Part VI: Summary of activities in the risk management plan by product

VI.1 Elements for summary tables in the EPAR

VI.1.1 Summary table of Safety concerns

Summary of safety concerns	
Important identified risks	• Hypersensitivity reactions, including anaphylactic reactions • Angina pectoris • Serious respiratory-related events and death • Cardiac arrhythmias • Paradoxical bronchospasm • Systemic effects of inhaled corticosteroid (Cushing's syndrome, Cushingoid features, adrenal suppression, decrease in bone mineral density, cataract and glaucoma and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression) • Pneumonia in patients with COPD
Important potential risks	• Adrenal suppression • Off-label use in children • Off-label use in COPD
Important missing information	• Patients with hepatic impairment • It is unknown whether salmeterol and fluticasone propionate/metabolites are excreted in human milk. • Information on children aged 4 to 11 years

VI.1.2 Table of on-going and planned additional PhV studies/activities in the Pharmacovigilance Plan

Not Applicable

VI.1.3 Summary of Post authorisation efficacy development plan

Not Applicable

VI.1.4 Summary table of risk minimisation measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Hypersensitivity reactions including anaphylactic reactions	Hypersensitivity reactions with the manifestations: Cutaneous hypersensitivity reactions, angioedema (mainly facial and oropharyngeal oedema), respiratory symptoms (bronchospasm) and anaphylactic reactions including anaphylactic shock (Frequency: Rare; <1/10,000). Respiratory symptoms (dyspnoea) Respiratory symptoms (bronchospasm) occur with uncommon frequency (≥1/1000 and <1/100). Risk of hypersensitivity reactions has been mentioned in section 4.3 (contraindications) and section 4.8 (undesirable effects). As per section 4.3 of the SPC, Salmeterol / Fluticasone propionate pressurised inhalation, suspension is contraindicated in patients with hypersensitivity to any of the active substances or to the excipients.	None
Angina pectoris	Risk of angina pectoris has	None

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
	been mentioned in section 4.8 (undesirable effects) of the SPC. Occurrence of angina pectoris is uncommon (≥1/1000 and <1/100). As per section 4.4 (Special warnings and precautions) Salmeterol / fluticasone propionate should be used with caution in patients with severe cardiovascular disorders, heart rhythm abnormalities, diabetes mellitus, thyrotoxicosis, uncorrected hypokalaemia or patients predisposed to low levels of serum potassium.	
Serious respiratory-related events and death	Possibility of serious respiratory-related adverse events and exacerbations during treatment with Salmeterol / Fluticasone propionate pressurised inhalation, suspension has been identified in section 4.4 of the SPC. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation on Salmeterol / Fluticasone propionate	None

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
	pressurised inhalation suspension.	
Cardiac arrhythmias	Rarely, Salmeterol and Fluticasone propionate pressurised inhalation suspension may cause cardiac arrhythmias e.g. supraventricular tachycardia, extrasystoles and atrial fibrillation, and a mild transient reduction in serum potassium at high therapeutic doses. Caution for use of Salmeterol / Fluticasone propionate pressurised inhalation, suspension in patients with severe cardiovascular disorders, heart rhythm abnormalities, diabetes mellitus, thyrotoxicosis, uncorrected hypokalaemia or patients predisposed to low levels of serum potassium has been advised in section 4.4 of the SPC.	None
Paradoxical bronchospasm	There have been rare (>1/10000) occurrence of paradoxical bronchospasm with the use of Salmeterol / Fluticasone propionate pressurised inhalation	None

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
	suspension. Immediate discontinuation of Salmeterol / Fluticasone propionate pressurised inhalation suspension has been advised in section 4.4 of SPC. Assessment of the patient and use of alternative therapy has been advised in section 4.4 of SPC.	
Systemic effects of inhaled corticosteroid (Cushing's syndrome, Cushingoid features, adrenal suppression, decrease in bone mineral density, cataract and glaucoma and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression)	Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. Risk of systemic effects including Cushing's syndrome, Cushingoid features, adrenal suppression, decrease in bone mineral density, cataract and glaucoma and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression has been documented in section 4.4 of the SPC. Regular review of the treatment, monitoring the patient and use of lowest effective dose had been	None

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
	advised in section 4.4 of the SPC.	
Pneumonia in patients with COPD	Increased reporting of pneumonia was observed in a 3 year study in patients with Chronic Obstructive Pulmonary Disease (COPD) receiving Seretide compared with placebo. In a 3 year COPD study, older patients, patients with a lower body mass index (<25kg/m2) and patients with very severe disease (FEV1<30% predicted) were at greatest risk of developing pneumonia regardless of treatment. The clinical features of such infections and exacerbation frequently overlap, hence physicians are advised to remain vigilant for the possible development of pneumonia and other lower respiratory tract infections in patients with COPD, in section 4.4 of SPC. Also if a patient with severe COPD has experienced pneumonia, re-evaluation of the treatment with Salmeterol / Fluticasone	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	pressurised inhalation suspension has been suggested in section 4.4 of the SPC.	

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

According to survey developed by World health Organization (WHO) in 2002-2003, a total of 178,215 individuals from 70 countries aged 18 to 45 years were studied. The global prevalence rates of doctor diagnosed asthma, clinical/treated asthma and wheezing in adults were 4.3%, 4.5%, and 8.6% respectively, and varied by as much as 21-fold amongst the 70 countries. Australia reported the highest rate of doctor diagnosed, clinical/treated asthma, and wheezing (21.0%, 21.5%, and 27.4%). Amongst those with clinical/treated asthma, almost 24% were current smokers, half reported wheezing, and 20% had never been treated for asthma. This study provided a global estimate of the burden of asthma in adults, and suggests that asthma continues to be a major public health concern worldwide. The high prevalence of smoking remains a major barrier to combating the global burden of asthma.[2]

VI.2.2 Summary of treatment benefits

Asthma:

Salmeterol and Fluticasone propionate pressurised inhalation suspension is indicated in the regular treatment of asthma where use of a combination product (long-acting beta-2-agonist and inhaled corticosteroid) is appropriate that is, patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short acting beta-2-agonist or patients already adequately controlled on both inhaled corticosteroid and long-acting beta-2-agonist.

Long-term asthma control medications, generally taken daily, are the cornerstone of asthma treatment. These medications keep asthma under control on a day-to-day basis and make it less likely that the patient may have an asthma attack. Types of long-term control medications include:

Inhaled corticosteroids: These medications include fluticasone, budesonide, mometasone, ciclesonide, flunisolide, beclomethasone and others. One may need to use these medications for

several days to weeks before they reach their maximum benefit. Unlike oral corticosteroids, these corticosteroid medications have a relatively low risk of side effects and are generally safe for long-term use.

Leukotriene modifiers: These oral medications — including montelukast, zafirlukast and zileuton — help relieve asthma symptoms for up to 24 hours. In rare cases, these medications have been linked to psychological reactions, such as agitation, aggression, hallucinations, depression and suicidal thinking. The patients should seek medical advice right away for any unusual reaction.

Long-acting beta agonists: These inhaled medications, which include salmeterol and formoterol. These medicines open the airways and reduce inflammation. Some research shows that they may increase the risk of a severe asthma attack, so take them only in combination with an inhaled corticosteroid. Because these drugs can mask asthma deterioration, don't use them for an acute asthma attac*k*

Combination inhalers: These medications — such as fluticasone-salmeterol, budesonide-formoterol and mometasone-formoterol — contain a long-acting beta agonist along with a corticosteroid. Because these combination inhalers contain long-acting beta agonists, they may increase the risk of having a severe asthma attack.

Theophylline: Theophylline is a daily pill that helps keep the airways open (bronchodilator) by relaxing the muscles around the airways. It's not used as often now as in past years.

VI.2.3 Unknowns relating to treatment benefits

There are no data available for use of Salmeterol and Fluticasone propionate pressurised inhalation suspension in patients with hepatic impairment.

There are no data in humans regarding effect of Salmeterol and Fluticasone propionate pressurised inhalation suspension on fertility.

It is unknown whether salmeterol and fluticasone propionate/metabolites are excreted in human milk.

No studies of the effect on the ability to drive and use machines have been performed.

There is no information available regarding safety and efficacy of Salmeterol and fluticasone propionate in children aged 4 to 11 years.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
Allergic reactions including whole body allergic reaction (Hypersensitivity reactions including anaphylactic reactions)	Allergic reactions including whole body reactions (anaphylactic reactions) can occur at rare frequency (<1/10,000).	Yes. Salmeterol and Fluticasone propionate pressurised inhalation, suspension is contraindicated in patients with hypersensitivity to any of the active substances or to the excipients.
Chest pain with tightness and discomfort (Angina pectoris)	Salmeterol and fluticasone propionate can cause heart related disorders.	Yes. As per section 4.4 (Special warnings and precautions) of the SPC, Salmeterol and fluticasone propionate should be used with caution in patients with severe heart conditions, heart rhythm abnormalities, diabetes mellitus, overactive thyroid gland (thyrotoxicosis), uncorrected low blood potassium (hypokalaemia) or patients predisposed to low levels of serum potassium.
Serious asthma- related problems and death (Serious asthma-related events and death)	Serious asthma related problems and worsening of asthma can occur with the use of Salmeterol/ Fluticasone propionate pressurised inhalation, suspension.	Yes. Patients should be asked to continue treatment but to seek medical advice if asthma remains uncontrolled or worsens after initiation on Salmeterol and Fluticasone propionate pressurised inhalation suspension.

Risk	**What is known**	**Preventability**
Irregular heartbeat (Cardiac arrhythmias)	Salmeterol and Fluticasone propionate pressurised inhalation suspension may cause irregular heartbeat.	Yes. Salmeterol and Fluticasone propionate pressurised inhalation, suspension should be used with caution in patients with severe heart problems, abnormal heartbeat, type 2 diabetes, thyrotoxicosis, low blood potassium levels.
Breathing difficulty caused by narrowing of airways (Paradoxical bronchospasm)	Breathing difficulty caused by narrowing of airways may occur with the use of Salmeterol and Fluticasone propionate pressurised inhalation suspension may occur with an immediate increase in wheezing after dosing.	Yes. If the patient experiences wheezing, then immediate medical attention should be sought. Salmeterol and Fluticasone propionate pressurised inhalation suspension should be immediately discontinued and appropriate treatment should be initiated.
Effects of corticosteroids on throughout the body [Systemic effects of inhaled corticosteroid (Cushing's syndrome, Cushingoid features, adrenal suppression, decrease in bone mineral density, cataract and glaucoma and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or	Effects of corticosteroids on throughout the body may occur with long term use of Salmeterol and Fluticasone propionate pressurised inhalation suspension. Such effects include but not limited to Cushing's syndrome, adrenal suppression, decreased amount of minerals in bones (decrease in bone mineral density), cataract, damage the eye's optic nerve (glaucoma),	Yes. Treatment with Salmeterol and Fluticasone propionate pressurised inhalation suspension should be reviewed on regular basis. The patient should be treated with lowest effective dose. The doctor should monitor the patient for appearance of any eye disorders, bone disorders or behavioural changes.

Risk	What is known	Preventability
aggression)]	sleep disorders, anxiety, depression or aggression.	
Inflammatory condition of the lung in patients with COPD (Pneumonia in patients with COPD)	Inflammatory condition of the lung in patients with COPD (Pneumonia in patients with COPD) can occur commonly (Up to 1 in 100 but less than 1 in 10 patients).	Yes. The doctor should carefully monitor the COPD patient for presence of any respiratory infections since the feature of infections and worsening frequently overlap. If patient with COPD experiences pneumonia with the use of Salmeterol and Fluticasone propionate pressurised inhalation suspension, then the physician should re-evaluate the therapy with Salmeterol and Fluticasone propionate pressurised inhalation suspension.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
A condition in which the adrenal glands do not produce adequate amounts of steroid hormones (Adrenal suppression)	Whole body effects such as a condition in which the adrenal glands do not produce adequate amounts of steroid hormones (adrenal suppression) may occur with the use of Salmeterol and Fluticasone propionate pressurised inhalation suspension.
Off-label use in children	Salmeterol and Fluticasone propionate pressurised inhalation, suspension 25 micrograms /125 micrograms and 25 micrograms /250 micrograms is indicated for patients above 12 years of age.

Risk	**What is known (Including reason why it is considered a potential risk)**
	As suitable strength for children below 12 years is not available, there is a potential for off label use in children
Off-label use in COPD	Salmeterol and Fluticasone propionate pressurised inhalation suspension is indicated in the regular treatment of asthma. However, there is a potential for off label use in treatment of COPD.

Important missing information

Risk	**What is known**
Patients with hepatic impairment	Fluticasone propionate has high systemic clearance mediated by cytochrome P450 3A4 in the gut and liver. Hepatic impairment may affect the clearance of fluticasone propionate. However, there are no data available for use of Salmeterol and Fluticasone propionate pressurised inhalation suspension in patients with hepatic impairment.
It is unknown whether salmeterol and fluticasone propionate/metabolites are excreted in human milk	Studies have shown that salmeterol and fluticasone propionate, and their metabolites, are excreted into the milk of lactating rats. It is unknown whether salmeterol and fluticasone propionate/metabolites are excreted in human milk.
Information on children aged 4 to 11 years	Information on safety and efficacy of salmeterol and fluticasone propionate in children aged 4 to 11 years is not available.

VI.2.5 Summary of additional risk minimisation measures by safety concern

These additional risk minimisation measures are for the following risks:

Safety concern in lay terms (medical term)

Risk minimisation measure(s): Not applicable
Objective and rationale: Not applicable
• Summary description of main additional risk minimisation measures: Not applicable

VI.2.6 Planned post authorisation development plan

Not Applicable

VI.2.7 Summary of changes to the Risk Management Plan over time

Not Applicable