PUBLIC SUMMARY OF THE RISK MANAGEMENT PLAN

ZYNYZ (retifanlimab)

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADR	adverse drug reaction
AE	adverse event
BMI	body mass index
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
ICI	immune checkpoint inhibitor
IRR	infusion-realted reaction
IV	intravenous
PD-(L)1	programmed death receptor-(ligand) 1
PL	package leaflet
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics

OVERVIEW

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 Zynyz 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 Zynyz in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Incyte Biosciences International Sàrl is fully responsible for the accuracy and correctness of the content of the published summary RMP of Zynyz.

SUMMARY OF RISK MANAGEMENT PLAN FOR ZYNYZ (RETIFANLIMAB)

This is a summary of the RMP for Zynyz. The RMP details important risks of Zynyz, and how more information will be obtained about Zynyz's risks and uncertainties (missing information).

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

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

I THE MEDICINE AND WHAT IT IS USED FOR

Zynyz is authorised for first-line treatment of adult patients with Merkel cell carcinoma (see SmPC for the full indication). It contains retifanlimab as the active substance and it is administered by IV infusion.

Further information about the evaluation of Zynyz's benefits can be found in Zynyz's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

II RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of Zynyz, together with measures to minimise such risks and the proposed studies for learning more about Zynyz'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 (eg, with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In the case of Zynyz, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risk, below.

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 Zynyz is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Zynyz 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 Zynyz. 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).

Table II.1: Lists of Important Risks and Missing Information

List of Important Risks and Missing Information	
Important identified risks	Immune-mediated adverse reactions Infusion-related reactions
Important potential risks	None
Missing information	Long term safety data

II.B Summary of Important Risks

Important identified risk: Immune-mediated adverse reactions	
Evidence for linking the risk to the medicine	ICI use is associated with a spectrum of adverse effects related to the mechanism of action. The adverse effects can affect multiple organs of the body and are known as immune-mediated AEs. ICI therapy can usually continue in the presence of mild immune-mediated AEs with close monitoring. However, moderate to severe immune-mediated AEs may be associated with severe declines in organ function and fatal outcomes have been reported. These events require early detection and proper management (Schneider et al 2021). Taking into account the seriousness and severity of immune mediated AEs, the clinical actions required to mitigate the risk of immune-mediated AEs in patients being treated with PD-(L)1 inhibitors, including retifanlimab, and in an effort to harmonize with other PD-(L)1 ihibitors, immune-mediated adverse reactions is considered an important identified risk.
Risk factors and risk groups	Recent retrospective studies and a systemic review and meta-analysis reported that a combination of ICIs and other agents, treatment lines of ICI initiation, cycles of ICI administration, BMI,

Important identified risk: Immune-mediated adverse reactions	
	derived neutrophil-to-lymphocyte ratio, serum albumin level, history of Type 1 hypersensitivity reactions, c-reactive protein, and smoking status could be associated with the incidence of immune-mediated AEs (Eun et al 2019, Nuzzo et al 2020, Shimozaki et al 2021, Suazo-Zepeda et al 2021). Some reports also suggest that the incidence of immune-mediated AEs is higher in patients with autoimmune diseases than in those without them; however, the relationship between preexisting autoimmune disorders and the development of immune-mediated AEs remains controversial (Calabrese et al 2018, Abdel-Wahab et al 2018, Abu-Sbeih et al 2020)
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2, 4.4, 4.8 PL section 2, 4 Legal status Additional risk minimisation measures: Patient Card

Important identified risk: Infusion-related reactions	
Evidence for linking the risk to the medicine	Infusion related reactions are common ADRs with monoclonal antibodies. Symptoms are timely related to the drug administration and may range from symptomatic discomfort to fatal events (Doessegger and Banholzer 2015).Taking into account the seriousness of infusion-related reactions, the clinical actions required to mitigate the risk of infusion-related reactions in patients being treated with PD-(L)1 inhibitors, including retifanlimab, and in an effort to harmonize with other PD-(L)1 inhibitors, infusion-related reactions is considered an important identified risk.
Risk factors and risk groups	No specific risk factors or risk groups are known. All patients are potentially at risk for IRRs.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2, 4.4, 4.8 PL section 2, 4 Legal status Additional risk minimisation measures: None

Missing information: Long term safety data	
Risk minimisation measures	Routine risk minimisation measures: Legal status

Missing information: Long term safety data	
	Additional risk minimisation measures: None

II.C Post-Authorisation Development Plan

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

There are no studies which are conditions of the marketing authorisation or specific obligation of Zynyz.

II.C.2 Other Studies in Post-Authorisation Development Plan

There are no studies required for Zynyz.

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