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Summary of the Risk Management Plan (RMP) for LAZCLUZE® (Lazertinib)

Marketing Authorisation Holder (MAH): Janssen-Cilag AG

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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 LAZCLUZE® 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 LAZCLUZE® 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 LAZCLUZE®.

Summary of Risk Management Plan for LAZCLUZE (lazertinib)

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

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

This summary of the RMP for LAZCLUZE 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 LAZCLUZE's RMP.

I. The Medicine and What it is Used For

LAZCLUZE, in combination with amivantamab, is authorized for the first-line treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) Exon 19 deletions or Exon 21 L858R substitution mutations (see SmPC for the full indication). It contains lazertinib as the active substance and it is given as 80-mg or 240-mg film-coated tablets for oral administration.

Further information about the evaluation of LAZCLUZE’s benefits can be found in LAZCLUZE’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 LAZCLUZE, together with measures to minimize such risks and the proposed studies for learning more about LAZCLUZE'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 LAZCLUZE are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. 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 LAZCLUZE. 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 Impaired fertility and embryofetal toxicity
Missing information	None

* Applies only to the combination of LAZCLUZE and amivantamab.

II.B. Summary of Important Risks

Important Identified Risk: Venous thromboembolic (VTE) events*	
Evidence for linking the risk to the medicine	Venous thromboembolic (VTE) events is an important identified risk for LAZCLUZE only when given in combination with amivantamab. The incidence of VTE events was higher in participants treated with the combination of LAZCLUZE and amivantamab versus LAZCLUZE or osimertinib monotherapy 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 LAZCLUZE monotherapy is consistent with background rates associated with NSCLC. Venous thromboembolism was identified as an adverse reaction for the combination of LAZCLUZE and amivantamab and is described in the SmPC for LAZCLUZE.
Risk factors and risk groups	Lung cancer is a risk factor for VTE events. Additional risk factors for VTE events associated with use of LAZCLUZE in combination with amivantamab 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: • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • An instruction for prophylactic-dose anticoagulation (direct acting oral anticoagulant [DOAC] or low-molecular weight heparin [LMWH]) to be used for the first 4 months of treatment is provided in SmPC Sections 4.2 and 4.4. • An instruction to monitor for signs and symptoms of VTE events is provided in SmPC Section 4.4 and PL Section 2. • 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. • Patients with signs or symptoms suggestive of a blood clot in the veins should notify their doctor immediately, as described in PL Section 2. • Legal status Additional risk minimization measures: • None

* Applies only to the combination of LAZCLUZE and amivantamab.

Important Potential Risk: Hepatotoxicity	
Evidence for linking the risk to the medicine	Hepatotoxicity is known as a risk in the EGFR-TKI class of drugs. Nonclinical studies with LAZCLUZE in rats showed liver enzyme increases that persisted in the recovery phase, which is indicative of hepatocellular damage. Cases of alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltransferase, and alkaline phosphatase increased have been reported in participants treated with LAZCLUZE in Trial NSC3003. Hepatotoxicity-related reactions, mostly elevations of serum transaminases, are described in the SmPC for LAZCLUZE. 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.

Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.2 • SmPC Section 4.8 • PL Section 4 • Recommendations regarding the management of hepatotoxicity (ie, criteria for treatment interruption and dose reduction) are provided in SmPC Section 4.2. • 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 data to assess the risk of LAZCLUZE during pregnancy. Clinical trials of LAZCLUZE excluded pregnant participants and required adequate contraceptive measures during treatment. There have been no participants who became pregnant while on treatment with LAZCLUZE in Trial NSC3003. Reproductive toxicity studies with LAZCLUZE showed a decrease in the number of oestrus cycles, an increase in post-implantation loss, a decrease in the number of live fetuses, and lower fetal weight in rats but not rabbits. In repeat-dose toxicity studies, decreased numbers of corpora lutea were noted in the ovaries of rats and degenerative changes were present in the testes of rats and dogs. Therefore, based on the mechanism of action and findings in animal models, LAZCLUZE may cause fetal harm when administered to a pregnant woman and may reduce female and male fertility. Impaired fertility and embryofetal toxicity is considered a class warning for EGFR inhibitors. The risk of impaired fertility and embryofetal toxicity is described in the SmPC for LAZCLUZE.
Risk factors and risk groups	Patients of childbearing potential are at high risk for developing embryofetal toxicity during administration of LAZCLUZE.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.6 • SmPC Section 5.3 • PL Section 2 • The potential harmful effects of LAZCLUZE on embryofetal development, and guidance to avoid pregnancy by using effective contraception during treatment and for 3 weeks after the last dose of

	LAZCLUZE, are provided in SmPC Section 4.6 and PL Section 2. • Patients should notify their doctor immediately about a potential or confirmed pregnancy before and during treatment with LAZCLUZE, 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

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

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

There are no studies required for LAZCLUZE.