Table VI-14 Risk miminisation by safety concern: off-label use of SYMBICORT pressurised inhalation, suspension for the treatment of asthma, in children, adolescents, or adults

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Off-label use of SYMBICORT pressurised inhalation, suspension for the treatment of asthma, in children, adolescents, or adults	SmPC SYMBICORT pressurised inhalation, suspension Approved indications and posology given in Section 4. CLINICAL PARTICULARS	None

Table VI-15 Risk miminisation by safety concern: off-label use of SYMBICORT pressurised inhalation, suspension as SMART therapy

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Off-label use of SYMBICORT pressurised inhalation, suspension as SMART therapy	SmPC SYMBICORT pressurised inhalation, suspension Approved indications and posology given in Section 4. CLINICAL PARTICULARS	None

VI: 2 ELEMENTS FOR A PUBLIC SUMMARY

SYMBICORT TURBUHALER

VI: 2.1 Overview of disease epidemiology

Asthma

Asthma is a common chronic inflammatory disease of the airways that affects children and adults of all ages. It is one of the most common chronic diseases worldwide, and can be life-threatening. Symptoms come and go and include shortness of breath, wheezing, chest tightness and cough. The cause of asthma is unknown; however, a family history of asthma, eczema or allergy makes it more likely an individual may develop asthma. Asthma occurs in all countries regardless of the level of development. There is evidence that its prevalence has

considerably increased in recent years, especially among children. Globally, the number of deaths related to asthma is estimated at around 250,000 per year.

Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is a long-term disease in which the airways and air sacs inside the lungs become damaged or blocked, leading to difficulty breathing. Symptoms of COPD usually develop over a number of years and can include breathlessness (especially after physical activity), persistent cough sometimes with mucus, wheezing, and frequent chest infections. The main cause is smoking, but other causes have been identified. The disease is worsened by bacterial and viral infections in the chest which cause exacerbations (flare-ups). Both exacerbations and chest infections can require admission to hospital and in some cases can lead to death. In 2012, COPD was, globally, the third most common cause of death, with over 3.1 million deaths, and approximately 200,000 to 300,000 people die each year in Europe because of COPD.

VI: 2.2 Summary of treatment benefits

SYMBICORT TURBUHALER is an inhaler that contains two different medicines: budesonide and formoterol. Budesonide belongs to a group of medicines called 'corticosteroids'. It works by reducing and preventing swelling and inflammation in your lungs. Formoterol belongs to a group of medicines called 'bronchodilators'. It works by relaxing the muscles in your airways so that you can breathe more easily.

SYMBICORT TURBUHALER is prescribed to treat asthma in children (from age 6), adolescents and adults with asthma that is not well controlled by inhaled corticosteroids alone. SYMBICORT TURBUHALER is prescribed to treat adults with chronic obstructive pulmonary disease (COPD).

Studies in asthma patients have shown daily use of SYMBICORT TURBUHALER improves breathing, reduces asthma symptoms, and reduces asthma exacerbations (temporary worsenings of asthma) compared to regular use of the corticosteroid budesonide alone. SYMBICORT TURBUHALER can also be used to relieve asthma symptoms that occasional occur because formoterol is as rapid acting as commonly used reliever medications. Asthma patients that take SYMBICORT TURBUHALER every day plus as-needed for the relief of symptoms when they occur (called SYMBICORT SMART) have fewer severe asthma exacerbations compared to patients that take SYMBICORT TURBUHALER daily, at the same or higher regular dose, but use a separate reliever medication.

Studies in COPD patients have shown daily use of SYMBICORT TURBUHALER reduces COPD exacerbations as compared with treatment with formoterol alone or placebo while providing similar improvements in breathing as formoterol alone.

VI: 2.3 Unknowns relating to treatment benefits

There are no data available for use of budesonide/formoterol in patients with reduced liver and kidney function.

VI: 2.4 Summary of safety concerns

This section presents a summary of important identified risks, important potential risks and missing information. These are defined as follows:

- An important identified risk is an unpleasant event for which there is enough evidence for it to be linked with the medicine of interest, and where the possibility of that event occurring could lessen the potential benefits of taking the medicine.
- An important potential risk is an unpleasant event for which there is some reason for suspicion of a link with the medicine of interest but where this link has not been confirmed. Inclusion of information relating to a potential risk should not be taken to imply that causal association with the use of SYMBICORT has been established.
- Missing information is information about the safety of a medicine which is not available that may represent a gap in the ability to predict the safety of the medicine in particular cases or patients.

Table VI-16 Important identified risks

Risk	What is known	Preventability
Heart problems due to formoterol (which belongs to a class of drugs called long-acting adrenergic $beta_2$-receptor agonists or LABAs)	Formoterol is a LABA and shares the actions of this class of 'bronchodilators'. Palpitations (awareness of the heart beating) have been reported commonly with budesonide/formoterol (affecting less than 1 in 10 people), fast heartbeat uncommonly (affecting less than 1 in 100 people), uneven heart beat rarely (may affect up to 1 in 1000 people), and chest pain or tightness in the chest (angina pectoris) very rarely (affecting less than 1 in 10,000 people)	Patients should talk to their doctor or pharmacist before using SYMBICORT if they have: - high blood pressure, or have ever had a heart problem (including an uneven heartbeat, a very fast pulse, narrowing of the arteries or heart failure); - problems with the thyroid - low levels of potassium in the blood.

Table VI-16 Important identified risks

Risk	What is known	Preventability
Drug allergy is an excessive, undesirable (damaging, discomfort-producing and sometimes fatal) reaction produced by the body's normal defences (ie immune system)	Drug allergic reactions are similar to allergic reactions resulting from food and other substances that we ingest. An individual's genetic make-up helps determine what they are allergic to and the severity of their allergies. Allergic reactions can be mild or deadly. Mild reactions include itching, rash, and hives. More serious reactions involve swelling of lips, tongue, and difficulty breathing. Any drug or a component in a drug can cause an allergic reaction.	Patients that are allergic to budesonide, formoterol, or any of the ingredients of SYMBICORT should tell their doctor. Other medications may be prescribed.
Temporary narrowing of the airways (paradoxical bronchospasm) that occurs suddenly, leading to difficulties in breathing or wheezing.	As with other inhalation therapy, a temporary narrowing of the airways may occur rarely after inhaling SYMBICORT, with an immediate increase in wheezing, shortness of breath and cough after dosing. Paradoxical bronchospasm was reported very rarely in patients taking budesonide/formoterol (may affect up to 1 in 10,000 people). If this occurs, patients should contact their doctor immediately as they may need to have their treatment changed.	None known.

Table VI-17 Important potential risks

Risk	What is known
Off-label use of SYMBICORT TURBUHALER as maintenance and reliever therapy (SMART) in patients under the age of 12	SYMBICORT maintenance and reliever therapy has been studied in children but is not approved for use in this population due to Health Authority concerns that children may not use SYMBICORT TURBUHALER as-needed appropriately. Children with asthma should be prescribed SYMBICORT TURBUHALER as a fixed maintenance dose.
Off-label use of SYMBICORT TURBUHALER as maintenance and reliever therapy (SMART) using the highest strength inhaler (320/9 µg/inhalation)	SYMBICORT maintenance and reliever therapy with the 320/9 µg/inhalation strength inhaler is not recommended as as-needed use of this strength may result in a total daily dose of SYMBICORT exceeding those proven to be safe and effective.
Off-label use of SYMBICORT TURBUHALER as maintenance and reliever therapy (SMART) to treat chronic obstructive pulmonary disease.	SYMBICORT SMART has not been studied in patients with COPD; thus, there is no information available regarding whether it is safe or effective in these patients. Patients with COPD should be prescribed SYMBICORT as a fixed maintenance dose.

There is no missing information with regard to the approved use of SYMBICORT TURBUHALER that is considered to be a safety concern.

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

All medicines have a Summary of Product Characteristics that provides physicians, pharmacists, and other health care professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising them. Information for patients is available in lay language in the Package Leaflet. The measures in these documents are known as routine risk minimisation measures.

The Summary of Product Characteristics and the Package Leaflet for SYMBICORT TURBUHALER can be found on the products' European Public Assessment Report web page.

SYMBICORT TURBUHALER has no additional risk minimisation measures.

VI: 2.6 Planned post authorisation development plan

The effectiveness and safety of SYMBICORT TURBUHALER has been well demonstrated in clinical studies and prescribed use in patients. No additional studies are planned to support the use of SYMBICORT products in the EU.

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

Not applicable, as this is the first version of the EU-RMP for the SYMBICORT inhalation products as a whole.

SYMBICORT pressurised inhalation, suspension

VI: 2.8 Overview of disease epidemiology

Asthma

Asthma is a common chronic inflammatory disease of the airways that affects children and adults of all ages. It is one of the most common chronic diseases worldwide, and can be life-threatening. Symptoms come and go and include shortness of breath, wheezing, chest tightness and cough. The cause of asthma is unknown; however, a family history of asthma, eczema or allergy makes it more likely an individual may develop asthma. Asthma occurs in all countries regardless of the level of development. There is evidence that its prevalence has considerably increased in recent years, especially among children. Globally, the number of deaths related to asthma is estimated at around 250,000 per year.

Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is a long-term disease in which the airways and air sacs inside the lungs become damaged or blocked, leading to difficulty breathing. Symptoms of COPD usually develop over a number of years and can include breathlessness (especially after physical activity), persistent cough sometimes with mucus, wheezing, and frequent chest infections. The main cause is smoking, but other causes have been identified. The disease is worsened by bacterial and viral infections in the chest which cause exacerbations (flare-ups). Both exacerbations and chest infections can require admission to hospital and in some cases can lead to death. In 2012, COPD was, globally, the third most common cause of death, with over 3.1 million deaths, and approximately 200,000 to 300,000 people die each year in Europe because of COPD.

VI: 2.9 Summary of treatment benefits

SYMBICORT pressurised inhalation, suspension is an inhaler that contains two different medicines: budesonide and formoterol. Budesonide belongs to a group of medicines called ‘corticosteroids’. It works by reducing and preventing swelling and inflammation in your lungs. Formoterol belongs to a group of medicines called ‘bronchodilators’. It works by relaxing the muscles in your airways so that you can breathe more easily.

SYMBICORT pressurised inhalation, suspension is prescribed to treat adults with chronic obstructive pulmonary disease (COPD).

In COPD studies with SYMBICORT pressurised inhalation, suspension, patients receiving SYMBICORT pressurised inhalation, suspension breathed better than patients treated with just formoterol or just budesonide. Patients also had fewer symptoms and fewer COPD exacerbations.

VI: 2.10 Unknowns relating to treatment benefits

There are no data available for use of budesonide/formoterol in patients with reduced liver and kidney function.

VI: 2.11 Summary of safety concerns

This section presents a summary of important identified risks, important potential risks and missing information. These are defined as follows:

- An important identified risk is an unpleasant event for which there is enough evidence for it to be linked with the medicine of interest, and where the possibility of that event occurring could lessen the potential benefits of taking the medicine.
- An important potential risk is an unpleasant event for which there is some reason for suspicion of a link with the medicine of interest but where this link has not been confirmed. Inclusion of information relating to a potential risk should not be taken to imply that causal association with the use of SYMBICORT has been established.
- Missing information is information about the safety of a medicine which is not available that may represent a gap in the ability to predict the safety of the medicine in particular cases or patients.

Table VI-18 Important identified risks

Risk	What is known	Preventability
Heart problems due to formoterol (which belongs to a class of drugs called long-acting adrenergic $beta_2$-receptor agonists or LABAs)	Formoterol is a LABA and shares the actions of this class of 'bronchodilators'. Palpitations (awareness of the heart beating) have been reported commonly with budesonide/formoterol (affecting less than 1 in 10 people), fast heartbeat uncommonly (affecting less than 1 in 100 people), uneven heart beat rarely (may affect up to 1 in 1000 people)., and chest pain or tightness in the chest (angina pectoris) very rarely (affecting less than 1 in 10,000 people)	Patients should talk to their doctor or pharmacist before using SYMBICORT if they have: - high blood pressure, or have ever had a heart problem (including an uneven heartbeat, a very fast pulse, narrowing of the arteries or heart failure); - problems with the thyroid - low levels of potassium in the blood.
Drug allergy is an excessive, undesirable (damaging, discomfort-producing and sometimes fatal) reaction produced by the body's normal defences (ie immune system)	Drug allergic reactions are similar to allergic reactions resulting from food and other substances that we ingest. An individual's genetic make-up helps determine what they are allergic to and the severity of their allergies. Allergic reactions can be mild or deadly. Mild reactions include itching, rash, and hives. More serious reactions involve swelling of lips, tongue, and difficulty breathing. Any drug or a component in a drug can cause an allergic reaction.	Patients that are allergic to budesonide, formoterol, or any of the ingredients of SYMBICORT should tell their doctor. Other medications may be prescribed.

Table VI-18 Important identified risks

Risk	What is known	Preventability
Temporary narrowing of the airways (paradoxical bronchospasm) that occurs suddenly, leading to difficulties in breathing or wheezing.	As with other inhalation therapy, a temporary narrowing of the airways may occur rarely after inhaling SYMBICORT, with an immediate increase in wheezing, shortness of breath and cough after dosing. Paradoxical bronchospasm was reported very rarely in patients taking budesonide/formoterol (may affect up to 1 in 10,000 people). If this occurs, patients should contact their doctor immediately as they may need to have their treatment changed.	None known.

Table VI-19 Important potential risks

Risk	What is known
Off-label use of SYMBICORT pressurised inhalation, suspension for the treatment of asthma	SYMBICORT pressurised inhalation, suspension is not approved for use in asthma within the EU. It has been approved for use in asthma outside of the EU.
Off-label use of SYMBICORT pressurised inhalation, suspension as maintenance and reliever therapy (SMART)	SYMBICORT TURBUHALER is approved for the treatment of asthma as SYMBICORT SMART, based upon it being shown to be effective and safe. The SYMBICORT SMART dosing has not been studied with SYMBICORT pressurised inhalation, suspension.

There is no missing information with regard to the approved use of SYMBICORT pressurised inhalation, suspension that is considered to be a safety concern.

VI: 2.12 Summary of additional risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics that provides physicians, pharmacists, and other health care professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising them. Information for patients

is available in lay language in the Package Leaflet. The measures in these documents are known as routine risk minimisation measures.

The Summary of Product Characteristics and the Package Leaflet for SYMBICORT pressurised inhalation, suspension can be found on the products' European Public Assessment Report web page.

SYMBICORT pressurised inhalation, suspension has no additional risk minimisation measures.

VI: 2.13 Planned post authorisation development plan

The effectiveness and safety of SYMBICORT pressurised inhalation, suspension has been well demonstrated in clinical studies and prescribed use in patients. No additional studies are planned to support the use of SYMBICORT products in the EU.

VI: 2.14 Summary of changes to the Risk Management Plan over time

Not applicable, as this is the first version of the EU-RMP for the SYMBICORT inhalation products as a whole.

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