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
	Blood and lymphatic system disorders
	Blood glucose increased
	Psychiatric disorders
	Syncope
	Cardiac disorders (ischaemic heart disease, myocardial infarction, cardiac arrhythmia, cardiac failure, angina pectoris)
	Vascular disorders (aneurysm, hypertension)
	Renal failure
	Overdose
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), 2291 cases pertained to cardiac disorders, 335 of which were associated with a fatal outcome.
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 Blood and lymphatic system disorders

Important potential risk of blood and lymphatic system disorders	
Evidence for linking the risk to the medicine	This topic is conveyed from an old/historic monitoring request originating from single case reports with abnormal blood cell counts. The cases were discussed in a clinical expert statement in 2006. None of the cases analysed were found to contain compelling evidence of a causal relationship to treatment with tiotropium. Nonetheless, for historic consistency reasons, BI continues to consider this topic an important potential risk and conducts pharmacovigilance risk monitoring for blood and lymphatic system disorders.
Risk factors and risk groups	Comorbidity and concomitant medications that typically are abundant in an elderly COPD patient population can reasonably be expected to account for a considerable number of blood cell count deviations. Enlarged lymph nodes and anaemia are prevalent in a number of predominantly chronic infections, cancers, and in autoimmune diseases (e.g. sarcoidosis).
Risk minimisation measures	No risk minimisation measures.
Additional pharmacovigilance activities	None.

PVI.Table 4 Blood glucose increased

Important potential risk of blood glucose increased	
Evidence for linking the risk to the medicine	In the COPD clinical trials, 1.3% of tiotropium inhalation solution-treated patients showed increased blood glucose versus 0.9% in the placebo group. In the post-marketing setting, 349 cases (COPD indication) describing events of increased blood glucose were reported, 135 of which were serious.
Risk factors and risk groups	The following groups of patients are at increased risk of developing increased blood glucose: patients with pre-existing diabetes mellitus, and patients with multiple pathophysiological alterations such as obesity, inflammation and oxidative stress, insulin resistance, or increase of endogenous or exogenous pro-diabetic hormones. Some metabolites, food, or medications such as corticosteroids, may also be associated with increased blood glucose.
Risk minimisation measures	No risk minimisation measures.
Additional pharmacovigilance activities	None.

PVI.Table 5 Psychiatric disorders

Important potential risk of psychiatric disorders	
Evidence for linking the risk to the medicine	In the clinical trial development programme, 4.8% tiotropium-treated COPD patients and 1.3% of tiotropium-treated asthma patients experienced psychiatric disorders. In the post marketing setting, 920 cases reported events pertaining to psychiatric disorders, 146 of which were serious.
Risk factors and risk groups	COPD and depression are comorbidities reported in at least more than 20% of patients with COPD. The impact of living with COPD can have tremendous psychological consequences for patients and their families. Psychological well-being and quality of life is very important to patients with COPD and therefore assessment and support of patients is central to medical management.
Risk minimisation measures	No risk minimisation measures.
Additional pharmacovigilance activities	None.

PVI.Table 6 Syncope

Important potential risk of syncope	
Evidence for linking the risk to the medicine	In the clinical trial development programme, 0.7% of tiotropium-treated COPD patients and 0.2% of tiotropium-treated asthma patients experienced syncope; most of these were serious. In the post-marketing setting, 228 cases describing events of syncope were identified, of which 10 cases were associated with a fatal outcome.
Risk factors and risk groups	In addition to advanced age, cardiovascular or neurological comorbidities are prevalent in patients with COPD, which are associated with an increased risk of syncope. Moreover, concomitant medications acting on the cardiovascular and central nervous systems also may predispose to syncope in this population.
Risk minimisation measures	No risk minimisation measures.
Additional pharmacovigilance activities	None.

PVI.Table 7 Cardiac disorders (ischaemic heart disease, myocardial infarction, cardiac arrhythmia, cardiac failure, angina pectoris)

Important potential risk of cardiac disorders (ischaemic heart disease, myocardial infarction, cardiac arrhythmia, cardiac failure, angina pectoris)	
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, 2291 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 8 Vascular disorders (aneurysm)

Important potential risk of vascular disorders (aneurysm)	
Evidence for linking the risk to the medicine	In the clinical trial development programme, 0.5% tiotropium-treated COPD patients experienced aneurysm; no asthma patients experienced this event. In the post-marketing setting, 102 cases describing events of aneurysm were identified cumulatively, 17 of which were associated with a fatal outcome.
Risk factors and risk groups	Risk factors for an aneurysm include diabetes, obesity, hypertension, tobacco use, alcoholism, high cholesterol, copper deficiency, increasing age, and tertiary syphilis infection. A minority of aneurysms are associated with genetic factors. Patients with COPD are usually tobacco smokers and have concomitant diseases such as diabetes, atherosclerosis, obesity, hypertension, and an increased age. Thus, there is a high likelihood that patients with COPD may be diagnosed with an aneurysm of any kind, independent of pulmonary medication.
Risk minimisation measures	No risk minimisation measures.
Additional pharmacovigilance activities	None.

PVI.Table 9 Vascular disorders (hypertension)

Important potential risk of vascular disorders (hypertension)	
Evidence for linking the risk to the medicine	In the clinical trial development programme, 3.8% of tiotropium-treated COPD patients and 1.3% tiotropium inhalation solution-treated asthma patients experienced hypertension. In the post-marketing setting, 719 cases describing events of hypertension were identified cumulatively, 22 of which were associated with a fatal outcome.
Risk factors and risk groups	Blood pressure 'tracks' over time in children and between adolescence and young adulthood. In the US, average systolic blood pressure is higher for men than for women during early adulthood, although among older individuals the age-related rate of rise is steeper for women. Consequently, among individuals age 60 years and older, systolic blood pressures of women are higher than those of men. Among adults, diastolic blood pressure also increases progressively with age until ~55 years, after which it tends to decrease. In African American patients, hypertension appears earlier, is generally more severe, and results in higher rates of morbidity and mortality from stroke, left ventricular hypertrophy, congestive heart failure, and end-stage renal disease than in white American patients. Studies of societies undergoing 'acculturation' and studies of migrants from a less to a more urbanised setting indicate a profound environmental contribution to blood pressure. Obesity and weight gain are strong, independent risk factors for hypertension. Among populations, hypertension prevalence is related to dietary sodium chloride intake, and the age-related increase in blood pressure may be augmented by a high sodium chloride intake. Low dietary intakes of calcium and potassium also may contribute to the risk of hypertension. The urine sodium-to-potassium ratio is a stronger correlate of blood pressure than is either sodium or potassium alone. Alcohol consumption, psychosocial stress, and low levels of physical activity also may contribute to hypertension. Family studies controlling for a common environment indicate that blood pressure heritabilities are in the range 15-35%. In twin studies, heritability estimates of blood pressure are ~60% for males and 30–40% for females. High blood pressure before age 55 years occurs 3.8 times more frequently among persons with a positive family history of hypertension.
Risk minimisation measures	No risk minimisation measures.
Additional pharmacovigilance activities	None.

PVI.Table 10 Renal failure

Important potential risk of renal failure	
Evidence for linking the risk to the medicine	In the clinical trial development programme, 0.7% of tiotropium-treated COPD patients and 0.2% of tiotropium-treated asthma patients experienced renal failure. In the post-marketing setting, 315 cases describing events of acute renal failure were identified in COPD patients cumulatively, 56 of which were associated with a fatal outcome.
Risk factors and risk groups	Diabetes mellitus and high blood pressure are the 2 leading causes of kidney disease. Both diabetes mellitus and high blood pressure damage the small renal blood vessels and can cause renal failure. Other risk factors for kidney disease include cardiovascular disease and family history. In addition, patients with advanced age and urinary obstruction, e.g. due to prostatic disorders, are at higher risk.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 where advice is given on patients with moderate to severe renal impairment as there is no long-term experience in patients with severe renal impairment.
Additional pharmacovigilance activities	None.

PVI.Table 11 Overdose

Important potential risk of overdose	
Evidence for linking the risk to the medicine	Cases of overdose are rare in a clinical trial setting. In the post-marketing setting, 1245 cases reporting overdose in COPD patients were identified cumulatively, 99 of which were serious. Cases reported for the indication of asthma were not significantly different from the overall cases reported.
Risk factors and risk groups	Tiotropium is indicated as maintenance therapy for COPD. However, patients with deterioration of COPD, who deliberately use tiotropium additionally as rescue medication (off-label), are at higher risk of overdose. Patients who use tiotropium concomitantly with other anticholinergic drugs may experience symptoms of overdose as a result of a pharmacodynamic interaction.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.9 where advice is given regarding high doses of tiotropium which may lead to anticholinergic signs and symptoms.
Additional pharmacovigilance activities	None.

PVI.Table 12 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 13 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 14 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
EMA	European Medicines Agency
EPAR	European Public Assessment Report
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
US	United States of America