## VI.2 Elements for a Public Summary

### VI.2.1 Overview of disease epidemiology[3]

Asthma is a common life-long chronic inflammatory disorder of the airways that affects adults and children of all ages. About 300 million people suffer from asthma globally and this number is estimated to increase to 400 million by 2025. The data from European Community Respiratory Health Survey and local health institutions suggest that the prevalence rate of asthma in adult across Europe ranges from 0.28% to 13%. Asthma is the leading serious chronic illness among children. In 50 percent of patients asthma starts during childhood. Asthma subsides in half of the children while reaching 13-14 years of age.

Asthma is a genetic disease, however, environmental factors (e.g allergen exposure and diet) play a significant role in shaping it up. In other words, tendency to get asthma is inherited, still it occurs only when one is exposed to trigger factors. Infection is predominant precipitating factor for asthma in children. Many a times it is termed as bronchitis instead of asthma. Female sex, smoking, earlier age of onset of disease, sensitization to household dust mites, and airway hyperresponsiveness are risk factors for persistence and relapse.

Inflammation of the sinuses (a feeling of tension or fullness in the nose, cheeks and behind the eyes, sometimes with a throbbing ache), rhinitis (sneezing, itchiness, blocked or runny nose), acid reflux, breathlessness during sleep, hormonal disorder and psychological disturbances are common conditions associated with asthma. These conditions may influence the diagnosis and assessment of the severity and control of asthma.

Asthma is not a communicable disease. It can not be transmitted from one person to another by any type of physical contact. Asthma may be fatal if not controlled properly.

### VI.2.2 Summary of treatment benefits

[Invented Name] contains two medicines: salmeterol and fluticasone propionate. Salmeterol belongs to a group of medicines called long-acting bronchodilators. Bronchodilators open up the airways in the lungs making it easier to breathe. The effects last for 12 hours or more. Fluticasone propionate belongs to a group of medicines called glucocorticosteroids. Glucocorticosteroids have an anti-inflammatory action and work by reducing swelling and irritation in the lungs. This medicine is prescribed to treat asthma and to help prevent breathing problems in adults.

A twelve month study (Gaining Optimal Asthma ControL, GOAL), in 3416 adult and adolescent patients with persistent asthma, compared the safety and efficacy of salmeterol/fluticasone propionate versus inhaled glucocorticosteroid (fluticasone propionate) alone, has demonstrated that well-Controlled asthma (defined as occasional symptom or occasional use of other drug or less than 80% predicted lung function and no night time awakening, no exacerbation and no side effects enforcing change in therapy) was achieved twice more rapidly with salmeterol/fluticasone propionate than with fluticasone propionate alone.

### VI.2.3 Unknowns relating to treatment benefits

The usefulness of [Invented Name] has not been established in patients below 18 years of age. Hence, the product is not indicated for use in children, 12 years of age and younger or adolescents, 13 to 17 years of age.

### VI.2.4 Summary of safety concerns

**Important Identified Risks**

| Risks | What is known | Preventability |
|---|---|---|
| Pneumonia in COPD and asthma patient populations | Pneumonia and bronchitis (lung infection) have been reported in people with chronic obstructive pulmonary disease (COPD) using salmeterol/fluticasone. COPD is a long-term lung disease that causes shortness of breath, coughing and frequent chest infections. The term COPD includes conditions known as chronic bronchitis and emphysema. | Prescriber to pay special attention and instruct patients to report if they notice increase in sputum (phlegm) production, change in sputum colour, fever, chills, increased cough, increased breathing problems while using the product. |
| Respiratory related events and death | Regarding the safety of regular long-acting β2 agonist inhalers in asthma (medicinesd from the same class as salmeterol, one of the compounds of [Invented Name]), compared with placebo (dummy medication, used in clinical trials to compare side effects of drugs), mortality increased with regular salmeterol, but this was not statistically | Regular salmeterol should be discontinued if no symptomatic benefit is achieved and the advice not to increase the dose of salmeterol during exacerbations should be made clear. Salmeterol should not be used as a substitute for inhaled glucocorticosteroids, and adherence with inhaled steroids should be kept under review if separate inhalers are used.6 Clinical decisions and information for patients regarding |

| Risks | What is known | Preventability |
|---|---|---|
| | significant. Non-fatal serious adverse events increased with salmeterol in comparison with placebo; for every 188 people treated with salmeterol for 28 weeks, one extra non-fatal event occurred in comparison with placebo. No significant differences were found comparing regular salmeterol with regular salbutamol. For patients whose asthma is not well-controlled on moderate doses of inhaled glucocorticosteroids, additional salmeterol can give symptomatic benefit but this may be at the expense of an increased risk of serious adverse events and asthma related mortality; risks which are not clearly abolished by inhaled glucocorticosteroids.[6] In addition, no statistically significant differences were found in fatal or non-fatal serious adverse events in trials in which regular salmeterol was randomly allocated with ICS, in comparison to ICS alone at the same dose. There were no asthma-related deaths and few | regular use of salmeterol have to take into account the balance between known symptomatic benefits of salmeterol and the degree of uncertainty and concern associated with its potential harmful effects.[7] |

| Risks | What is known | Preventability |
|---|---|---|
| | asthma-related serious adverse events.[7] | |
| Cushing's syndrome and adrenal suppression | The normal production of steroid hormones in the body can be affected by inhaled glucocorticosteroids. This is more likely if patients use high doses for a long time. This can cause Cushing's Syndrome and a rounded (moon shaped) face. | The doctor should review the asthma treatment regularly to ensure that the patients uses the lowest dose of salmeterol/fluticasone to control asthma. |
| Growth retardation in paediatrics | The normal production of steroid hormones in the body can be affected by inhaled glucocorticosteroids. This is more likely if patients use high doses for a long time. This can cause children and adolescents to grow more slowly. | The doctor should review the asthma treatment regularly to ensure that the patients uses the lowest dose of salmeterol/fluticasone to control asthma. |
| Drug interactions between [Invented Name] and other medicines (Interaction with CYP450 3A4 inhibitors) | Other medicines may increase the amount of salmeterol or fluticasone propionate in the patients' body and thus increase the risk of experiencing side effects, or may make side effects worse. | Patients taking antiviral and antifungal medicines (such as ritonavir, ketoconazole and itraconazole) should inform the doctor if using these in the same time with salmeterol/fluticasone |
| Hypersensitivity reactions including anaphylactic reactions | Signs of an allergic reaction: could be worseness in breathing, wheeziness, cIn addition, patients may exoerience itching, a rash (hives) and swelling (usually of | Patients are advised to stop using the medicine and contact their doctor immediately or the AE department of the nearest hospital and to use their fast-acting "reliever" inhaler to help |

| Risks | What is known | Preventability |
|---|---|---|
| | the face, lips, tongue, or throat), or they may suddenly feel their heart beating very fast or feel faint and light headed (which may lead to collapse or loss of consciousness). | them breathing if they experience hypersensitivity reactions. |
| Cardiac arrhythmias | Salmeterol/fluticasone may cause uneven, rapid and irregular heart beat (atrial fibrillation) or extra heart beats (arrhythmias) in some patients. | Patients should contact their doctor immediately if they notice such events. |
| Angina | Salmeterol/fluticasone may cause chest pain in some patients. | Patients should contact their doctor immediately if they notice such events. |

**Important Potential Risks**

| Risks | What is known |
|---|---|
| Use of the drug outside its indications in the leaflet (Off-label use in patients with COPD) | Since the Innovator has an additional strength of this drug combination and its products are indicated in treatment of patients with Chronic Obstructive Pulmonary Disease (COPD), there is a risk for [Invented Name] to be prescribed for the same and experience increased number of colds, inflammation of the sinuses (a feeling of tension or fullness in the nose, cheeks and behind the eyes, sometimes with a throbbing ache), low levels of potassium in the blood (hypokaelemia), and an irregular heartbeat, muscle weakness and cramp. Patients should be aware of these undesirable effects and should tell the prescriber immediately if such reactions occur. |
| Use of the drug outside its indications in the leaflet (Off label use in children and | The safety and efficacy of [Invented Name] in children have not been established. [Invented Name] is therefore not |

| Risks | What is known |
|---|---|
| adolescents under 18 years of age) | recommended for use in children and adolescents under 18 years of age. |
| Use of the drug outside its indications in the leaflet (Off label use in adults for low dose titration/ treatment) | The SmPC clearly states that "[Invented Name] is not available in the lowest strength of this combination as currently available on the market and therefore an alternative product would need to be prescribed." |
| Use of the drug outside its indications in the leaflet (Off label use with the Volumatic spacer) | Use of an AeroChamber Plus® spacer device with [Invented Name] is recommended in patients who have, or are likely to have, difficulties in coordinating actuation with inspiration. The use of a spacer device with a metered dose inhaler may increase drug delivery to the lungs and this could potentially lead to an increase in the risk of systemic adverse effects. Single dose pharmacokinetic data have demonstrated that the systemic exposure to salmeterol and fluticasone propionate may be increased as much as two-fold when the AeroChamber Plus® spacer device is used with a fixed-dose combination of salmeterol and fluticasone propionate as compared with the Volumatic spacer device. The prescriber should explain to the patient that other spacing devices should not be used with [Invented Name] and that they should not switch from one spacer device to another. Additionally, patients should be instructed in the proper use and care of their inhaler and spacer and their technique checked to ensure optimum delivery of the inhaled drug to the lungs.<br><br>Patients who find it difficult to use the inhaler should be instructed by either the doctor or other healthcare provider how to use a spacing device such as the AeroChamber Plus® and how to care for it. Patients who are using a spacer device with the inhaler should not stop using it without talking to the doctor or nurse first and they |

| Risks | What is known |
|---|---|
| | should not use other spacing devices or switch from one spacer device to another.<br><br>In case the patient stops using a spacer device the doctor may need to change the dose of medicine required to control asthma. |
| Use in pregnancy | No malformative or foeto/neonatal toxicity of have been observed with the use of salmeterol and fluticasone propionate. However, animal studies have shown harm in foetus. Therefore administration of [Invented Name] to pregnant women should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus. The lowest effective dose of fluticasone propionate needed to maintain adequate asthma control should be used in the treatment of pregnant women. Patients should ask their doctor or pharmacist for advice before taking this medicine if they are pregnant or breast-feeding, think they may be pregnant or are planning to have a baby. |

**Missing information**

| Risks | What is known |
|---|---|
| Use in breastfeeding | It is unknown whether salmeterol and fluticasone propionate and its 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. A risk to breastfed newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue [Invented Name] therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. |

| Risks | What is known |
|---|---|
| Use in patients with hepatic impairment | The SmPC clearly states that there are no data available for use of [Invented Name] in patients with hepatic impairment. |

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

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet. The measures in these documents are known as routine risk minimisation measures. This medicine has no additional risk minimisation measures.

### VI.2.6 Planned post authorisation development

Consideration is being given to the development of the low strength product.

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

This is the updated RMP (version 5.0) for the hybrid application of Sirdupla (salmeterol/fluticasone propionate) 25 microgram/125 microgram and Sirdupla 25 microgram/250 microgram per metered dose pressurised inhalation, suspension, by Mylan, updated in line with safety concerns in Seretide Diskus RMP, as requested during assessment of the repeat use application for procedure UK/H/5607 in the EU.