PART VI SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR SPIRIVA (TIOTROPIUM BROMIDE)

This is a summary of the Risk Management Plan (RMP) for Spiriva. The RMP details important risks of Spiriva, how these risks can be minimised, and how more information will be obtained about Spiriva's risks and uncertainties (missing information).

Spiriva's Summary of Product Characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Spiriva should be used.

I. THE MEDICINE AND WHAT IT IS USED FOR

Spiriva is authorised for maintenance treatment to relieve symptoms of patients with chronic obstructive pulmonary disease (COPD). Spiriva Respimat is authorised for add-on maintenance treatment in patients aged 6 years and older with severe asthma who experienced 1 or more severe asthma exacerbations in the preceding year (see SmPCs for the full indication). They contain tiotropium bromide as the active substance and they are given by inhalation.

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

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

Together, these measures constitute routine risk minimisation measures.

If important information that may affect the safe use of Spiriva is not yet available, it is listed under ‘missing information’ below.

II.A List of important risks and missing information

Important risks of Spiriva 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 Spiriva. 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).

PVI.Table 1 List of important risks and missing information

Important identified risks	None
Important potential risks	Cardiac mortality
	Cardiac disorders (ischaemic heart disease including myocardial infarction and angina pectoris, cardiac arrhythmia, cardiac failure)
Missing information	Pregnant and breast-feeding women
	Long term safety for the asthma indication
	Patients with a recent history of myocardial infarction, unstable or life-threatening cardiac arrhythmia, paroxysmal tachycardia, and decompensated heart failure

II.B Summary of important risks

Summaries of the important risks and missing information for Spiriva are provided in the following tables.

PVI.Table 2 Cardiac mortality

Important potential risk of cardiac mortality	
Evidence for linking the risk to the medicine	Patients with recent myocardial infarction <6 months, any unstable or life threatening cardiac arrhythmia or cardiac arrhythmia requiring intervention or a change in drug therapy in the past year, or hospitalisation of heart failure within the past year were excluded from the clinical trials as these conditions may be affected by the anticholinergic mechanism of action. In 7 COPD trials with tiotropium inhalation solution, tiotropium-treated patients with cardiac mortality showed a frequency of 0.9% versus 0.5% in the placebo group. In the post-marketing setting (for COPD), 390 cases pertaining to cardiac disorders were associated with a fatal outcome; in addition, 598 fatal MACE cases were reported.
Risk factors and risk groups	Determining the degree to which cardiac disorders are responsible for the death of COPD patients remains a major medical question. It is generally difficult to determine the underlying cause of death, since usually COPD patients have multiple comorbidities, often with a common risk factor, such as tobacco use, responsible for several of them. Similarly, obesity, hyperlipidaemia, sedentary lifestyle, diabetes mellitus, and hypertension may increase the risk of COPD mortality through a cardiac or a non-cardiac mechanism. Finally, the administration of pulmonary medications with pro-arrhythmic effects, such as xanthines, beta-adrenergic agonists, or other anticholinergics, may increase the risk of cardiac disorders and subsequently cardiac mortality in COPD patients. A comparison between asthma and COPD patients shows that cardiac disorders, particularly with volume overload, are more frequent in COPD patients, who are also older and have higher BMI, heavy smoking history, increased C-reactive protein and greater airway obstruction. However, cardiovascular diseases are the most frequent cause of death in patients with asthma.
Risk minimisation measures	No risk minimisation measures.
Additional pharmacovigilance activities	None.

PVI.Table 3 Cardiac disorders (ischaemic heart disease, myocardial infarction, cardiac arrhythmia, cardiac failure, angina pectoris)

Important potential risk of cardiac disorders (ischaemic heart disease including myocardial infarction and angina pectoris, cardiac arrhythmia, cardiac failure)	
Evidence for linking the risk to the medicine	In the clinical trial development programme for COPD, 7.7% tiotropium-treated patients experienced cardiac disorders. In the indication of asthma, 1.0% of tiotropium-treated patients experienced cardiac disorders. In the post-marketing setting, 3787 cases reporting events of cardiac disorders were identified cumulatively.
Risk factors and risk groups	Tobacco smoking, obesity, hyperlipidaemia, sedentary lifestyle, diabetes mellitus, and hypertension are major risk factors for ischaemic (coronary) heart disease. Ischaemic heart disease, previous myocardial infarction together with pulmonary heart disease, and congestive heart failure are the most prominent physiological risk factors for cardiac arrhythmia. These risk factors have a high prevalence in patients with COPD. In addition, pharmacological risk factors cannot be excluded such as co-administration of e.g. pulmonary medications with pro-arrhythmic effects such as xanthines, beta-adrenergic agonists, or other anticholinergics.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 where advice is given on patients with recent myocardial infarction; any unstable cardiac arrhythmia or hospitalisation of heart failure in the past year.
Additional pharmacovigilance activities	None.

PVI.Table 4 Pregnant and breast-feeding women

Missing information of pregnant and breast-feeding women	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.6 where it is noted that as a precautionary measure, it is preferable to avoid the use of tiotropium during pregnancy. It is unknown whether tiotropium bromide is excreted in human breast milk. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	None.

PVI.Table 5 Long term safety for indication asthma

Missing information of long term safety for indication asthma	
Risk minimisation measures	No risk minimisation measures.
Additional pharmacovigilance activities	None.

PVI.Table 6 Patients with a recent history of myocardial infarction, unstable or life threatening cardiac arrhythmia, paroxysmal tachycardia, and decompensated heart failure

Missing information of patients with a recent history of myocardial infarction, unstable or life threatening cardiac arrhythmia, paroxysmal tachycardia, and decompensated heart failure	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 where advice is given on patients with recent myocardial infarction; any unstable cardiac arrhythmia or hospitalisation of heart failure in the past year. Additional risk minimisation measures: None.
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 for the marketing authorisation or specific obligation for Spiriva.

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

There are no ongoing or planned studies that are required for Spiriva.

ABBREVIATIONS

COPD	Chronic obstructive pulmonary disease
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics