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

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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.swissmedic.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, as monotherapy, 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, after failure of platinum-based therapy (see SmPC for the full indication). It contains amivantamab as the active substance and it is given by intravenous infusion.

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.

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	Infusion-related reaction
Important potential risks	Hepatotoxicity Impaired fertility and embryofetal toxicity
Missing information	None

II.B. Summary of Important Risks

Important Identified Risk: Infusion-related reaction	
Evidence for linking the risk to the medicine	Cases of infusion-related reaction (IRR) have been reported in subjects treated with RYBREVANT in clinical trials and IRR was identified as adverse reaction. The risk for IRR and IRR as an adverse reaction are described in the SmPC for RYBREVANT.
Risk factors and risk groups	No risk factors for the development of IRRs have been identified.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 3 • PL Section 4 • Recommendations to administer RYBREVANT in a setting with appropriate medical support, for administration of pre-infusion medicinal products, for RYBREVANT initial infusion administration in split doses on Week 1 (Days 1 and 2), and for RYBREVANT administration via specific infusion rates are provided in SmPC Sections 4.2 and 4.4, and PL

	Section 3. • Recommendations regarding the management of IRRs (eg, interruption or discontinuation of infusion, administration of supportive medicinal products) are provided in SmPC Sections 4.2 and 4.4, and PL Section 4. • Patients with side effects during infusion of RYBREVANT should notify their doctor or nurse immediately, as described in PL Sections 2 and 4. • Legal status. Additional risk minimization measures: • None

Important Potential Risk: Hepatotoxicity	
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. Cases of ALT, AST, blood alkaline phosphatase (ALP), and gamma-glutamyltransferase increased have been reported in subjects treated with amivantamab in clinical trials. ALT, AST, and ALP increased were identified as adverse reactions and 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 histamine type 2 blockers, cytochrome P450 3A4 inducers, or other concomitant hepatotoxic medications.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.8 (ALT, AST, and ALP increased) • PL Section 4 • Legal status. Additional risk minimization measures: • 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 in pregnancy. Clinical trials of RYBREVANT excluded pregnant women and required adequate contraceptive measures during treatment. There have been no subjects who became pregnant while on treatment with RYBREVANT during clinical trials. 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 woman. Embryofetal toxicity is considered a class warning for EGFR and MET inhibitors. The risk of impaired fertility and embryofetal toxicity is described in the SmPC for RYBREVANT.
Risk factors and risk groups	Women of childbearing potential, who are patients, are at high risk for developing embryofetal toxicity during administration of RYBREVANT.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.6 • SmPC Section 5.3 • PL Section 2 • Warnings for the potential harmful effects of EGFR inhibition on embryofetal development, and precautions 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. • 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. • Legal status. Additional risk minimization measures: • None

II.C. Postauthorization Development Plan

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

The following study is a condition of the marketing authorization:

61186372NSC3001 - A randomized, open-label Phase 3 study of combination amivantamab and carboplatin-pemetrexed therapy, compared with carboplatin-pemetrexed, in patients with EGFR Exon 20ins mutated locally advanced or metastatic non-small cell lung cancer.

Purpose of the study: To assess the efficacy, as demonstrated by progression-free survival, the clinical benefit, and the safety in participants treated with amivantamab in combination with chemotherapy, versus chemotherapy alone.

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

There are no other studies required for RYBREVANT.