Summary of Risk Management Plan for Lunsumio (Mosunetuzumab)

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

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

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

I. THE MEDICINE AND WHAT IT IS USED FOR

Lunsumio as monotherapy is authorized for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) who have received at least two prior systemic therapies (see SmPC for the full indication). It contains mosunetuzumab as the active substance, and is administered as an intravenous infusion.

Further information about the evaluation of Lunsumio's benefits can be found in Lunsumio's EPAR, including in its plain-language summary, available on the EMA Website, under the medicine's Web Page.

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

Important risks of Lunsumio, together with measures to minimize such risks and the proposed studies for learning more about Lunsumio'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 package leaflet 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 as 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 or without prescription) can help to minimize its risks.

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

In the case of Lunsumio, these measures are supplemented with *additional risk-minimization* measures mentioned under relevant risks below:

- Patient Card

In addition to these measures, information about adverse events is collected continuously and regularly analyzed, including 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 Lunsumio is not yet available, it is listed under “missing information” below.

II.A List of Important Risks and Missing Information

Important risks of Lunsumio 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 Lunsumio. 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 about 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	• Cytokine release syndrome • Tumor flare • Serious Infections
Important potential risks	None
Missing information	• Long-term safety • Safety in patients with prior CAR-T therapy

II.B Summary of Important Risks

Important Identified Risk: Cytokine release syndrome	
Evidence for linking the risk to the medicine	Non-clinical studies showing transient T-cell activation and cytokine release and in clinical studies, the majority of CRS events occurred in the first cycle of mosunetuzumab administration, mostly associated either with Day 1 or Day 15 doses and evidence is also based on Study GO29781.
Risk factors and risk groups	Patient-specific factors which may account for the greater likelihood to have excessive cytokine release are yet to be clearly defined but may include tumor burden, peripheral/circulating target cells, higher levels of macrophages or monocytes or the presence of hyperactive T-cells primed to react.
Risk-minimization measures	**Routine risk-minimization measures:** **SmPC:** Section 4.2 Posology and method of administration Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects **Package Leaflet:** Section 2 What you need to know before you use Lunsumio Section 4 Possible side effects **Additional risk-minimization measures:** • Patient Card

aRMM=additional risk minimization measures; CRS=cytokine release syndrome; SmPC=summary of product characteristics.

Important Identified Risk: Tumor flare	
Evidence for linking the risk to the medicine	Evidence is based on Study GO29781.
Risk factors and risk groups	Tumor flare events tend to occur within the first few weeks following mosunetuzumab administration. In addition, depending on tumor size and anatomic location, tumor flare may potentially result in mass effects on vital structures including airways, major blood vessels, gastrointestinal tract (risk of perforation and hemorrhage), and/or major organs.
Risk-minimization measures	**Routine risk-minimization measures:** **SmPC:** Section 4.2 Posology and method of administration Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects **Package Leaflet:** Section 2 What you need to know before you use Lunsumio Section 4 Possible side effects **Additional risk-minimization measures:** No additional risk-minimization measures

aRMM=additional risk minimization measures; SmPC=summary of product characteristics; TF=tumor flare.

Important Identified Risk: Serious Infections	
Evidence for linking the risk to the medicine	Nonclinical chronic toxicity study showed infections that were deemed secondary to immunosuppression due to mosunetuzumab-induced prolonged B-cell depletion and evidence is also based on Study GO29781.
Risk factors and risk groups	Serious infections is a recognized risk associated with B-cell depletion treatment effect and a major cause of morbidity and mortality in patients with hematological malignancies. Underlying medical conditions in the patient population including history of recurring or chronic infections (e.g., chronic, active Epstein-Barr Virus) and prior immunosuppressive treatment are risk factors that may predispose to infections.
Risk-minimization measures	**Routine risk-minimization measures:** **SmPC:** Section 4.2 Posology and method of administration Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects **Package Leaflet:** Section 2 What you need to know before you use Lunsumio Section 4 Possible side effects **Additional risk-minimization measures:** No additional risk-minimization measures

aRMM=additional risk minimization measures; SmPC=summary of product characteristics.

Missing information: Long-term safety	
Risk-minimization measures	**Routine risk minimization measures:** No routine risk-minimization measures **Additional risk minimization measures:** No additional risk-minimization measures
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Study GO42909

Missing information: Safety in patients with prior CAR-T therapy	
Risk-minimization measures	**Routine risk minimization measures:** No routine risk-minimization measures **Additional risk minimization measures:** No additional risk-minimization measures

II.C Post-Authorization Development Plan

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

The following studies are conditions of the marketing authorization.

Study short name: Study GO42909

Purpose of the study: This study will evaluate the efficacy and safety of M+Len compared with R+Len in patients with R/R FL who were treated with at least one prior systemic therapy.

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

There is one other study in the post-authorization development plan for Lunsumio:

Study short name: Study GO42909

Purpose of the study: Phase III randomized, open-label, multicenter study evaluating efficacy and safety of mosunetuzumab in combination with lenalidomide (M+Len) in comparison to rituximab in combination with lenalidomide (R+Len) in patients with follicular lymphoma after at least one line of systemic therapy. In this case, this study will be used to evaluate the long-term safety and tolerability of mosunetuzumab, which will address the missing information of long-term safety of mosunetuzumab.