VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Today, approximately 300 million people worldwide suffer from asthma, comprising people of all ages and ethnic backgrounds. According to the European Federation of Allergy and Airway Diseases Patients Association (EFA), 30 million people suffer from asthma in Europe alone. It is generally accepted that the amount of people with asthma increase with the rate of urbanisation and westernisation of a country. It is estimated that the occurrence of asthma increases globally by 50% every 10 years. This increase is among others attributable to a rise in atopic sensitization and in other allergic conditions such as rhinitis and eczema. 250 000 patients die each year worldwide from the consequences of asthma. Most deaths related to asthma occur in patients older than 45 years and are largely preventable. In general, mortality rates decreased overall since the 1980s due to changes in asthma management and the increased use of inhaled corticosteroids.

VI.2.2 Summary of treatment benefits

The addition of long-acting inhaled β_2-agonists (LABAs), such as Salmeterol, is today an integral part in the treatment of asthma. The Global Initiative for Asthma (GINA), who developed guidelines for asthma treatment, recommends the addition of inhaled LABAs to a treatment with inhaled corticosteroids (ICS), such as Budesonide, if asthma control is not achieved with low doses of ICS alone. According to the GINA guidelines, the combination of a LABA with an ICS is in general recommended for patients with moderate to severe asthma, which represent approximately 40% of the asthma population (representing 12 million people in Europe).

The clinical development program for Busal (code name for Zephira® and Busalair®) consisted out of 9 pharmacokinetic studies; four phase III studies and three phase II studies that were conducted by Laboratoires SMB SA. In total, these studies randomized 1401 patients.

Study BUSAL-III-02-1 was considered as the pivotal study in the development of Busal. In this study, the efficacy and safety of Busal 150/25 µg and Busal 300/25 µg was compared to PULMICORT® TURBUHALER® 2x200 µg (budesonide) during 12 weeks. The study included an additional 12-week period to evaluate the safety of Busal.

The primary efficacy variable in each phase III study was the mean change in morning "Peak expiratory flow rate" (PEF – a person's maximum speed of expiration, which measures the obstruction in the airways) from baseline to Week 12 based on the data recorded in the patients' diaries.

The secondary efficacy variables were the mean change over the weeks from baseline to Week 12 in variables recorded in the patients' diaries (evening PEF, asthma symptom scores, sleep disturbance score and number of bronchodilator (salbutamol) rescue inhalations) and during the site visits.

Both Busal 150/25 µg and Busal 300/25 µg treatments were shown to be superior to the PULMICORT® TURBUHALER® 400 µg treatment at Week 2, 4, 6, 8, 10 and 12.

VI.2.3 Unknowns relating to treatment benefits

The treatment benefits of Busal have only been established in adults of Caucasian ethnicity. The safe use of Busal has not been studied in children and adolescents younger than 18 years. Therefore, the

use of Busal is only destined for adults. There are however fixed dose combinations containing active substances of the same pharmacological class that are safe to use in children and adolescents.

A large clinical trial suggested that African-Americans have an increased risk of developing respiratory related events when using salmeterol containing asthma medications. In the clinical trial programme of Busal only Caucasian patients were included, so no definite conclusions can be drawn on the safety and efficacy of Busal in patients with another ethnic origin.

No formal tests have been done to evaluate the safe use of Busal in patients with COPD. Therefore it is unknown whether Busal would provide clinical effects in these patients, even though other combination products of the same pharmacological class have been approved for the treatment of COPD.

VI.2.4 Summary of safety concerns

IMPORTANT IDENTIFIED RISKS

Risk	What is known	Preventability
Worsening of asthma (Asthma exacerbation)	It is possible that asthma symptoms worsen during treatment with Busal. In clinical studies with a similar product, 1.8% of patients experienced a serious worsening of their asthma symptoms.	Busal is not intended for initial management of asthma nor should patients start to take Busal during an exacerbation. If asthma symptoms remain uncontrolled, or worsen, patients should seek medical advice, but continue their treatment. Additionally, patients should always have their medicinal product available for relief in an acute asthma attack.
Constriction of airways after treatment (Paradoxical bronchospasm)	After taking the medicine, it may occur that in stead of giving therapeutic effect, a constriction of the airways occurs, which would immediately increase weezing and shortness of breath after dosing.	If this occurs, patients should immediately stop treatment with their medication. This event should be treated immediately using a rapid-acting broncho-dilator (rescue medication).
Effects on the heart (adrenergic cardiac effects)	Salmeterol, one of the active ingredients of Busal, can cause arrhythmias (increased heart rate, atrial fibrillation, extrasystole).	Busal should be administered with caution in patients with severe cardiovascular disorders, such as ischaemic heart disease, tachyarrhythmias or severe heart failure. Besides treatment with medication that increased salmeterol concentrations in the blood (ketoconazole) should be evaluated before administration.

Risk	What is known	Preventability
Respiratory problems	Prolonged use of inhaled corticosteroids, such as Budesonide, may increase the risk of developing different respiratory tract infections. Immunocompromised patients, or patients that are also being treated with oral CS are at risk.	The effects are dose dependent, and it is recommended to take a maximum of 2 doses per day to reduce the risk of dysphonia and candidiasis. Rinsing the mouth with water, or brushing the teeth after inhaling the prescribed dose, to minimize the risk of oral candidiasis.
Increase blood sugar levels (Hyperglycaemia)	The use of glucocorticoids is associated with an increased risk of high blood sugar levels in patients without diabetes mellitus and difficult control of blood sugar levels in patients with diabetes.	Patients with a history of diabetes mellitus should be monitored carefully when being treated with Busal. Blood sugar controls should be considered in these patients.
Decreased levels of potassium (Hypokalaemia)	Potentially serious hypokalaemia may result from β_2-agonist therapy (salmeterol) and can have several consequences like muscular problems, cardiac complications, renal and metabolic problems.	This effect may be potentiated by concomitant treatment with xanthine derivatives, steroids and diuretics as they may add to a possible hypokalaemic effect of the β_2-agonist. It is recommended that serum potassium levels are monitored during these circumstances.
Changes electrocardiogram (QTc-prolongation)	Salmeterol can induce a prolongation between the Q-wave and the T-wave that are present in an electrocardiogram. This prolongation is associated with a high risk of cardiac arrhythmias, syncope and even in some cases death.	Caution should be taken in patients who already have a prolongation of the QT-interval or who take other medications that can induce the same effect. Additionally, concomitant medications that can increase salmeterol concentration should be taken with caution.
Adrenal glands work insufficiently (Adrenal suppression)	Systemic effects of inhaled corticosteroids may occur, particularly at high doses prescribed for prolonged periods. These effects are much less likely to occur than with oral corticosteroids. One of these effects is adrenal suppression.	It is important that the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control of asthma is maintained.
Slower growth (Growth retardation)	Systemic effects of inhaled corticosteroids may occur, particularly at high doses prescribed for prolonged periods.	It is important that the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control of asthma is maintained.

Risk	What is known	Preventability
	These effects are much less likely to occur than with oral corticosteroids. One of these effects is growth retardation.	
Eye problems (Cataracts, Glaucoma)	Systemic effects of inhaled corticosteroids may occur, particularly at high doses prescribed for prolonged periods. These effects are much less likely to occur than with oral corticosteroids. Eye disorders such as cataracts or glaucoma can be one of those effects.	It is important that the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control of asthma is maintained.
Weaker bones (Bone density decreased)	Systemic effects of inhaled corticosteroids may occur, particularly at high doses prescribed for prolonged periods. These effects are much less likely to occur than with oral corticosteroids. One of these effects is a decreased density of the bone which can lead to fractures.	It is important that the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control of asthma is maintained.
Hypersensitivity	Hypersensitivity reactions can occur when the patient is allergic to budesonide, salmeterol or one of the excipients.	Patients who are hypersensitive to one of the active substances or the excipients present in Busal, should not take this medicinal product.

IMPORTANT POTENTIAL RISKS

Risk	What is known (Including reason why it is considered a potential risk)
Off label use	Busal is indicated in the regular treatment of asthma in adults where use of a combination product (inhaled corticosteroid and long-acting β_2-agonist) is appropriate: - Patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short acting β_2-agonists. - Patients already adequately controlled on both inhaled corticosteroids and long-acting β_2-agonists. The use of Busal as initial asthma treatment, COPD treatment or asthma treatment in children and adolescents younger than 18 years is hence considered as off label use. In these cases, the safe use of Busal has not been evaluated.

IMPORTANT MISSING INFORMATION

Risk	What is known
Use by children and adolescents younger than 18 years	The safety and efficacy of Busal has not been established in children and adolescents younger than 18 years. There are no data with Busal in children under 18 years. There are however other fixed dose combinations of the same pharmacological class available on the market that are also indicated for children and adolescents.
Use by elderly	There is no need to adjust the dose in elderly patients, but caution should be exercised during treatment because only limited information on efficacy and safety is available.
COPD	Busal has not been evaluated for use in COPD. Nevertheless, there are other fixed dose combinations of the same pharmacological class available on the market that are also indicated for the treatment of COPD.
Other ethnical subgroup than Caucasian	As only Caucasian patients were included in the clinical studies with Busal, limited safety information on other ethnical subgroups are available.
Long term safety profile of the product	Only limited information on the long-term safety of Busal is available.
Use of patients with hepatic pathology	As budesonide and salmeterol are primarily eliminated via hepatic metabolism, an increased exposure can be expected in patients with severe liver cirrhosis.

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

Not applicable.

VI.2.6 Planned post authorisation development plan (if applicable)

Not applicable

VI.2.7 Summary of changes to the risk management plan over time

Not applicable