Summary of Risk Management Plan (RMP)

Radicava®

Solution for infusion
Edaravone 30 mg/100ml

Oral suspension
Edaravone 105 mg/5ml

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Based on RMP version 4.0

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Disclaimer

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Radicava® is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Radicava® in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Mitsubishi Tanabe Pharma GmbH, Düsseldorf, Zweigniederlassung Zürich, is fully responsible for the accuracy and correctness of the content of the published summary RMP of Radicava®.

SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for RADICAVA® (edaravone) intravenous and oral formulations

This is a summary of the Risk Management Plan (RMP) for RADICAVA®. The RMP details important risks of RADICAVA, how these risks can be minimised, and how more information will be obtained about RADICAVA's risks and uncertainties (missing information).

RADICAVA's summary of product characteristics (SmPC), and its package leaflet, give essential information to healthcare professionals and patients on how RADICAVA should be used.

Important new concerns or changes to the current ones will be included in updates of the RMP for RADICAVA.

I. The medicine and what it is used for

RADICAVA is authorised for the treatment of patients with amyotrophic lateral sclerosis (ALS) (see the SmPC for the full indication). It contains edaravone as the active substance. RADICAVA is given by intravenous (IV) infusion or can be taken orally or via a feeding tube.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of RADICAVA, together with measures to minimise such risks and the proposed studies for learning more about RADICAVA's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the patient (e.g. with special prescription) - can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report (PSUR) assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of RADICAVA is not yet available, it is listed

under 'missing information' below.

II.A List of important risks and missing information

Important risks of RADICAVA are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of RADICAVA. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information

Important identified risks	None
Important potential risks	• Hypersensitivity reaction, anaphylactic reaction
Missing information	• Patients with ALS severity grade > 3 and/or decreased respiratory function (%FVC < 80%) • Long-term safety (> 12 cycles)

Abbreviations: ALS = amyotrophic lateral sclerosis; FVC = forced vital capacity.

II.B Summary of important risks

Important potential risk: Hypersensitivity reaction, anaphylactic reaction	
Evidence for linking the risk to the medicine	No events of anaphylactoid/hypersensitivity reaction have been reported in the Phase III placebo-controlled studies with intravenous edaravone or the Phase III study with oral edaravone. In the ALS clinical development programme, skin and subcutaneous tissue disorders adverse events such as eczema, dermatitis contact, rash, and erythema have been reported in association with edaravone in placebo-controlled clinical studies. In the post-marketing experience, hypersensitivity reactions (redness, wheals, and erythema multiforme) and anaphylactoid reactions (urticaria, blood pressure decreased, and dyspnoea) have been reported. These events are described in the prescribing information.
Risk factors and risk groups	Patients with ALS with history of hypersensitivity to edaravone or any of the inactive ingredients of edaravone.
Risk minimisation measures	Routine risk minimisation measures: • SmPC (Contraindications section, Warnings and precautions section, and Undesirable effects section); • Patient information leaflet; • Recommendation to immediately discontinue edaravone if a hypersensitivity reaction occurs (SmPC Dosage/Administration section and Warnings and precautions section); • Instructions regarding monitoring and treatment (SmPC section Warnings and precautions section); • Instruction to patient to discuss with a doctor or pharmacist any health conditions such allergies and anaphylaxis is provided in the patient information leaflet; • Legal status: Prescription only. Treatment with edaravone should only be initiated by specialist physicians with experience in the management of motor neuron diseases. Additional risk minimisation measures: • None.

Abbreviations: ALS = amyotrophic lateral sclerosis; SmPC = Summary of Product Characteristics.

Important missing information: Patients with ALS severity grade > 3 and/or decreased respiratory function (%FVC < 80%)	
Risk minimisation measures	Routine risk minimisation measures: • Legal status: Prescription only. Treatment with edaravone should only be initiated by specialist physicians with experience in the management of motor neuron diseases. Additional risk minimisation measures: • None.

Abbreviations: ALS = amyotrophic lateral sclerosis; FVC = forced vital capacity.

Important missing information: Long term safety (> 12 cycles)	
Risk minimisation measures	Routine risk minimisation measures: • Legal status: Prescription only. Treatment with edaravone should only be initiated by specialist physicians with experience in the management of motor neuron diseases. Additional risk minimisation measures: • None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Japan Special Drug Use-Results Survey; • South Korean Post-Marketing Observational Study. See section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

MT-1186-A02: A Phase IIIb, multicentre, randomised, double-blind study to evaluate the efficacy and safety of oral edaravone administered for a period of 48 weeks in subjects with ALS.

Purpose of the study: Evaluate the current dose regimen versus a more frequent dosing. 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. Note: This study is required by the United States (U.S.) Food and Drug Administration (FDA) Health Authority as a condition for marketing authorisation.

II.C.2 Other studies in post-authorisation development plan

Japan Special Drug Use-Results Survey: RADICUT Injection 30 mg/RADICUT Bag for Intravenous Infusion 30 mg special drug use-results survey (ALS)

Purpose of the study: To collect and evaluate information with regard to the safety and efficacy under the actual drug use and the effect on long-term prognosis in patients who receive a treatment with RADICUT for ALS. This study will further characterise the missing information of Long-term safety (> 12 cycles). Note: This study is required by the Pharmaceuticals and Medical Devices Agency (PMDA) Health Authority (Japan).

South Korean Post-Marketing Observational Study: MTPK_ALS_Radicut: Post-marketing observational study for evaluation of the safety and efficacy of RADICUT (edaravone) in patients with ALS

Purpose of the study: To evaluate the safety and efficacy of RADICUT (edaravone) in ALS patients through a post-marketing observational study. This study will further characterise the missing information of Long-term safety (> 12 cycles). Note: This study is required by the Ministry of Food and Drug Safety (MFDS) Health Authority of South Korea.