PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Pulmixal 9.5%/0.28% medicinal gas, compressed (He/CO/O2/N2 9.5%/0.28/21%/QS) –Pulmixal 14%/0.28% medicinal gas, compressed (He/CO/O2/N2 mixture 14%/0.28%/21/QS)

This is a summary of the risk management plan (RMP) for Pulmixal 9.5%/0.28% and Pulmixal 14%/0.28%. The RMP details important risks of Pulmixal 9.5%/0.28% and Pulmixal 14%/0.28%, how these risks can be minimized, and how more information will be obtained about Pulmixal 9.5%/0.28% and Pulmixal 14%/0.28%'s risks and uncertainties (missing information).

Pulmixal 9.5%/0.28% and Pulmixal 14%/0.28% 's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Pulmixal 9.5%/0.28% and Pulmixal 14%/0.28% should be used. This summary of the RMP for Pulmixal 9.5%/0.28% and Pulmixal 14%/0.28% should be read in the context of all this information including the assessment report and its plain-language summary, all which is part of the PAR.

Important new concerns or changes to the current ones will be included in updates of Pulmixal 9.5%/0.28%'s and Pulmixal 14%/0.28%'s RMP.

I. The medicine and what it is used for

Pulmixal 9.5%/0.28% and Pulmixal 14%/0.28% are authorized for the diagnostic testing of the pulmonary function: with the determination of the diffusion capacity/transfer factor as main parameter and the estimation of lung volume as additional parameter. CO and He are the active substances of these two medicinal products which are administered by inhalation.

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Pulmixal 9.5%/0.28%and Pulmixal 14%/0.28%, together with measures to minimize such risks and the proposed studies for learning more about Pulmixal 9.5%/0.28% and Pulmixal 14%/0.28% 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 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 (e.g. with or without prescription) can help to minimise its risks.

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

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 Pulmixal 9.5% 0.28%/ Pulmixal 14% 0.28% is not yet available, it is listed under 'missing information' below".

II.A List of important risks and missing information

Important risks of Pulmixal 9.5%/0.28% and Pulmixal 14%/0.28% 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 Pulmixal 9.5%/0.28% and Pulmixal 14%/0.28%. 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 (e.g. on the long-term use of the medicine);

List of important risks	
Important identified risks	None
Important potential risks	Myocardial ischemia
Missing information	Safety in pediatric population

II.B Summary of important risks

Myocardial ischemia	
Evidence for linking the risk to the medicine	Cardiovascular effects of inhalation exposures to carbon monoxide have been evaluated in controlled human clinical studies that provided convincing evidence for adverse cardiovascular effects in association with carbon monoxide exposures that result in blood COHb levels ≥2.4%, with effects occurring at the lowest levels in subjects with compromised cardiovascular function (e.g., coronary artery disease). Considering the seriousness of myocardial ischemia and its consequences, this risk is considered as important.
Risk factors and risk groups	Patients with a history of coronary artery disease may be at risk for ST segment depression induced by CO.
Risk minimisation measures	<Routine risk minimisation measures:> SmPC section 4.4 and PL section 2: Precautions regarding patients with a history of coronary artery disease are provided <Additional risk minimisation measures:> No risk minimisation measures
Additional pharmacovigilance activities	None

Safety in pediatric population

Evidence for linking the risk to the medicine	Toxicity data in the pediatric population are missing for Pulmixal 9.5%/0.28% and Pulmixal 14%/0.28%.
Risk factors and risk groups	Pediatric population
Risk minimisation measures	SmPC section 4.2 where it is specified that same recommendation on posology applies irrespectively of age SmPC section 4.4 where it is specified that the product should be used with caution in children because of the lack of systemic toxicity data for this mixture. PL section2 where it is specified that the product should be use with caution in children <Additional risk minimisation measures:> No risk minimisation measures
Additional pharmacovigilance activities	None

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Pulmixal 9.5%/0.28% medicinal gas, compressed and Pulmixal 14%/0.28% medicinal gas, compressed.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Pulmixal 9.5%/0.28% medicinal gas, compressed and Pulmixal 14%/0.28% medicinal gas, compressed.