VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Asthma

Asthma is a disease in the lungs that happens when the muscles surrounding the smaller airways in the lungs become tight (bronchoconstriction) and when the airways themselves become swollen and irritated (inflammation). Symptoms come and go and include shortness of breath, wheezing, chest tightness and cough. It is not known why a person may get asthma, although a family history of asthma, eczema, or allergy makes it more likely an individualthat a person may develop asthma.

An estimated 300 million people in the world are affected by asthma, with most people diagnosed in childhood; although this varies from 1% to 18% across different countries (the reasons for these differences are not clear). The number of deaths across the world is estimated at around 250,000.

Chronic Obstructive Pulmonary (Lung) Disease (COPD)

Chronic Obstructive Pulmonary (Lung) Disease (COPD) is a collection of lung diseases including chronic bronchitis and emphysema. It is a disease that makes it hard to breathe. Symptoms of COPD develop over a period of years and can cause coughing, production of large amounts of mucus (a slimy substance), wheezing, shortness of breath, and chest tightness.

COPD gets worse and worse over time, and it cannot be cured. It may require continuous treatment and is the leading cause of death and other health problems worldwide. By the year 2020, it is expected to be the 3rd leading cause of death worldwide.

People with COPD have damage and scarring to the lungs, which is what makes it hard to breathe and reduces the ability to exchange oxygen and carbon dioxide in the lungs as part of the breathing process. Cigarette smoking is the leading cause of COPD. This is because smoking irritates and inflames the lungs, which results in scarring. Some cases of COPD are caused by long-term exposure to other things that irritate the lungs, including fumes, dust, and air pollution. Some people may also have a genetic disorder, but these causes are not as frequent as smoking.

COPD is associated with a higher risk of chest infections, including pneumonia, compared to people without COPD. People with COPD will also have episodes where their breathing is worse, called exacerbations. Both exacerbations and chest infections can require admission to hospital and in some cases can lead to death.

COPD is seen more frequently in people aged 45 years or over, with an estimated 6 new cases for every 1000 men and 3 new cases for every 1000 women each year. In 2004, an estimated 64 million people had COPD worldwide [World Health Organisation 2012].

VI.2.2 Summary of treatment benefits

SERETIDE™ contains two active ingredients, salmeterol and fluticasone propionate:

- Salmeterol helps the airways in the lungs to stay open, making it easier to breathe
- Fluticasone propionate reduces swelling and irritation in the lungs.

A doctor will prescribe SERETIDE to patients with COPD and/or asthma to help them breathe better and reduce the number of flare-ups of symptoms.

A twice daily dose of SERETIDE has been tested in a 3-year study involving 6,112 patients with COPD. The investigators wanted to find out if treatment with SERETIDE would reduce the risk of death. After 3 years, 132 patients (12.6%) taking SERETIDE had died compared with 193 patients (15.2%) taking a dummy drug (placebo). These results indicate that patients taking SERETIDE were slightly more likely to survive, however this finding could be due to chance.

Two other studies looked at the number of flare-ups patients with COPD had over 1 year. A total of 1,554 patients took either SERETIDE or just salmeterol (without fluticasone propionate). Both studies showed that patients taking SERETIDE had fewer COPD flare-ups in 1 year, than patients who were taking salmeterol only.

SERETIDE was tested in a twelve month study in 3416 adult and adolescent patients who had continual symptoms of asthma. The investigators wanted to find out if treatment with SERETIDE was better than treatment with an inhaled corticosteroid (Fluticasone Propionate). The study results showed more patients treated with SERETIDE achieved asthma control than patients treated with inhaled corticosteroid alone and this control was attained at a lower corticosteroid dose.

VI.2.3 Unknowns relating to treatment benefits

Breastfeeding women, patients with liver problems, and children less than 4 years of age were excluded from SERETIDE clinical studies. SERETIDE has been on the market since 1998, therefore no further studies are necessary to test the benefits in patients with COPD and/or asthma. Based on the many years of experience with SERETIDE use in patients with COPD, the benefits to COPD and/or asthma patients are well defined.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Pneumonia/lung infection (Pneumonia)	In the main patient study, investigators reported that patients taking SERETIDE were more likely to get pneumonia compared with those taking either the dummy drug (placebo) or salmeterol only. This finding has been observed and confirmed in more studies. Older patients, those with very severe disease and those with a lower body mass index (BMI) have a greater risk of pneumonia, regardless of the treatment they receive. It is unclear why patients who are taking SERETIDE have a greater risk of pneumonia. Despite the increase in pneumonia seen in patients taking SERETIDE, there is not an associated increase in deaths due to pneumonia. There is also no evidence to suggest that patients taking SERETIDE who develop pneumonia are more like to develop pneumonia a second time.	Investigators have not found any risk factors that could identify patients who are more likely to get pneumonia while taking SERETIDE. The prescribing information (SmPC) for SERETIDE advises doctors and other prescribers (e.g. pharmacists) that pneumonia may develop. The symptoms of pneumonia (e.g. breathlessness and a cough) are similar to those of a severe flare-up of COPD. Regardless of the cause, it is highly likely that a patient experiencing these symptoms will be seen by his/her doctor and will receive the appropriate treatment. Patients with a history of recent worsening of COPD may be more likely to benefit from SERETIDE.
Respiratory-related events or deaths	A large study with one of the drugs (salmeterol) contained in SERETIDE showed an increase in some patients with asthma having increased risk of severe outcomes, including death. This effect does not appear to occur when such drugs are given with inhaled corticosteroids, and has not been observed in patients with COPD.	Patients should use SERETIDE exactly as prescribed and seek medical advice if asthma symptoms remain uncontrolled or worsen whilst using SERETIDE.
Cushing's syndrome and adrenal suppression	Adrenal insufficiency is a condition where the adrenal glands do not make enough steroid hormones. This can	Healthcare professionals should check patients regularly for any of these side effects and make sure the lowest dose of

Risk	What is known	Preventability
	happen when you stop taking oral corticosteroid medicines (such as prednisone) and start taking a medicine containing an inhaled steroid (such as SERETIDE). When your body is under stress such as from fever, trauma (such as a car accident), infection, surgery, or worse COPD symptoms, adrenal insufficiency can get worse and may cause death. Symptoms of adrenal insufficiency include: • feeling tired • lack of energy • weakness • nausea and vomiting • low blood pressure	SERETIDE to control asthma is taken.
Growth retardation in paediatrics	SERETIDE contains an inhaled corticosteroid. The use of inhaled corticosteroids in children has been associated with slowed growth, and in a few studies with less adult height by about 1 cm, but how much this affects final adult height is not well understood. There may be more risk with higher doses used in younger aged children.	Healthcare providers should regularly measure the height of children receiving prolonged treatment with inhaled corticosteroid. The dose of inhaled corticosteroid should be reduced to the lowest dose at which effective control of asthma is maintained (no symptoms of asthma).
Drug interaction with CYP450 3A4 inhibitors	Some medicines used to treat viruses and fungus infections (such as ritonavir, ketoconazole and itraconazole) may increase the amount of SERETIDE in a patient's body. This can increase the risk of experiencing side effects with SERETIDE, including irregular heart beats, Cushing's Syndrome, or may make other side-effects worse.	Patients should tell their doctor or pharmacist if they are taking or have recently taken any other medicines.
Hypersensitivity reactions including anaphylactic reactions	Severe allergic reactions, including anaphylactic reactions, have been reported with SERETIDE treatment. In addition the SERETIDE DISKUS	Patients should not take SERETIDE if they are allergic (hypersensitive) to salmeterol xinafoate, fluticasone propionate or to the other ingredient lactose

Risk	What is known	Preventability
	formulation contains lactose. There have been reports of serious allergic reactions in patients with severe milk protein allergy after inhalation of SERETIDE DISKUS. Signs of serious allergic reactions can include rash, hives, swelling of the face, mouth and/or tongue and breathing problems.	monohydrate. They should not take any more if they develop any signs of a serious allergic reaction and seek medical attention immediately.
Arrhythmias	Patients treated with SERETIDE may be at more risk of side effects associated with the heart, such a rhythm problems and chest pain, as one of the drugs contained in SERETIDE (salmeterol, a bronchodilator known as a long-acting beta-2 agonist), can stimulate the heart.	SERETIDE should be used with caution in patients with heart disease, including an irregular or fast heart beat, and in patients with diabetes mellitus, overactive thyroid gland, or low levels of potassium in their blood.
Angina	Patients treated with SERETIDE may be at more risk of side effects associated with the heart, such a rhythm problems and chest pain, as one of the drugs contained in SERETIDE (salmeterol, a bronchodilator known as a long-acting beta-2 agonist), can stimulate the heart.	SERETIDE should be used with caution in patients with heart disease, including an irregular or fast heart beat, and in patients with diabetes mellitus, overactive thyroid gland, or low levels of potassium in their blood.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
No new risks identified	N/A

Missing information

Risk	What is known
Safety in breastfeeding	It is unknown whether the ingredients in SERETIDE are transferred to mother's breast milk, therefore a risk to breastfed babies cannot be ruled out. Your doctor will decide if you should continue taking SERETIDE during this time.
Safety in children less than 4	SERETIDE is not licensed for use in children less than 4 years of

Risk	What is known
years of age	age.
Safety in patients with liver problems	No information is available for the use of SERETIDE in patients with liver problems.

VI.2.5 Summary of additional 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 (PL). The measures in these documents are known as routine risk minimisation measures.

There are two ongoing safety studies (SAS115358 and SAS115359) that will evaluate SERETIDE therapy and the risk of serious asthma-related events.

VI.2.6 Planned post authorisation development plan

No studies are planned.

Studies which are a condition of the marketing authorisation

Not applicable.

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

Table 21 Major Changes to the Risk Management Plan Over Time

Version	Date	Safety Concerns	Comment
01	31/12/2006	Pneumonia	To support submission of the main patient study [SCO30003 (TORCH)]
02	31/12/2007	Pneumonia	To report the results of two patient studies which examined the effects of salmeterol-FP 50/250mcg on flare-up rate in COPD patients, and 5 population studies looking at the occurrence of pneumonia in COPD [SCO100250, SCO40043, WEUKSTV1076, WEUKBRE1148, WEUKBRE1155, WEUKBRE1156, WEUKBRE1157]
03	31/10/2010	Pneumonia	To report the results of a new patient study [SCO104960 (ECLIPSE)]
04	19/08/2013	Pneumonia	To report the results of two studies that add to the knowledge base of the identified safety concern of pneumonia [WEUSKOP6416 and 200068]