10.1 Part VI.2 Elements for a Public Summary

13.2.1 Part VI.2.1 Overview of disease epidemiology

Asthma (a lung disease that inflames and narrows the airways)

Globally around 235 million people currently experience asthma. It is a common disease among children. It occurs in all countries regardless of the level of development [WHO, 2013]. The highest prevalence was observed in Australia, Northern and Western Europe and Brazil [GAN, 2014]. In Europe, almost 10 billion people <45 years of age have asthma. The occurence of asthma in the European Union (EU) is 8.2% in adults and 9.4% in children [Selroos O, 2015]. Among children, more boys have asthma than girls. But among adults, more women have the disease than men [WHO, 2013]. The burden of asthma, measured by disability (limiting movement) and premature (before time) death, is greatest in children oncoming adolescence (ages 10-14) and the elderly (ages 75-79). 14% of the world's children experience asthma symptoms. 8.6% of young adults (aged 18-45) experience asthma symptoms [GAN, 2014].

Chronic Obstructive Pulmonary Disease (COPD) (a group of lung diseases that block airflow and make it difficult to breathe)

According to WHO, 65 million people have moderate to severe COPD [WHO, 2017]. COPD affects an estimated 30 million individuals in the U.S [COPD, 2017]. COPD occurrence was much more higher in males than in females, but there were no significant differences in the severity (grade of seriousness) between age groups [Kwon HY, 2016]. The occurrence of COPD increases with age, with a five-fold increased risk for those aged over 65 years compared with patients aged less than 40 years. COPD affects twice as many males as females [Raherison C, 2009]. The percentage increase in COPD cases between 1990 and 2010 was the highest in the Eastern Mediterranean region (118.7%), followed by the African region (102.1%), while the European region recorded the lowest increase (22.5%) [Adeloye D, 2015].

13.2.2 Part VI.2.2 Summary of treatment benefits

In a 12-week double-blind (study in which neither the participants nor the experimenters know the treatment being received), randomized (study design that randomly assigns participants into an experimental group or a control group), double-dummy (technique for retaining the blinding of a clinical trial) study, the efficacy of budesonide/formoterol in the fixed combination (160 µg/4.5 µg), two inhalations twice daily (BID) was compared with corresponding doses delivered via separate inhalers and with budesonide alone. Budesonide/formoterol combination treatments resulted in a significant improvement in lung function, relief of asthmatic symptoms such as wheeze, than its separate components administered concurrently [Kuna P, 2008].

In a study, 1571 COPD patients were treated with budesonide/formoterol (either two inhalations of 160 µg/4.5 µg or one inhalation of 320/9 µg) or placebo twice daily, showed that treatment with budesonide/formoterol decreased worsening of symptoms in patients with moderate-to-very-severe COPD within 3 months of starting treatment along with improved lung function.[Caverley PM, 2016]. In a study conducted to assess the efficacy of budesonide

and formoterol (single and combination) in children ≥ 6 to 12 years with asthma, budesonide/formoterol 80/4.5 µg x two inhalations (160 µg/9 µg) BID treatment resulted in significant improvements in lung function when compared with budesonide 80 mg x 2 inhalations (160 µg) BID alone [Pearlman DS, 2017]. In a study with 9130 asthma patients, formoterol/budesonide reduced the number of people having worsening of symptoms of asthma requiring oral steroids and the number requiring hospitalization or an emergency room visit compared with fixed-dose combination inhalers [Kew KM, 2013].

13.2.3 Part VI.2.3 Unknowns relating to treatment benefits

None

13.2.4 Part VI.2.4 Summary of safety concerns

Table 13-5 Important identified risks

Risk	What is known	Preventability
Heart affecting illness (Cardiac disorders)	Combination treatment with quinidine, disopyramide, procainamide (medicines for treating abnormal heart rhythm), phenothiazines, antihistamines (terfenadine) (medicine for treating allergic conditions) and tricyclic antidepressants (medicines for treating depression) can prolong the QTc-interval (a measurement from electrocardiogram that determines the electrical activity of heart.) and increase the risk of ventricular arrhythmias (abnormal heart rhythms from ventricles) also. There is an elevated risk of arrhythmias (abnormal heart beat) in patients receiving concomitant anesthesia (medicines which causes loss of sensation an awareness) with halogenated hydrocarbons (carbon containing compounds consisting of C-C, C-H and C-X bonds where. X is a halogen atom (F, Cl, Br, I)).	Patient should inform their doctor or pharmacist, if they have high blood pressure or ever had a heart problem (including an uneven heartbeat, a very fast pulse, narrowing of the arteries or heart failure), have problems with thyroid or adrenal glands, low levels of potassium in blood before taking budesonide/formoterol.
	Palpitations are common side effect of budesonide/formoterol and, they are usually mild and usually disappear during use.	Budesonide/formoterol should be administered with caution in patients with hypertrophic obstructive cardiomyopathy (portion of heart muscle was enlarged), idiopathic subvalvular aortic stenosis (increase in the size of left ventricle), severe hypertension (severe high blood pressure), aneurysm (a balloon like bulge in the wall of blood vessel) or other severe cardiovascular disorders, such as ischemic heart disease (reduce blood supply to the heart), tachyarrhythmias (high heart rate) or severe heart failure.
	Tachycardia (fast heartbeat is the uncommon side effect of budesonide/formoterol.	Patients should inform their doctor or pharmacist, if they are using:
	Angina pectoris (chest pain or	β-blocker medicines (medicines

Risk	What is known	Preventability
tightness in the chest), uneven heartbeat, prolongation of QTc-interval and changes in blood pressure are very rare side effects of budesonide/formoterol. Hypokalemia (decrease in potassium levels) may increase the disposition towards arrhythmias in patients who are treated with digitalis glycosides. An overdose of formoterol would likely lead to effects that are typical for β_2 adrenoceptor agonists like palpitations. Symptoms reported from isolated cases are tachycardia, hypokalemia, prolonged QTc-interval, and arrhythmia.	If budesonide/formoterol therapy has to be withdrawn due to overdose of the formoterol component of the drug, provision of appropriate ICS therapy must be considered.	for treating high blood pressure such as atenolol or propranolol), including eye drops (such as timolol for glaucoma (eye disease). Medicines for a fast or uneven heart beat (such as quinidine) Digoxin, often used to treat heart failure. Diuretics (medicines which increase outflow of salts and water from the body as urine), also known as 'water tablets' (such as furosemide). These are used to treat high blood pressure.
Change in the state of body with increased response to outside substances by body's defense system (Hypersensitivity)	During transfer from oral therapy to budesonide/formoterol, a generally lower systemic steroid action will be experienced which may result in the appearance of allergic or arthritic symptoms such as rhinitis (irritation and inflammation of the mucous membrane inside the nose) and eczema (a condition of skin inflammation). The components of the medication contains small amount of milk proteins which may cause allergic reactions. Bronchospasm (tightening of the muscles in the airways which causes wheezing), Exanthema, urticaria, pruritis, dermatitis, anaphylactic reactions, Swelling of face, particularly around the mouth (tongue and/or throat and/or difficulty swallowing) or hives together with difficulty breathing (angioedema) and/or sudden	Patients should not use budesonide/formoterol, if they are allergic to budesonide, formoterol or other ingredient of this medicine. Patients should stop using budesonide/formoterol, if they have swelling of face, particularly around the mouth (tongue and/or throat and/or difficulty swallowing) hives together with difficulty breathing (angioedema). This may mean that the patient is having an allergic reaction. If the patients get wheezing suddenly after using budesonide/formoterol, they should stop using budesonide/formoterol and talk to their doctor immediately.

Risk	What is known	Preventability
feeling of faintness. This may mean that you are having an allergic reaction. This happens	rarely (less than 1 in 1,000 people)	
Difficult to understand breathing and wheezing (breathe with a whistling or rattling sound in the chest) problems (Paradoxical bronchospasm)	Paradoxical bronchospasm may occur rarely affecting less than 1 in 10,000 people with the use of budesonide/formoterol. Sudden progressive deteriorating asthma or COPD may be life threatening. The patient may experience immediate increase in wheezing (breathe with a whistling or rattling sound in the chest) and shortness of breath after taking budesonide/formoterol. The patients should not be started on budesonide/formoterol therapy if the patient have significantly worsening or acutely deteriorating asthma.	The patients should be advised to always keep their inhalers available at all the times. The patient should immediately contact a physician and in case of worsening of symptoms should discontinue treatment with budesonide/formoterol. On decision of the physician, If necessary the patient should be placed on alternative therapy.
Increased risk of lung swelling in a long-term lung disease patients (Increased risk of pneumonia in COPD patients)	An increase in the incidence of pneumonia, including pneumonia requiring hospitalization, has been observed in patients with COPD receiving inhaled corticosteroids (ICSs; anti-inflammatory medicines taken through inhaler, portable device for administering a drug which is to be breathed in). There is some evidence of an increased risk of pneumonia with increasing steroid dose but this has not been demonstrated conclusively. Risk factors for pneumonia in patients with COPD include current smoking, older age, low body mass index (BMI), measure of body fat based on height and weight (BMI) (a measure of body fat based on weight and height) and severe COPD Pneumonia in COPD patients is a common side effect of budesonide/formoterol.	Patients should inform to their doctor or pharmacist, if they have fever or chills (feeling of coldness with shivering), increased mucus (secretion produced by mucous membrane) production, change in mucus color, increased cough or increased breathing difficulties as these could be symptoms of lung infection. Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of such infections overlap with the symptoms of COPD attacks

Table 13-6 Important potential risks

None

Table 13-7 Missing information

None

13.2.5 Part VI.2.5 Summary of additional risk minimization measures by safety concern

All medicines have a summary of product characterstics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimizing 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 minimization measures.

The SmPC and the Package leaflet for budesonide/formoterol can be found in the budesonide/formoterol's EPAR page.

This medicine has no additional risk minimization measures.

13.2.6 Part VI.2.6 Planned post authorization development plan

None

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

N/A (first submission)