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APPLICATION NUMBER:

215446Orig1s000

SUMMARY REVIEW

Summary Review

Date	May 12, 2022
From	Laura Jawidzik, MD Teresa Buracchio, MD
Subject	Summary Review
NDA/BLA # and Supplement#	NDA 215446
Applicant	Mitsubishi Tanabe Pharma
Date of Submission	November 12, 2021
PDUFA Goal Date	May 12, 2022
Proprietary Name	Radicava ORS
Established or Proper Name	Edaravone
Dosage Form(s)	Oral suspension
Recommended Indication(s)/Population(s)	Treatment of amyotrophic lateral sclerosis
Recommended Dosing Regimen(s)	105 mg/ 5 mL taken as follows: • Initial treatment cycle: 5 mL daily dosing for 14 days followed by a 14-day drug-free period • Subsequent treatment cycles: 5 mL daily dosing for 10 days out of 14-day periods, followed by 14-day drug-free periods
Recommendation on Regulatory Action	Approval

1. Background

This application contains data in support of the efficacy of Radicava ORS (edaravone), administered as an oral suspension, for the treatment of amyotrophic lateral sclerosis (ALS). The intravenous (IV) formulation of edaravone, Radicava (NDA 209176), was approved in May 2017. The Applicant is seeking approval of Radicava ORS by relying on the safety and effectiveness of the IV formulation of Radicava, data from a relative bioavailability study for establishing a pharmacokinetic (PK) bridge between the IV and oral suspension formulations of edaravone, and safety data from an open-label extension study. The proposed dose of the oral suspension is 105 mg/ 5mL with the same dosing regimen as the approved IV formulation of Radicava:

- Initial treatment cycle: 5 mL daily dosing for 14 days followed by a 14-day drug-free period
- Subsequent treatment cycles: 5 mL daily dosing for 10 days out of 14-day periods, followed by 14-day drug-free periods

Under IND 138145, the Applicant had a preIND meeting with the Division in March 2018. At that time the Applicant was advised that a bridging approach from the IV formulation to the suspension appeared reasonable, and that the products should be bioequivalent for both the AUC and the Cmax. The Applicant was advised that if the PK parameters exceeded the approved product, long-term safety data would be needed. The Applicant had an end-of-phase 2 (EOP2) meeting with the Division in August 2019. At that time, the Applicant was advised that bridging study MT-1186-J03 appears to adequately establish a bridge from the IV to the suspension, and that open-label safety data would be needed to support the safety of the increased Cmax and metabolites relative to the IV product. The Division agreed to accept 6 months of long-term safety data given that the planned dosing regimen and exposure of the suspension was the same as the IV formulation. The Applicant had a preNDA meeting with the Division in September 2021. The Division agreed to accept the 24-week data from Study A01 to support the safety of Radicava ORS (oral edaravone). The active moiety, edaravone, received orphan drug designation in 2015. The Applicant has an ongoing study to complete a postmarketing commitment to study daily dosing of edaravone under NDA 209176.

The application, submitted November 12, 2021, contained Study MT-1186-J03, a relative bioavailability study to establish the efficacy and safety of edaravone oral suspension by PK bridge to edaravone IV, and 6 months of safety data from Study MT-1186-A01, an open-label safety study, to support long-term safety of the product.

2. Product Quality

The final recommendation from the Office of Pharmaceutical Quality (OPQ) review team is to approve the application. From a quality perspective, the review team finds that the application provides for adequate assurance that the product will be suitable for use by the intended patient population

The technical lead on the Office of Product Quality (OPQ) review was Dr. Martha Heimann. The OPQ integrated review lists the entire OPQ team that was involved with the review of this application. Please refer to the OPQ review for details of the product quality assessment.

According to the OPQ review, the drug substance is produced with adequate quality for use as an oral suspension. No deficiencies were identified by the drug substance reviewers. The proposed specification is adequate to ensure the identity, strength, quality, purity, and potency of the product for the proposed shelf-life.

The drug product is a suspension that will be marketed in 60 mL bottles containing 35 mL or 50 mL of the suspension. The initial treatment cycle requires two 35 mL bottles. One 50 mL bottle contains sufficient drug for each subsequent treatment cycle. According to the OPQ drug product reviewers, stability and release testing were found to be acceptable. The stability data provides adequate support for a shelf-life of 18 months when stored refrigerated.

The container closure system is 60 mL amber glass bottle with a child resistant, (b) (4) screw cap. The product is co-packaged with an adapter and two oral dispensers. The Applicant has performed extractables and leachables (E&L) for the container closure system. However, the E&L studies were deemed inadequate. Because of the acceptable quality of the drug product, and the relatively low risk of leachables for an oral dosage, the Applicant will be issued a postmarketing commitment (PMC) to repeat the E&L studies under more rigorous conditions.

OPQ determined that the manufacturing processes for the drug product were acceptable. The manufacturing and test facilities for this application were found to be acceptable.

The biopharmaceutics reviewers found the dissolution method and acceptance criterion to be acceptable. The Applicant was able to provide acceptable bridging data between drug products manufactured at different sites and with different batch scales.

OPQ recommends the following PMC to be included in the action letter:

PMC 4266-1 Provide updated extractable/leachable studies to confirm that the container closure system does not adversely impact the drug product.

3. Nonclinical Pharmacology/Toxicology

The primary nonclinical reviewer for the application was Dr. David Carbone and Dr. Lois Freed performed the secondary review. The Division of Pharmacology-Toxicology for Neuroscience (DPT-N) concludes that the nonclinical data support approval of Radicava ORS.

The following are the key issues from the nonclinical review:

- The Applicant relied on the same nonclinical package reviewed under NDA 209176 for Radicava to support development of Radicava ORS. However, due to concerns over peripheral neuropathy that was observed in dogs and monkeys following continuous IV infusion (but not IV bolus) with edaravone, the Applicant conducted two additional

chronic toxicity studies to assess the potential for similar effects following oral administration.

1. Daily oral administration of edaravone for 26 weeks in male and female Sprague Dawley (SD) rats (0, 25, 75, and 250 mg/kg)
2. Daily oral administration for 39 weeks in male and female beagle dogs (0, 10, 30, 100, and 300 mg/kg)

- The primary toxicity observed with oral administration of edaravone was peripheral neuropathy in dogs for which the NOAEL was 30 mg/kg and resulted in an approximate 2-fold safety margin based on exposure at the recommended human dose for Radicava ORS.
    1. In the rat chronic toxicity study, daily oral doses resulted in decrease in body weight gain and regenerative anemia at the highest dose. Neither finding was observed at the end of the recovery period.
    2. In dogs (at doses above 30 mg/kg), clinical signs were similar to what was observed with continuous IV infusion (i.e., abnormal gait, loss of patellar reflex, inability to stand). Histopathology signs at necropsy showed spinal cord white matter vacuolation and degeneration, and atrophy of the sciatic nerve.

- Carcinogenicity (*reviewed under NDA 209176 under a postmarketing requirement)*: Edaravone was negative in a complete battery of genetic toxicity assays and was negative in a 26-week carcinogenicity study inTg.rasH2 mice and a 2-year carcinogenicity study in SD rats.

- Reproductive toxicology: A complete battery of reproductive and developmental toxicity studies was reviewed under NDA 209176. Reproductive and developmental toxicity following oral dosing was not assessed. Because peripheral neuropathy was observed following continuous IV or oral administration in adult dog and continuous IV infusion in adult monkey was not seen in rat, the potential for neurodevelopmental toxicity following oral administration of edaravone should be further assessed with an enhanced pre and postnatal development study in monkey should the sponsor propose a daily oral dosing regimen for humans

4. Clinical Pharmacology

The Office of Clinical Pharmacology (OCP) review was performed by clinical pharmacology reviewer Dr. Ramakrishna Samala with Dr. Bilal AbuAsal as the team leader. OCP recommends approval of Radicava ORS for the treatment of ALS.

The Applicant submitted the following studies for review:

- Study J03: pivotal relative bioavailability study to evaluate single-dose bioequivalence of 105 mg oral suspension and 60 mg IV formulation in the fasting state in health adults
- Study A01: open-label safety study in ALS patients
- Study J02: drug interaction study, effect of food and race on PK of oral edaravone
- Study J06: food effect study to evaluate the effects of various fed conditions on the PK of edaravone oral suspension

- Study Z-101: comparative bioavailability study to edaravone when administered orally and via nasogastric tube
- Study J01: single ascending dose, multiple ascending doses in health adult males

OCP has concluded that the pharmacokinetic Study J03 conducted by the Applicant meets bioequivalence criteria for AUC, but not for Cmax (Table 1).

Per Dr. Samala, the 105 mg oral suspension of edaravone has equivalent AUC_{0-t} and $AUC_{0-\infty}$ of unchanged edaravone to the approved 60 mg/60 min IV formulation [Geometric mean ratio (90% CI): 0.974 (0.914-1.038) for AUC_{0-t} and 0.977 (0.917-1.041) for $AUC_{0-\infty}$]. However, the geometric mean ratio of Cmax of 105 mg oral suspension compared to 60 mg/60 min IV formulation and its lower limit of 90% CI were within the range of 0.80 to 1.25, while the upper limit of 90% CI exceeded 1.25 [Geometric mean ratio (90% CI): 1.217 (1.090-1.359)]. In addition, edaravone has two metabolites: edaravone sulfate and edaravone glucuronide. Both sulfate and glucuronide exposures (C_{max} and AUC) after oral administration were greater than 1.3-fold than those after intravenous administration.

Table 1: Study J03: Statistical analysis for comparative bioavailability of plasma pharmacokinetics parameter of unchanged edaravone

	Geometric LS mean		Ratio (PO / IV)
Plasma PK parameter	PO	IV	(90% CI)
C_{max} (ng/mL)	1500	1232	1.217 (1.090-1.359)
AUC_{0-t} (ng·h/mL)	1645	1689	0.974 (0.914-1.038)
$AUC_{0-\infty}$ (ng·h/mL)	1665	1704	0.977 (0.917-1.041)

Source: Table 6 clinical pharmacology review

Table 2 Summary of Additional OCP Findings

General PK	Edaravone oral suspension is to be administered on empty stomach after overnight fasting without eating or drinking for 1 hour after administration. Terminal elimination half-life of unchanged edaravone after oral administration is 4.5 -9.75 hours.
Absorption	Following its oral administration, edaravone is rapidly absorbed reaching peak plasma concentrations (T_{max}) within one hour with a bioavailability of 57%. More than dose proportional increase in C_{max} and AUC_{0-24h} was observed between 30- 300 mg oral doses.
Distribution	Edaravone has a serum protein binding of > 92% and its volume of distribution 63.1 L.
Metabolism	Edaravone has two metabolites, edaravone sulfate and edaravone glucuronide. Prominent plasma conjugate is edaravone sulfate, and its formation is mediated by sulfotransferases. Prominent urine conjugate is edaravone glucuronide, and its formation is mediated by UGT1A1,

	UGT1A6, UGT1A7, UGT1A8, UGT1A9, UGT1A10, UGT2B7, and UGT2B17. Following RADICAVA ORS (edaravone 105 mg) oral administration, edaravone metabolite exposures are 1.3 to 2.2-fold higher than those after RADICAVA (edaravone 60 mg/60 min IV).
Excretion	Edaravone and its metabolites are excreted into urine. More than 80% of the administered dose is recovered in urine, of which 70-90% is glucuronide conjugate, 6-8% is sulfate conjugate, and < 1% is unchanged edaravone.
QT prolongation	Based on the results of the QT study and the pivotal BE study, the Applicant concluded that, "at a dose of 5 times the recommended dose, edaravone does not prolong the QT interval to any clinical relevant extent". The Interdisciplinary Review Team for Cardiac Safety (QT-IRT) was consulted requesting their scientific opinion on the Applicant's conclusion and agreed with the conclusion.
Drug-drug interactions	Edaravone has no meaningful effect on CYP3A4 induction, or BCRP and OAT3 inhibition, and does not alter the PK of these substrates.
Food effect/ Nasogastric tube feeding	A significant reduction in edaravone plasma exposures occurs when taken thirty minutes after high fat meal (1000 calories, 50% fat), four hours after high fat meal, and two hours after low fat meal (400 calories, 25% fat). No significant reduction in edaravone exposures occurs when taken one hour before a high fat meal, eight hours after a high fat meal, four hours after a low-fat meal, and two hours after caloric supplement (250 calories). No significant changes in plasma edaravone sulfate or edaravone glucuronide exposures were observed in any of the studied gastric conditions. Results suggest that edaravone oral suspension should be taken on empty stomach (overnight fasting of 8 hours) and continue the fasting for at least one hour of post dosing. Alternatively, edaravone oral suspension can be administered 2, 4, and 8 hours after consumption of caloric supplement, low-fat meal, and high-fat meal, respectively Plasma exposure parameters C_{max} and AUC are in similar range between healthy subjects with or without nasogastric (NG) tube and ALS patients with or without percutaneous endoscopic gastrostomy (PEG) tube. These results suggest that edaravone can be administered via PEG/NG tube without the need for dose adjustment and no significant change in plasma PK

The Office of Study Integrity and Surveillance (OSIS) was consulted for clinical and bioanalytical site inspections for the pivotal bioavailability/bioequivalence study MT-1186-J03. OSIS conducted a remote review of the analytical portion of the study and observed changes in peak integration parameters after obtaining results from the initial integration. However, the OSIS audit report concluded that the changes in peak integration parameters had no impact on the integrity of the data and the audited data are reliable.

5. Clinical Microbiology

The integrated OPQ review notes that the microbiology assessment was adequate.

6. Clinical/Statistical- Efficacy

The clinical effectiveness of edaravone oral suspension was established through the demonstration of bioequivalence of the AUC to edaravone IV in conjunction with a Cmax for the oral suspension that exceeded the Cmax of the IV formulation.

7. Safety

The safety reviewer for this application was Dr. John Troiani. Dr. Troiani reviewed the safety data in the application which primarily came from Study A01. The safety of the edaravone IV was previously established with the approval of Radicava in 2017. To justify the observed increase in exposures for edaravone oral suspension and its metabolites, and to evaluate the safety of oral administration, the Applicant conducted a long-term safety study of edaravone 105 mg oral suspension (Study A01).

Per Dr. Troiani's review the safety database and overall exposure for edaravone suspension was adequate as previously agreed at the pre-NDA meeting. In study A01, 185 subjects received edaravone oral suspension of which 168 subjects received edaravone oral suspension for at least 6 months (i.e., 6 cycles).

There were 6 deaths in Study A01. Dr. Troiani attributed these deaths to ALS progression or complications from ALS. There was one reported suicide. None of the deaths were deemed to be drug related. There were 21 SAEs reported. The majority were related to ALS or complications from ALS. Discontinuations due to adverse events were generally ALS-related. Dr. Troiani noted that the approved product labeling for edarvone captured the majority of the TEAEs that were also associated with the use of the oral suspension with the exception of fatigue. Fatigue was reported in 14 (7.6%) of subjects in Study A01, but was not reported in any of the subjects in the IV legacy study.

Dr. Troiani examined adverse events that might be unique to administration by oral suspension. He noted that there were 24 (13%) subjects with gastrointestinal AEs. Of those, two subjects experienced dry mouth, oral discomfort/pain (2), throat irritation (1), and oral paresthesia (1). Dr. Troiani concludes that the GI AEs were heterogeneous, and not suggestive of an effect of oral irritation with use of edaravone.

Dr. Troiani did not identify any new safety signals in regard to laboratory findings, vital signs, or electrocardiograms.

Dr. Troiani did not identify any new safety concerns with the edaravone oral suspension, except for fatigue, which was not previously identified as a common adverse event in the studies of the IV formulation.

8. Advisory Committee Meeting

N/A.

9. Pediatrics

Because edaravone has orphan product designation, pediatric studies were not required under the Pediatric Research Equity Act (PREA).

10. Other Relevant Regulatory Issues

- There were no good clinical practice (GCP) issues identified by Dr. Troiani.
- Dr. Troiani concludes that the Applicant has adequately disclosed financial interests/arrangements with clinical investigators.
- The Office of Study Integrity and Surveillance (OSIS) was consulted for clinical and bioanalytical site inspections and found no significant impacts on the analytic data.

11. Labeling

Prescribing Information

With the initial application, the Applicant provided separate product labeling for Radicava ORS. At the recommendation of the Division, the Applicant provided a combined label for the two formulations (Radicava and Radicava ORS). Refer to the final agreed upon labeling.

12. Postmarketing Recommendations

Postmarketing Requirements (PMRs) and Commitments (PMCs)
The following PMC will be included in the approval letter:

PMC 4266-1 Provide updated extractable/leachable studies to confirm that the container closure system does not adversely impact the drug product

13. Recommendation on Regulatory Action

I recommend approval of this NDA for Radicava ORS. The Applicant has provided substantial evidence of the effectiveness of Radicava ORS based on bioequivalence to Radicava (IV formulation). Radicava ORS 105 mg meets the bioequivalence criteria to the 60 mg dose of Radicava for AUC and no new serious safety signals were detected during the review of the long-term safety data for Radicava ORS.

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/s/

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