VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Asthma

The WHO estimates that 235 million people currently suffer from asthma. Asthma affects all age groups and it is the most common chronic disease among children. Asthma is characterized by attacks of breathlessness and wheezing, which vary in severity and frequency.

Asthma appears throughout the world. Most asthma-related deaths occur in low- and lower-middle income countries. It is often under-diagnosed and also under-treated. It creates substantial burden to individuals and families often restricting individuals' activities for a lifetime.

The causes of asthma are not completely understood. The strongest risk factors for developing asthma are a combination of genetic predisposition with environmental exposure to inhaled substances and particles that may provoke allergic reactions or irritate the airways. Further triggers can include cold air, extreme emotional arousal or physical exercise and certain medications.

COPD

Chronic obstructive pulmonary disease is a lung disease that is characterized by a persistent blockage of airflow from the lungs. It is an under-diagnosed, life-threatening lung disease that interferes with normal breathing and is not fully reversible.

Globally, ~10% of people older than 40 have moderate or worse airflow limitation; up to 25% may have mild airflow limitation. Undiagnosed are approximately 60-85% of people with COPD (mostly mild/moderate severity).

Besides tobacco smoking, second-hand smoke, air pollution and work exposures to fumes and dusts cause COPD in susceptible people.

COPD is the 4th leading cause of death worldwide; its mortality is rising, while cardiovascular disease's is falling; COPD is expected to be the 3rd leading cause of death over the next 20 years.

VI.2.2 Summary of treatment benefits

Bufomix Easyhaler is a combination product containing two active substances, budesonide and formoterol. The strengths 160/4.5 and 320/9 are intended to be used for the treatment of adult and adolescents patients with asthma. Additionally, these strengths are used in the treatment of patients with severe chronic obstructive pulmonary disease (COPD). The strength 80/4.5 is intended to be used for the treatment of adult, adolescents and children with asthma.

The active substances of Bufomix Easyhaler have different modes of action. Budesonide is a corticosteroid which prevents and reduces inflammation and swelling in the lungs resulting into reduced symptoms and fewer exacerbations of the disease. Formoterol stimulates β2 receptors in the airways thus dilating the bronchial tubes and making breathing easier.

Bufomix Easyhaler is a hybrid medicine. This means that the combination of the active substances in Bufomix Easyhaler is similar to the reference medicine, Symbicort Turbuhaler, but the inhaler device used for giving the medicine is different. Because Bufomix Easyhaler is a hybrid medicine the benefits and risks are considered the same as with the reference medicine. The therapeutic equivalence between different strengths of Bufomix Easyhaler and Symbicort Turbuhaler has been demonstrated in laboratory tests and in tests with humans. In human trials the lung dose and exposure to active substances have been shown to be the same with Bufomix Easyhaler and Symbicort Turbuhaler.

Human trials have shown that the combination of formoterol and budesonide improves lung function, reduces exacerbations and relieves symptoms in patients with asthma and COPD.

VI.2.3 Unknowns relating to treatment benefits

There is no data available for use of budesonide/formoterol in patients with hepatic or renal impairment. As both of these medicines are primarily eliminated via hepatic metabolism, an increased exposure can be expected in patients with severe liver cirrhosis.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
Systemic corticosteroid effects	If high doses of inhaled corticosteroids are used for long periods of time systemic corticosteroid effects may occur. Possible systemic effects include for example feeling restless, nervous or agitated, disturbed sleep, depression, changes in behaviour (especially in children), changes in bone mineral density (thinning of the bones) and a slowing of the rate of growth of children and adolescents. Systemic effects may also include cataract (clouding of the lens in the eye), glaucoma (increased pressure in the eye) and rare diseases such as central serous chorioretinopathy (a condition that causes fluid to build up underneath the center of the retina) which may cause blurred vision and other visual disturbances.	The product should be used in smallest effective doses because the systemic effects are dependent on dose. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes.
Cardiac effects of long acting beeta-agonists, such as palpitations, fast heart rate and irregular heart rhythm (Cardiac LABA effects)	Formoterol stimulates β2-receptors in the body. This pharmacologic action has the potential to increase heart rate and exacerbate cardiac rhythm disturbances.	The product should be used in smallest effective doses. Patients with certain risk factors for adverse effects in heart should only be treated with Bufomix Easyhaler after careful consideration.
Life-threatening and fatal asthma events	Serious asthma-related adverse events and worsening of asthma symptoms may occur during treatment with Bufomix Easyhaler.	If patients find the treatment ineffective, or exceed the highest recommended dose of Bufomix Easyhaler, medical attention must be sought. Patients should take their Bufomix Easyhaler maintenance dose as prescribed, even when they don’t feel any symptoms. Patients should not be initiated

Risk	What is known	Preventability
		on Bufomix Easyhaler if they have significantly worsening asthma.
Increased risk of pneumonia in COPD patients *	An increased risk of pneumonia has been observed in patients with COPD receiving inhaled corticosteroids. There is also some evidence of increased risk of pneumonia with increasing steroid dose, but this has not been demonstrated conclusively across all studies. Risk factors for pneumonia in patients with COPD include current smoking, older age, low body mass index (BMI) and severe COPD.	Monitoring for early symptoms. Patients who have fever or chills, increased mucus production, change in mucus colour, increased cough or increased breathing difficulties should contact their doctor since these can be symptoms of a lung infection.
Hypersensitivity reactions	Patients who are allergic to budenoside, formoterol or lactose, may experience allergic reactions when treated with Bufomix Easyhaler.	Patients who know that they are allergic to budenoside, formoterol or lactose should not use Bufomix Easyhaler.
Constriction of bronchi	As with other inhalation therapy, paradoxical bronchospasm (sudden acute wheezing or shortness of breath immediately after using your inhaler) may occur very rarely after taking Bufomix Easyhaler.	If the patient experiences sudden acute wheezing or shortness of breath immediately after using Bufomix Easyhaler, treatment should be discontinued immediately, the patient should be assessed and an alternative therapy instituted, if necessary.

***** Important identified risk only for strengths 320 µg/9 µg/inhalation and 160 µg/4.5 µg/ inhalation

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Use in unapproved indication	Potential for unapproved use of the high dose (320/9 µg/ inhalation) inhaler for maintenance and reliever therapy. High dose inhaler is not appropriate for as-needed use as this could result in a high dose and an increased risk for drug-related adverse events. Potential for unapproved use of maintenance and reliever therapy for children under 12 years of age. Maintenance and reliever therapy is not recommended for children under 12 years of age. Potential for unapproved use of maintenance and reliever therapy for COPD patients. Maintenance and reliever therapy is approved

Risk	What is known (Including reason why it is considered a potential risk)
	only for the treatment of asthma.

Missing information

Risk	What is known
Use in patients with liver disease	There is no data available of the use of budesonide/formoterol in patients with hepatic impairment. As both of these medicines are primarily eliminated via metabolism in the liver, an increased exposure can be expected in patients with severe liver cirrhosis.
Use in patients with kidney disease	There is no data available of the use of budesonide/formoterol in patients with renal impairment.
Use during pregnancy	For Bufomix Easyhaler or the concomitant treatment with formoterol and budesonide, no clinical data on exposed pregnancies are available. During pregnancy, Bufomix Easyhaler should only be used when the benefits outweigh the potential risks. The lowest effective dose of budesonide needed to maintain adequate asthma control should be used.
Use during breastfeeding	Budesonide is excreted in breast milk but at therapeutic doses no effects on the suckling child are anticipated. It is not known whether formoterol passes into human breast milk. Administration of Bufomix Easyhaler to women who are breastfeeding should only be considered if the expected benefit to the mother is greater than any possible risk to the child.
Effect on fertility	There is no information concerning the effect of Bufomix Easyhaler on the fertility in humans.

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 (PL). The measures in these documents are known as routine risk minimisation measures.

The Summary of Product Characteristics and the Package leaflet for Bufomix Easyhaler can be found in the national authority's web page.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

Not applicable.

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

Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
6.1	21.12.2017	No new safety concerns added.	SPC and PIL attached in Annex 2.
6.0	18.10.2017	No new safety concerns added.	Information concerning maintenance and reliever therapy for children and adolescents updated based on the SPC.
5.0	22.3.2017	No new safety concerns added.	Information concerning the Important identified risk of Systemic GCS effects was updated to include visual disturbances according to PRAC recommendation after Budesonide PSUSA /00000449/201604 procedure.
4.0	4.7.2016	No new safety concerns added.	Information concerning pneumonia in COPD updated according to the outcome of Article 31 referral of ICS-containing products in the treatment of COPD EMEA/H/A-31/1415.
3.0	02.04.2015	No new safety concerns added. Important identified risk of Pneumonia in COPD specified to concern Bufomix 320 µg/9 µg and 160 µg/4.5 µg inhalations.	New strength of 80 µg/4.5 µg inhalation added. Section VI.2.2 Summary of treatment benefits has been updated.
2.0	30.09.2014	No new safety concerns added.	Information concerning pneumonia in COPD was updated based on the SPC.
1.2	First version of RMP	Not applicable.	-