10-times higher than that for edaravone at 0.5 hours- and 24-hours post-start of infusion (Study MCI186-10, MCI186-14, and MCI186-E02). In the bioequivalence study (MT-1186-J03), the mean C_{max} of the sulfate conjugate after 60 mg IV and 105 mg orally were 4843 ng/mL and 7291 ng/mL, respectively, while the corresponding Cmax of edaravone were 1232 ng/mL and 1500 ng/mL respectively. The increases in C_{max} and AUC of edaravone are more than dose-proportional at the dose range of 30 - 300 mg. Urine is the major route of excretion of edaravone and its metabolites, with the glucuronide conjugate being the major moiety in urine. Age, sex, and race have no influence on edaravone PK. Moderate renal impairment is associated with 1.25-fold and 1.29-fold higher C_{max} and AUC of edaravone, respectively, compared to normal subjects. Moderate and severe hepatic impairment was associated with about 1.2-fold higher C_{max} of edaravone compared to normal subjects. Edaravone is not expected to exhibit significant drug-drug interaction with cytochrome P450 or UGT enzymes. Co-administration with food is expected decrease edaravone C_{max} and AUC by up to 82% and 61% respectively. Based on this pharmacokinetic information, the anticipated high

clinical exposure scenario is when edaravone is administered in patient with moderate renal impairment (up to 1.25-fold increase in C_{max}).

The sponsor assessed the potential for QT prolongation of edaravone in a randomized, placebo-controlled, three-way cross-over study (Study MCI-186-J25). Study subjects (N=27) received a single IV dose (i.e., 1-h infusion) of edaravone as therapeutic (60 mg) or supra-therapeutic dose (300 mg), or a matching dose of placebo in a fasted state. The primary endpoint was ΔQTcF and the primary analysis was concentration-QTc analysis.

The CSS-IRT reviewed the sponsor's QTc assessments previously (Study MCI-186-J25). In brief, no significant QTc prolongation effect of edaravone was detected after both the therapeutic (60 mg) and supratherapeutic dose (300 mg). Table 1 shows the results from the concentration-QTc analysis.

The mean C_{max} after oral administration of 105 mg of edaravone is 1656 ng/mL, which is about 4.6-folds lower compared to the C_{max} of 7565.8 ng/mL after the supratherapeutic dose of 300 mg IV in the QT assessment study. Given the 1.25-fold increase in C_{max} in subjects with moderate renal impairment, the supratherapeutic dose (300 mg IV) produces mean C_{max} that is about 3.6-fold higher than the anticipated high clinical exposure scenario, and therefore supports waiving the requirement for a separate positive control (ICH E14 Q&A (R3) 5.1). Given that the sulfate conjugate is about 3-times higher than edaravone at 0.5-hours post-start of infusion, the mean C_{max} of the sulfate conjugate after 300 mg infusion over 1 hour is expected to be around 22000 ng/ml, which covers by about 3-folds the mean C_{max} of the sulfate conjugate of 7291 ng/ml after oral administration of 105 mg. Therefore, the QT prolongation potential of edaravone was evaluated at a supratherapeutic dose of 300 mg IV, which covers the anticipated high clinical exposure of edaravone and its predominant metabolite by more than 2-folds.

Table 1. The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for edaravone (60 mg and 300 mg)

ECG parameter	**Treatment** (edaravone)	**Concentration** (ng/mL)	**ΔΔQTcF** (ms)	**90% CI** (ms)
QTc	60 mg IV	1029.6	-0.6	(-1.2 to 0.0)
QTc	300 mg IV	7565.8	0.3	(-1.7 to 2.3)

Source Previous IRT review for NDA209176 dated 01/17/2020 in DARRTS (Link)

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	March 11, 2022
Requesting Office or Division:	Division of Neurology 1 (DN 1)
Application Type and Number:	NDA 215446
Product Name and Strength:	Radicava ORS (edaravone) oral suspension, 105 mg/5 mL
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Mitsubishi Tanabe Pharma Corporation
FDA Received Date:	November 12, 2021, February 28, 2022
OSE RCM #:	2021-2228
DMEPA 2 Safety Evaluator:	Chad Morris, PharmD, MPH
DMEPA 2 Acting Team Leader:	Stephanie DeGraw, PharmD

1 REASON FOR REVIEW

As part of the approval process for Radicava ORS (edaravone) oral suspension, the Division of Neurology 1 (DN 1) requested that we review the proposed Radicava ORS Prescribing Information (PI), Patient Prescribing Information (PPI), Instructions for Use (IFU), carton labeling, and container labels for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C (N/A)
FDA Adverse Event Reporting System (FAERS)*	D (N/A)
Other	E (N/A)
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 CONCLUSION AND RECOMMENDATIONS

Our evaluation of the proposed PPI did not identify areas of vulnerability that may lead to medication errors. We have no recommendations for the PPI at this time.

However, the proposed PI, IFU, carton labeling, and container labels may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for the Division and in Section 5 for Mitsubishi Tanabe Pharma Corporation.

4 RECOMMEDATIONS FOR DIVISION OF NEUROLOGY 1 (DN 1)

Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
Prescribing Information – General Issues			
1.	The treatment regimens (except dose) are the same for both dosage forms of Radicava, however, the language does not align between the two dosage forms.	We are concerned prescribers may misinterpret the (b) (4) (b) (4)" statement as (b) (4) recommendation.	If the treatment regimen is always 14 on/14 off for the first month of therapy, then 10 days out of 14 on/14 off for all future months of therapy for both dosage forms of Radicava, then we recommend the (b) (4) (b) (4) (b) (4) for Radicava ORS.
Highlights of Prescribing Information			
1.	The schedule of administration for the initial and maintenance regimens for both dosage forms of Radicava are the same; however, they are listed twice.	The schedule can be improved for clarity and readability and to reduce redundancy.	We recommend only listing the schedule of administration one time for both dosage forms.
2.	The daily frequency for administration is listed as "(b) (4)" for Radicava ORS but is not stated for Radicava injection.	We are concerned users may interpret "(b) (4)" as "(b) (4)" and overlook the (b) (4).	We recommend aligning the dosing language for Radicava ORS with Radicava injection. We are not aware of medication error reports for Radicava describing confusion of the frequency of administration; therefore, we recommend removing "(b) (4) (b) (4)" from the Radicava ORS dosing statement.
Full Prescribing Information – Section 2 Dosage and Administration			
1.	The directions to "Take Radicava ORS in the morning after overnight fasting" are ambiguous.	"Overnight fasting" is not a defined amount of time, which may be interpreted differently by prescribers	We recommend including a specific amount of time for the fasting period. Consider aligning this statement with

Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		and patients. This may lead to drug absorption fluctuations.	the statement in the Instructions for Use which specifies (b) (4). For example, (b) (4) (b) (4)„.
2.	There are alternate "fasting" options; however, that specific recommendations are not prominent.	We do not want the prescriber to overlook this important dosing information.	This is important information for the prescriber and should be placed in Sections 2, 17, and the PPI. We recommend adding this information in tabular format.
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	The temperature range [for example, 2°C–8°C (36°F–46°F)] contains a symbol.	Symbols can be error prone and may lead to improper storage and drug deterioration errors.	We recommend replacing the "-" symbol with its intended meaning "to" [for example, 2°C to 8°C (36°F to 46°F)].

5 RECOMMENDATIONS FOR MITSUBISHI TANABE PHARMA CORPORATION

Table 3. Identified Issues and Recommendations for Mitsubishi Tanabe Pharma Corporation (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Labels and Carton Labeling			
1.	The format for expiration date is not defined.	A clearly defined expiration date will help minimize confusion and risk for deteriorated drug medication errors.	Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
2.	The established name lacks prominence commensurate with the proprietary name.	The established name is not presented in accordance with 21 CFR 201.10(g)(2).	Increase the prominence (e.g., bolding or enlarging the font) of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).
3.	The area of the principal display panel containing	The readability of this information can be	We recommend using a new line for each statement to

Table 3. Identified Issues and Recommendations for Mitsubishi Tanabe Pharma Corporation (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	the dosage form and strength is cluttered, which is impacting the readability of the dosage form and strength statements.	improved to facilitate easier identification of the product dosage form and strength.	ensure they are prominently displayed. Additionally, consider enlarging the font size for these statements as space will allow. In doing this, please ensure the strength statement is not near the net quantity statement and has more prominence than the net quantity statement.
4.	The statement, "(b) (4) (b) (4) (b) (4)" can be improved.	Labels for prescription drugs are required to bear a statement of the recommended or usual dosage per 21 CFR 201.100(b)(2). Furthermore, to ensure consistency with the Physician Labeling Rule (PLR) formatted prescribing information, we recommend the phrase "Recommended Dosage: See prescribing information."	Revise the statement: "(b) (4) (b) (4)" to read "Recommended Dosage: See prescribing information".
5.	The symbol "-" is used in the storage temperature statements to represent the word "to".	Symbols may be misinterpreted. The presentation of the storage statement should be clearly stated to avoid improper storage and drug deterioration errors.	Replace the symbol "-" with its intended meaning "to" in the storage temperature statements. For example, 20°C to 25°C (68°F to 77°F).
Container Labels			
1.	A 2D matrix barcode is included on the label; however, a linear barcode is not present.	The linear barcode is often used as an additional verification before drug administration in the hospital setting; therefore,	We request you remove the 2D matrix barcode from the container labels, and add the product's linear barcode to each individual bottle as

Table 3. Identified Issues and Recommendations for Mitsubishi Tanabe Pharma Corporation (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		it is an important safety feature that should be part of the label whenever possible. Also, multiple barcodes may be confusing.	required per 21CFR 201.25(c)(2). In doing this, please assure the barcode is surrounded by sufficient white space to allow scanners to correctly read the barcode.
2.	As currently presented, the area for the date of first opening statement is small and does not alert the user to write a complete date.	If the date of first opening is not correctly recorded, users may administer/ingest expired medication.	We recommend increasing the space for the user to write the date. We also recommend you use the following format: "Date of first opening __/__/__".
Carton Labeling			
1.	The (b) (4) statement is more prominent than other important information, such as the strength and net quantity statements.	Important information may be overlooked which may increase the risk for confusion.	We recommend removing the (b) (4) statement from the labeling. Alternatively, consider moving this information to the "Contents of this package" section of the side panel.
2.	As currently presented, the inclusion of a product identifier is not indicated.	In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act (DSCSA)*. The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively.	We recommend that you review the draft guidance. If you determine that the product identifier requirements apply to your product's labeling, we request you add a placeholder for the human-readable and machine readable (2D data matric barcode) product identifier to the carton labeling.

Table 3. Identified Issues and Recommendations for Mitsubishi Tanabe Pharma Corporation (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		* The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf	
Packaging			
1.	The "(b) (4)" statement on the 7-dose carton labeling and container label for an individual 35 mL bottle is inaccurate.	The two 35 mL bottles of medication are only a component of the (b) (4) (b) (4).	We recommend removing the "(b) (4)" statement from the 7-dose carton labeling and container label of the 35 mL bottle.
Instructions for Use			
1.	Figure I shows a final volume that (b) (4) the 5 mL dose.	This figure can be improved for precision and clarity to prevent wrong dose medication errors.	We recommend replacing Figure I with a close up of the syringe that correctly identifies the dose as exactly 5 mL. Also, if the proposed syringe contains ridges or black rings that may cause confusion when measuring the prescribed dose, we recommend identifying those elements in reference to the prescribed dose.
2.	The "water" in Figures M and O is not distinguished from the "medication" in the remaining Figures.	This may increase the risk for overdose if patients or caregivers erroneously flush the feeding tube with medication rather than water.	We recommend prominently labeling the liquid in Figures M and O as water.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Radicava ORS that Mitsubishi Tanabe Pharma Corporation submitted on February 28, 2022.

Table 4. Relevant Product Information for Radicava ORS	
Initial Approval Date	n/a
Active Ingredient	Edaravone
Indication	Treatment of amyotrophic lateral sclerosis (ALS)
Route of Administration	Oral or PEG tube or NG tube
Dosage Form	Oral suspension
Strength	105 mg/5 mL
Dose and Frequency	The recommended dosage is 105 mg (5 mL) taken orally or via feeding tube [Nasogastric (NG) tube or Percutaneous Endoscopic Gastrostomy (PEG) tube] according to the following schedule: • (b) (4) daily dosing for 14 days followed by a 14-day drug-free period. • Daily dosing for 10 days out of 14-day periods, followed by 14-day drug-free periods.
How Supplied	RADICAVA ORS Starter Kit (14-day treatment cycle), (b) (4) (b) (4) including two (2) inner cartons, each containing one (1) bottle of 735 mg/35mL (105 mg/5 mL dose), two oral dosing syringes and one bottle adapter. RADICAVA ORS Kit (10-day treatment cycle), including one (1) bottle of 1050 mg/50 mL (105 mg/5 ml dose) with two oral dosing syringes and one bottle adapter.

Storage	<u>Pharmacy</u> Store refrigerated between 2°C to 8°C (36°F to 46°F) and protect from light. Do not freeze. Store upright. <u>Patient</u> Store upright at room temperature between 20°C to 25°C (68°F to 77°F). Protect from light. Discard 15 days after opening bottle or if unopened 30 days from date of shipment indicated on the carton pharmacy label.
Container Closure[a]	(b) (4) amber glass bottle, (b) (4) bottle adapter, child resistant screw cap

[a] Container closure specifications are available at: \\CDSESUB1\evsprod\nda215446\0001\m3\32-body-data\32p-drug-prod\mt-1186-oral-suspension-pci-pharma-services-tredegar\32p7-cont-closure-sys\container-closure-system.pdf

APPENDIX B. PREVIOUS DMEPA REVIEWS

On March 2, 2022, we searched for previous DMEPA reviews relevant to this current review using the terms, Radicava ORS, edaravone, MT-1186, IND 138145, and NDA 215446. Our search identified one previous review[b], and we confirmed that our previous recommendations were implemented.

Table 5. Summary of Previous DMEPA Reviews for Radicava ORS

OSE RCM #	Review Date	Summary of Recommendations
2021-156	04/22/2021	We reviewed the URRA and HF validation study protocol. We determined that based on the overall risk associated with use of similar commercially available presentations, the sponsor does not need to submit the HF validation study results for Agency review. However, we evaluated the proposed product user interface including product sample, labels and labeling, and packaging. We provided recommendations for the carton and container labels to the Sponsor.

[b] Yokum, A. Human Factors Validation Study Review for edaravone (IND 138145). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 APR 22. RCM No.: 2021-156.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Radicava ORS labels and labeling submitted by Mitsubishi Tanabe Pharma Corporation.

- Container labels received on November 12, 2021
- Carton labeling received on November 12, 2021
- Instructions for Use (Image not shown) received on November 12, 2021, available from \\CDSESUB1\evsprod\nda215446\0001\m1\us\114-labeling\draft\labeling\radicava-ors-instructions-for-use.docx
- Prescribing Information (Image not shown) received on February 28, 2022, available from \\CDSESUB1\evsprod\nda215446\0007\m1\us\114-labeling\draft\labeling\radicava-injection_ors_combined_uspi_tracked-change.docx
- Patient Prescribing Information (Image not shown) received on February 28, 2022, available from \\CDSESUB1\evsprod\nda215446\0007\m1\us\114-labeling\draft\labeling\radicava-injection_ors_combined_ppi-tracked-change.docx

[c] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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