PART VI: SUMMARY OF ACTIVITIES IN THE RISK MANAGEMENT PLAN for Trimbow®/ Riarify®/Trydonis® (Beclometasone dipropionate plus Formoterol fumarate dihydrate plus Glycopyrronium)

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

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

This summary of the RMP for Trimbow® 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 Trimbow®'s RMP.

I. The medicine and what is it used for?

Trimbow® is authorised for the following indications and strengths in the EEA:

COPD:

<Trimbow 87/5/9>(Pressurised Metered Dose Inhalation or pMDI)>

<Trimbow 88/5/9(Dry Powder Inhaler or DPI)>

Trimbow® is authorised for the maintenance treatment in adult patients with moderate to severe chronic obstructive pulmonary disease (COPD) who are not adequately treated by a combination of an inhaled corticosteroid and a long-acting beta2-agonist or a combination of a long-acting beta2-agonist and a long-acting muscarinic antagonist (for effects on symptoms control and prevention of exacerbations (see SmPC for the full indication).

Asthma:

<Trimbow 87/5/9>(Pressurised Metered Dose Inhalation or pMDI)>

Trimbow® 87/5/9 Medium Strength (MS) is authorised for the maintenance treatment of asthma, in adults not adequately controlled with a maintenance combination of a long-acting beta2-agonist and medium dose of inhaled corticosteroid, and who experienced one or more asthma exacerbations in the previous year. (see SmPC for the full indication).

<Trimbow 172/5/9>(Pressurised Metered Dose Inhalation or pMDI)>

Trimbow® 172/5/9 High strength (HS) is authorised for the maintenance treatment of asthma, in adults not adequately controlled with a maintenance combination of a long-acting beta2-agonist and high dose of inhaled corticosteroid, and who experienced one or more asthma exacerbations in the previous year. (see SmPC for further details).

Trimbow® contains beclometasone dipropionate, formoterol fumarate dihydrate and glycopyrronium as active substances and is given by inhalation.

Further information about the evaluation of Trimbow's benefits can be found in Trimbow's EPAR, including its plain language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/trimbow.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Trimbow® together with measures to minimise such risks and the proposed studies for learning more about Trimbow®'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 product information 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 reactions is collected continuously and regularly analysed, including PSUR 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 Trimbow® are risks that need special risk management activities to further investigate or minimise 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 Trimbow®. 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 and missing information	
Important identified risks	None
Important potential risks	Heart diseases and stroke (Cardio- and cerebro-vascular events)
Missing information	None

II.B Summary of important risks

Important Potential risk: **Cardio-and cerebrovascular events**	
Evidence for linking the risk to the medicine	It is known that other Long Acting Muscarinic Antagonists drugs (LAMA) such as glycopyrronium bromide, have been associated with effects on the heart and cerebrovascular events (stroke). During clinical studies with Trimbow®, cases of cardio-and cerebrovascular have been reported.

Risk factors and risk groups	There are many risk factors associated with coronary heart disease and stroke like family history, ethnicity and age. Other risk factors include smoking, hypertension, high cholesterol, obesity, physical inactivity, diabetes, unhealthy diets, and harmful use of alcohol.
Risk minimisation measures	Routine activities to further investigate and to minimise the risk are necessary. In addition, information on the risk is stated in sections 4.4 and 4.8 of the SmPC and in sections 2 and 4 of the leaflet.
Additional pharmacovigilance activities	In order to assess and address the important potential risk of cardio and cerebrovascular events, a post-authorisation safety study is planned (PASS). The proposed PASS study is related to the long-term use of Dry Powder Inhaler vs. Pressurised Metered Dose Inhaler.

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 Trimbow®.

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

A post-authorisation safety study (PASS) is planned to perform further evaluation of the important potential risk of heart diseases and stroke (cardio and cerebrovascular events) for DPI dosage.

Study short name: Multinational database cohort study to assess adverse cardiovascular and cerebrovascular outcomes in patients with chronic obstructive pulmonary disease initiating a fixed triple therapy containing beclometasone dipropionate, formoterol fumarate and glycopyrronium administered via dry powder inhaler (DPI) compared to pressurized metered dose inhaler (pMDI).

Purpose of the study: A post-authorisation safety study (PASS) is planned to perform further evaluation of the important potential risk of heart diseases and stroke (cardio and cerebrovascular events) for DPI dosage.

Primary Objective:

The primary objective of this study will be to assess the incidence of 'Major Adverse Cardiovascular Events' (MACEs), defined as any of the following events:

- Myocardial infarction
- Stroke (ischemic and haemorrhagic stroke)
- Hospitalization due to acute coronary syndrome
- Hospitalization due to heart failure

Secondary Objectives:

The secondary objectives of the study will be to assess separately the incidence of each of the following specific events:

- Myocardial infarction
- Cerebrovascular disorders (ischemic and haemorrhagic stroke, transient ischemic attack)
- Hospitalization due to acute coronary syndrome
- Hospitalization due to heart failure
- Arrhythmias (new-sustained supraventricular and sustained ventricular)
- All-cause death