Johnson&Johnson

# Summary of the Risk Management Plan (RMP) for RYBREVANT® (Amivantamab)

Marketing Authorisation Holder (MAH): Janssen-Cilag AG

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and

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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 RYBREVANT® 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 RYBREVANT® in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedicinfo-pro.ch) approved and authorized by Swissmedic. Janssen-Cilag AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of RYBREVANT®.

## Summary of Risk Management Plan for RYBREVANT (amivantamab)

This is a summary of the risk management plan (RMP) for RYBREVANT. The RMP details important risks of RYBREVANT, how these risks can be minimized, and how more information will be obtained about RYBREVANT's risks and uncertainties (missing information).

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

This summary of the RMP for RYBREVANT should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of RYBREVANT's RMP.

## I. The Medicine and What it is Used For

RYBREVANT is authorized for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) Exon 20 insertion (Exon 20 ins) mutations, Exon 19 deletions, or Exon 21 L858R substitution mutations (see SmPC for the full indication). It contains amivantamab as the active substance and it is given by intravenous (IV) infusion or subcutaneous (SC) injection.

Further information about the evaluation of RYBREVANT's benefits can be found in RYBREVANT's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage link to the EPAR summary landing page: https://www.ema.europa.eu/en/medicines/human/EPAR/rybrevant.

## II. Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

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

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

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized 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 (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed including Periodic Benefit-Risk Evaluation Report/Periodic Safety Update Report assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

## II.A. List of Important Risks and Missing Information

Important risks of RYBREVANT are risks that need special risk management activities to further investigate or minimize 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 RYBREVANT. 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 (eg, on the long-term use of the medicine).

| **List of Important Risks and Missing Information** | |
|---|---|
| Important identified risks | Venous thromboembolic (VTE) events* |
| Important potential risks | Hepatotoxicity<br>Impaired fertility and embryofetal toxicity |
| Missing information | None |

* Applies only to the combination of RYBREVANT and lazertinib.

## II.B. Summary of Important Risks

| **Important Identified Risk: Venous thromboembolic (VTE) events*** | |
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| Evidence for linking the risk to the medicine | Venous thromboembolic (VTE) events is an important identified risk for RYBREVANT only when given in combination with lazertinib.<br><br>The incidence of VTE events was higher in participants treated with the combination of RYBREVANT IV and lazertinib versus osimertinib in Trial NSC3003. The greatest discordance in events occurred during the first 4 months of study treatment. Importantly, the incidence rate of VTE events associated with RYBREVANT IV monotherapy in Trial EDI1001 and with RYBREVANT +carboplatin-pemetrexed in Trials NSC3001 and NSC3002 is consistent with background rates associated with NSCLC. The incidence of VTE events was lower in participants treated with amivantamab SC and lazertinib in Trial NSC2002 than in participants receiving amivantamab IV and lazertinib in Trial NSC3003. Venous thromboembolism was identified as an adverse reaction for the combination of RYBREVANT and lazertinib and is described in the SmPC for RYBREVANT. |

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| Risk factors and risk groups | Lung cancer is a risk factor for VTE events. Additional risk factors for VTE events associated with use of RYBREVANT in combination with lazertinib identified in open-label trials include age ≥60 years, Eastern Cooperative Oncology Group (ECOG)=1, and Responders (ie, patients with partial response or complete response). |
| Risk minimization measures | Routine risk minimization measures:<br>• SmPC Section 4.2<br>• SmPC Section 4.4<br>• SmPC Section 4.8<br>• PL Section 2<br>• PL Section 4<br>• An instruction for prophylactic-dose anticoagulation (DOAC or LMWH) use is provided in SmPC Sections 4.2 and 4.4.<br>• An instruction to monitor for signs and symptoms of VTE events is provided in SmPC Section 4.4 and PL Section 2.<br>• Instructions regarding the management of VTE events (ie, treatment with anticoagulation and criteria for treatment interruption and discontinuation) are provided in SmPC Sections 4.2 and 4.4 and PL Section 2.<br>• Patients with signs or symptoms suggestive of a blood clot in the veins should notify their doctor immediately, as described in PL Section 2.<br>• Legal status.<br>Additional risk minimization measures:<br>• None |

* Applies only to the combination of RYBREVANT and lazertinib.

| **Important Potential Risk: Hepatotoxicity** | |
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| Evidence for linking the risk to the medicine | In repeat-dose toxicity studies in cynomolgus monkeys, slight elevations in serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were not considered adverse.<br>Cases of ALT, AST, blood alkaline phosphatase (ALP), bilirubin, and gamma-glutamyltransferase increased have been reported in participants treated with amivantamab IV and SC in clinical trials. Hepatotoxicity-related reactions, mostly elevations of serum transaminases, are described in the SmPC for RYBREVANT. There have been no confirmed cases of drug-induced liver injury. |
| Risk factors and risk groups | Risk factors associated with EGFR inhibitor-associated hepatotoxicity include pre-existing liver disease, worsening liver metastases, and the use of concomitant hepatotoxic medications. |

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| Risk minimization measures | Routine risk minimization measures:<br>• SmPC Section 4.8<br>• PL Section 4<br>• Legal status.<br>Additional risk minimization measures:<br>• None |

| **Important Potential Risk: Impaired fertility and embryofetal toxicity** | |
|---|---|
| Evidence for linking the risk to the medicine | There are no human or animal data to assess the risk of RYBREVANT during pregnancy. Clinical trials of RYBREVANT excluded pregnant participants and required adequate contraceptive measures during treatment. There have been no participants who became pregnant while on treatment with RYBREVANT IV or SC during clinical trials.<br>Administration of other EGFR and mesenchymal-epidermal transition (MET) inhibitors to pregnant animals has resulted in an increased incidence of impairment of embryofetal development, embryolethality, and abortion. Therefore, based on the mechanism of action and findings in animal models, RYBREVANT could cause fetal harm when administered to a pregnant patient. Embryofetal toxicity is considered a class warning for EGFR and MET inhibitors.<br>The risk of impaired fertility and embryofetal toxicity is described in the SmPC for RYBREVANT. |
| Risk factors and risk groups | Patients of childbearing potential are at high risk for developing embryofetal toxicity during administration of RYBREVANT. |
| Risk minimization measures | Routine risk minimization measures:<br>• SmPC Section 4.6<br>• SmPC Section 5.3<br>• PL Section 2<br>• The potential harmful effects of EGFR inhibition on embryofetal development, and guidance to avoid pregnancy by using effective contraception during treatment and for 3 months after the last dose of RYBREVANT, are provided in SmPC Section 4.6 and PL Section 2.<br>• Patients should notify their doctor or nurse immediately about a potential or confirmed pregnancy before and during treatment with RYBREVANT, as described in PL Section 2.<br>• Legal status.<br>Additional risk minimization measures:<br>• None |

## II.C. Postauthorization Development Plan

### II.C.1. Studies Which are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorization or specific obligation of RYBREVANT.

### II.C.2. Other Studies in Postauthorization Development Plan

There are no other studies required for RYBREVANT.

## III. Swiss Specific Annex to European Union Risk Management Plan

### III.A. Safety Specifications

There are no Swiss specific safety specifications of RYBREVANT.

### III.B. Pharmacovigilance Plan

| **Additional Pharmacovigilance Activities** | |
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| **Study** | |
| Study name and title | 61186372NSC3004 - A Phase 3, open-label, randomized study of lazertinib with subcutaneous amivantamab compared with intravenous amivantamab in patients with EGFR-mutated advanced or metastatic non-small cell lung cancer after progression on osimertinib and chemotherapy. |
| Rationale and study objectives | Rationale: This study is intended to compare the pharmacokinetics, efficacy, and safety of combining lazertinib with amivantamab SC administered via manual injection versus amivantamab IV. |
| Safety concern(s) addressed | Venous thromboembolic (VTE) events* |
| Study design | Randomized, open-label, parallel, Phase 3 trial. The study participants are randomized in a 1:1 ratio to receive either amivantamab SC and lazertinib or amivantamab IV and lazertinib. All participants were recommended to receive prophylactic anticoagulants as per local guidelines during the first 4 months of combination therapy. |
| Study population | Participants with NSCLC harboring an Exon 19 deletion or Exon 21 L858R mutation in EGFR who have progressed on or after both a third-generation TKI and platinum-based chemotherapy. |
| Milestones | VTE analysis report: Q1 2025 |

* Applies only to the combination of lazertinib and amivantamab.

### III.C. Risk Minimization Measures

There are no Swiss specific risk minimization measures of RYBREVANT.