HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use SYMBICORT AEROSPHERE safely and effectively. See full prescribing information for SYMBICORT AEROSPHERE.

SYMBICORT AEROSPHERE® (budesonide and formoterol fumarate) inhalation aerosol, for oral inhalation use
Initial U.S. Approval: 2006

---------- RECENT MAJOR CHANGES ----------

Indications and Usage (1.1)	04/2026
Dosage and Administration (2.2)	04/2026
Contraindications (4)	04/2026
Warnings and Precautions (5.1, 5.14)	04/2026

---------- INDICATIONS AND USAGE ----------

SYMBICORT AEROSPHERE is a combination of budesonide, a corticosteroid, and formoterol fumarate, a long-acting $beta_2$-adrenergic agonist (LABA), indicated for:

- the treatment of asthma in adult and pediatric patients aged 12 years and older. (1.1)
- the maintenance treatment of chronic obstructive pulmonary disease (COPD) in adult patients. (1.2)

Limitations of Use: Not indicated for the relief of acute bronchospasm. (1.3)

---------- DOSAGE AND ADMINISTRATION ----------

- For oral inhalation only. (2.1)
- Prime SYMBICORT AEROSPHERE before first time use and re-prime if not used for more than 7 days, dropped, or after rinsing. (2.1)
- Recommended Dosage:
  - Treatment of Asthma in Patients Aged 12 Years and Older: SYMBICORT AEROSPHERE 160 mcg/9.6 mcg or SYMBICORT AEROSPHERE 320 mcg/9.6 mcg by oral inhalation twice daily. (2.2)
  - Maintenance Treatment of COPD in Adults: SYMBICORT AEROSPHERE 320 mcg/9.6 mcg by oral inhalation twice daily. (2.3)

---------- DOSAGE FORMS AND STRENGTHS ----------

Inhalation aerosol: Pressurized metered dose inhaler with a combination of

- 80 mcg/4.8 mcg (budesonide 80 mcg and formoterol fumarate 4.8 mcg) per actuation. (3)
- 160 mcg/4.8 mcg (budesonide 160 mcg and formoterol fumarate 4.8 mcg) per actuation (3)

---------- CONTRAINDICATIONS ----------

- Primary treatment of status asthmaticus or other acute episodes of asthma or COPD requiring intensive measures. (4)
- Hypersensitivity to budesonide, formoterol fumarate, or to any of the excipients. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- LABA as monotherapy (without an inhaled-corticosteroid) is associated with an increased risk of serious asthma-related events. (5.1)
- Do not initiate in acutely deteriorating asthma or COPD. Do not use to relieve acute symptoms. (5.2)
- Do not use in combination with an additional therapy containing a LABA because of the risk of overdosage. (5.3)
- Oropharyngeal candidiasis may occur. Monitor patients periodically. Advise the patient to rinse his/her mouth with water without swallowing after inhalation to help reduce the risk. (5.4)
- Increased risk of pneumonia in patients with COPD. Monitor patients for signs and symptoms of pneumonia. (5.5)
- Potential worsening of infections (e.g., existing tuberculosis; fungal, bacterial, viral, or parasitic infections; ocular herpes simplex). Use with caution in patients with these infections. More serious or even fatal course of chickenpox or measles can occur in susceptible patients. (5.6)
- Risk of impaired adrenal function when transferring from systemic corticosteroids. Taper patients slowly from systemic corticosteroids if transferring to SYMBICORT AEROSPHERE. (5.7)
- Hypercorticism and adrenal suppression may occur with very high dosages or at the regular dosage in susceptible individuals. If such changes occur, consider appropriate therapy. (5.8)
- If paradoxical bronchospasm occurs, discontinue SYMBICORT AEROSPHERE and institute alternative therapy. (5.10)
- Cardiovascular effects may occur. Use with caution in patients with cardiovascular disorders because of beta-adrenergic stimulation. (5.12)
- Assess for decrease in bone mineral density initially and periodically thereafter. (5.13)
- Monitor growth of pediatric patients. (5.14)
- Glaucoma and cataracts may occur with long-term use of ICS. Consider referral to an ophthalmologist in patients who develop ocular symptoms or use SYMBICORT AEROSPHERE long term. (5.15)
- Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis. (5.16)
- Be alert to hypokalemia and hyperglycemia. (5.17)

---------- ADVERSE REACTIONS ----------

- Asthma: Most common adverse reactions (incidence ≥ 2%) are nasopharyngitis, COVID-19, rhinitis allergic, bronchitis bacterial, upper respiratory tract infection, arthralgia, gout, hypertension, diarrhea, influenza like illness. (6.1)
- COPD: Most common adverse reactions (incidence ≥ 2%) are upper respiratory tract infection, COPD, back pain, headache, bronchitis, oral candidiasis, dysphonia, muscle spasm. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS ----------

- Strong cytochrome P450 3A4 inhibitors (e.g. ritonavir): Use with caution. May cause systemic corticosteroid effects. (7.1)
- Diuretics, xanthine derivatives or steroids: May potentiate hypokalemia or ECG changes. Use with caution. (7.3)
- Monoamine oxidase inhibitors and tricyclic antidepressants: Use with extreme caution. May potentiate effect of formoterol fumarate on cardiovascular system. (7.5)
- Beta-blockers: Use with caution. May block bronchodilatory effects of beta-agonists and produce severe bronchospasm. (7.6)

---------- USE IN SPECIFIC POPULATIONS ----------

Hepatic impairment: Budesonide and formoterol fumarate systemic exposure may increase in patients with severe hepatic impairment. Monitor patients for signs of increased drug exposure. (8.6, 12.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA approved patient labeling.

Revised: 04/2026

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Treatment of Asthma

SYMBICORT AEROSPHERE is indicated for the treatment of asthma in adult and pediatric patients aged 12 years and older.

1.2 Maintenance Treatment of Chronic Obstructive Pulmonary Disease

SYMBICORT AEROSPHERE is indicated for the maintenance treatment of chronic obstructive pulmonary disease (COPD) in adult patients.

1.3 Limitations of Use

SYMBICORT AEROSPHERE is not indicated for the relief of acute bronchospasm.

2 DOSAGE AND ADMINISTRATION

2.1 Preparation and Administration Information

- Administer SYMBICORT AEROSPHERE by oral inhalation.
- After inhalation, rinse mouth with water without swallowing to help reduce the risk of oropharyngeal candidiasis *[see Warnings and Precautions (5.4)]*.

Priming Before Use

- Priming SYMBICORT AEROSPHERE is essential to ensure appropriate drug content in each actuation. Prime SYMBICORT AEROSPHERE before using for the first time. Prime SYMBICORT AEROSPHERE by releasing 4 sprays into the air away from the face, shaking well before each spray.
- Re-prime SYMBICORT AEROSPHERE if the inhaler has not been used for more than 7 days, is dropped, or after weekly rinsing. Prime SYMBICORT AEROSPHERE by releasing 2 sprays into the air away from the face, shaking well before each spray.

Dose Counter

SYMBICORT AEROSPHERE canister has an attached dose indicator (also known as puff indicator), which indicates how many inhalations (puffs) remain. The dose indicator display has a pointer which will move after every actuation. When nearing the end of the usable inhalations, the pointer is in the yellow zone. SYMBICORT AEROSPHERE should be discarded when the pointer is at 0 in the red zone of the dose indicator.

2.2 Recommended Dosage for Treatment of Asthma

The recommended dosage of:

SYMBICORT AEROSPHERE is budesonide 160 mcg and formoterol fumarate 9.6 mcg (administered as 2 actuations of SYMBICORT AEROSPHERE 80 mcg/4.8 mcg [budesonide/formoterol fumarate 80 mcg/4.8 mcg]) twice daily (in the morning and in the evening, approximately 12 hours apart) by oral inhalation.

or

SYMBICORT AEROSPHERE is budesonide 320 mcg and formoterol fumarate 9.6 mcg (administered as 2 actuations of SYMBICORT AEROSPHERE 160 mcg/4.8 mcg [budesonide/formoterol fumarate 160 mcg/4.8 mcg]) twice daily (in the morning and in the evening, approximately 12 hours apart) by oral inhalation.

- The recommended starting dosages for SYMBICORT AEROSPHERE are based upon patients' asthma severity or level of control of asthma symptoms, and risk of exacerbations on current inhaled corticosteroids.
- For patients who do not respond adequately to the starting dose of therapy with SYMBICORT AEROSPHERE 160 mcg/9.6 mcg twice daily, additional asthma control may be provided by replacement with a dose of SYMBICORT AEROSPHERE 320 mcg/9.6 mcg twice daily. For patients who do not respond adequately to a dose of SYMBICORT AEROSPHERE 320 mcg/9.6 mcg twice daily, the therapeutic regimen should be re-evaluated and additional therapeutic options should be considered.
- Do not use more than two inhalations twice daily.

2.3 Recommended Dosage for Maintenance Treatment of Chronic Obstructive Pulmonary Disease

The recommended dosage of SYMBICORT AEROSPHERE is budesonide 320 mcg and formoterol fumarate 9.6 mcg (administered as 2 actuations of SYMBICORT AEROSPHERE 160 mcg/4.8 mcg [budesonide/formoterol fumarate 160 mcg/4.8 mcg]) twice daily (in the morning and in the evening, approximately 12 hours apart) by oral inhalation.

3 DOSAGE FORMS AND STRENGTHS

Inhalation aerosol: a pressurized metered dose inhaler (a pressurized canister with an attached dose indicator, a white plastic actuator and mouthpiece, and a grey dust cap) that delivers a combination of

- 80 mcg/4.8 mcg (budesonide 80 mcg and formoterol fumarate 4.8 mcg) per actuation
- 160 mcg/4.8 mcg (budesonide 160 mcg and formoterol fumarate 4.8 mcg) per actuation.

4 CONTRAINDICATIONS

SYMBICORT AEROSPHERE is contraindicated in the following conditions:

- Primary treatment of status asthmaticus or other acute episodes of asthma or COPD where intensive measures are required *[see Warnings and Precautions (5.2)]*.
- Hypersensitivity to budesonide, formoterol, or any of the excipients *[see Warnings and Precautions (5.11) and Description (11)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Asthma-Related Events – Hospitalizations, Intubations and Death

Use of long-acting beta$_2$-adrenergic agonists (LABA) as monotherapy [without inhaled corticosteroid (ICS)] for asthma is associated with an increased risk of asthma-related death. Available data from controlled clinical trials also suggest that use of LABA as monotherapy increases the risk of asthma-related hospitalization in pediatric patients. These findings are considered a class effect of LABA monotherapy. When a LABA is used in fixed dose combination with ICS, data from large clinical trials do not show a significant increase in the risk of serious asthma-related events (hospitalizations, intubations, death) compared with ICS alone (see *Serious Asthma-Related Events with ICS/LABA*).

Available data do not suggest an increased risk of death with use of LABA in patients with COPD.

Serious Asthma-Related Events with ICS/LABA

Four large, 26-week, randomized, blinded, active-controlled clinical safety trials were conducted to evaluate the risk of serious asthma-related events when LABA were used in fixed-dose combination with ICS compared to ICS alone in patients with asthma. Three trials included adult and adolescent patients aged ≥12 years: one trial compared budesonide/formoterol to budesonide; one trial compared fluticasone propionate/salmeterol inhalation powder to fluticasone propionate inhalation powder; and one trial compared mometasone furoate/formoterol to mometasone furoate. The fourth trial included pediatric patients 4 to 11 years of age and compared fluticasone propionate/salmeterol inhalation powder to fluticasone propionate inhalation powder. SYMBICORT AEROSPHERE is not indicated for patients 4 to 11 years of age. The primary safety endpoint for all four trials was serious asthma-related events (hospitalizations, intubations and death). A blinded adjudication committee determined whether events were asthma-related.

The three adult and adolescent trials were designed to rule out a risk margin of 2.0, and the pediatric trial was designed to rule out a risk of 2.7. Each individual trial met its pre-specified objective and demonstrated non-inferiority of ICS/LABA to ICS alone. A meta-analysis of the three adult and adolescent trials did not show a significant increase in risk of a serious asthma-related event with ICS/LABA fixed-dose combination compared with ICS alone (Table 1). These trials were not designed to rule out all risk for serious asthma-related events with ICS/LABA compared with ICS.

Table 1: Meta-Analysis of Serious Asthma-Related Events in Patients with Asthma Aged 12 Years and Older

	ICS/LABA (N=17,537)*	**ICS (N=17,552)***	**ICS/LABA vs ICS Hazard ratio (95% CI)†**
Serious asthma-related event‡	116	105	1.10 (0.85, 1.44)
Asthma-related death	2	0	
Asthma-related intubation (endotracheal)	1	2	
Asthma-related hospitalization (≥24-hour stay)	115	105	

ICS=Inhaled Corticosteroid, LABA=Long-acting Beta$_2$-adrenergic Agonist

*Randomized patients who had taken at least 1 dose of study drug. Planned treatment used for analysis.

†Estimated using a Cox proportional hazards model of time to first event with baseline hazards stratified by each of the 3 trials.

‡Number of patients with event that occurred within 6 months after the first use of study drug or 7 days after the last date of study drug, whichever date was later. Patients can have one or more events, but only the first event was counted for analysis. A single, blinded, independent adjudication committee determined whether events were asthma-related.

The pediatric safety trial included 6208 pediatric patients 4 to 11 years of age who received ICS/LABA (fluticasone propionate/salmeterol inhalation powder) or ICS (fluticasone propionate inhalation powder). In this trial, 27/3107 (0.9%) patients randomized to ICS/LABA and 21/3101 (0.7%) patients randomized to ICS experienced a serious asthma-related

event. There were no asthma-related deaths or intubations. ICS/LABA did not show a significantly increased risk of a serious asthma-related event compared to ICS based on the pre-specified risk margin (2.7), with an estimated hazard ratio of time to first event of 1.29 (95% CI: 0.73, 2.27). SYMBICORT AEROSPHERE is not indicated for use in pediatric patients aged 11 years and younger.

Salmeterol Multicenter Asthma Research Trial (SMART)

A 28-week, placebo-controlled U.S. trial that compared the safety of salmeterol with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in patients receiving salmeterol (13/13,176 in patients treated with salmeterol vs. 3/13,179 in patients treated with placebo; relative risk: 4.37 [95% CI 1.25, 15.34]). Use of background ICS was not required in SMART. The increased risk of asthma-related death is considered a class effect of LABA monotherapy.

Formoterol Monotherapy Studies

Clinical studies with formoterol used as monotherapy suggested a higher incidence of serious asthma exacerbation in patients who received formoterol than in those who received placebo. The sizes of these studies were not adequate to precisely quantify the difference in serious asthma exacerbations between treatment groups.

5.2 Deterioration of Disease and Acute Episodes

SYMBICORT AEROSPHERE should not be initiated in patients with acutely deteriorating asthma or COPD, which may be a life-threatening condition. SYMBICORT AEROSPHERE has not been studied in patients with acutely deteriorating asthma or COPD. The initiation of SYMBICORT AEROSPHERE in this setting is not appropriate.

Increasing use of inhaled, short-acting beta$_2$-agonists is a marker of deteriorating asthma. In this situation, the patient requires immediate re-evaluation with reassessment of the treatment regimen, giving special consideration to the possible need for additional therapeutic options. Patients should not use more than 2 inhalations twice daily (morning and evening) of SYMBICORT AEROSPHERE.

SYMBICORT AEROSPHERE should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. SYMBICORT AEROSPHERE has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with either an inhaled short-acting beta$_2$-agonist/corticosteroid combination (asthma only) or an inhaled short-acting beta$_2$-agonist (asthma or COPD).

When beginning treatment with SYMBICORT AEROSPHERE, patients who have been taking oral or inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief of acute respiratory symptoms. When prescribing SYMBICORT AEROSPHERE, the healthcare provider should also prescribe either an inhaled short-acting beta$_2$-agonist/corticosteroid combination (asthma only) or an inhaled, short acting beta$_2$-agonist (asthma or COPD) and instruct the patient on how it should be used.

COPD symptoms may deteriorate acutely over a period of hours or chronically over several days or longer. If SYMBICORT AEROSPHERE no longer controls symptoms, or the patient's inhaled, short-acting beta$_2$-agonist becomes less effective or the patient needs more inhalations of short-acting beta$_2$-agonist than usual, these may be markers of deterioration of disease. In this setting, re-evaluate the patient and the COPD treatment regimen at once. The daily dosage of SYMBICORT AEROSPHERE should not be increased beyond the recommended dose.

5.3 Avoid Excessive Use of SYMBICORT AEROSPHERE, and Avoid Use with Other Long-acting Beta$_2$-agonists

As with other inhaled drugs containing beta$_2$-adrenergic agents, SYMBICORT AEROSPHERE should not be used more often than recommended *[see Dosage and Administration (2.2 and 2.3)]*, at higher doses than recommended, or in conjunction with other medications containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using SYMBICORT AEROSPHERE should not use another drug containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.

5.4 Oropharyngeal Candidiasis

SYMBICORT AEROSPHERE contains budesonide, an ICS. Localized infections of the mouth and pharynx with *Candida albicans* have occurred in patients treated with orally inhaled drug products containing budesonide. Monitor patients periodically. When such an infection develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while treatment with SYMBICORT AEROSPHERE continues. In some cases, therapy with SYMBICORT AEROSPHERE may need to be interrupted. Advise the patient to rinse his/her mouth with water without swallowing following administration of SYMBICORT AEROSPHERE to help reduce the risk of oropharyngeal candidiasis.

5.5 Risk of Pneumonia

Lower respiratory tract infections, including pneumonia, have been reported following the inhaled administration of corticosteroids. Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of pneumonia and exacerbations frequently overlap.

5.6 Immunosuppression and Risk of Infections

Patients who are on drugs that suppress the immune system are more susceptible to infection than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in susceptible children or adults using corticosteroids. In such children or adults who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated (see the respective package inserts for complete VZIG and IG prescribing information). If chicken pox develops, treatment with antiviral agents may be considered.

ICS should be used with caution, if at all, in patients with active or quiescent tuberculosis infections of the respiratory tract; untreated systemic fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.

5.7 Transferring Patients from Systemic Corticosteroid Therapy

HPA Suppression/Adrenal Insufficiency

Particular care is needed for patients who have been transferred from systemically active corticosteroids to ICS because deaths due to adrenal insufficiency have occurred in patients during and after transfer from systemic corticosteroids to less systemically available ICS. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function.

Patients who have been previously maintained on dose of 20 mg or more per day of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although SYMBICORT AEROSPHERE may provide control of asthma or COPD symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of glucocorticoid systemically and does not provide the mineralocorticoid activity that is necessary for coping with these emergencies.

During periods of stress, a severe asthma attack or a severe COPD exacerbation, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their healthcare practitioner for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic corticosteroids during periods of stress, a severe asthma attack or a severe COPD exacerbation.

Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to SYMBICORT AEROSPHERE. Prednisone reduction can be accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during therapy with SYMBICORT AEROSPHERE. Lung function (mean forced expiratory volume in 1 second [FEV_1]), beta-agonist use, and asthma or COPD symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition, patients should be observed for signs and symptoms of adrenal insufficiency, such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension.

Unmasking of Allergic Conditions Previously Suppressed by Systemic Corticosteroids

Transfer of patients from systemic corticosteroid therapy to SYMBICORT AEROSPHERE may unmask allergic conditions previously suppressed by the systemic corticosteroid therapy (e.g., rhinitis, conjunctivitis, eczema, arthritis, eosinophilic conditions).

Corticosteroid Withdrawal Symptoms

During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal (e.g., joint and/or muscular pain, lassitude, depression) despite maintenance or even improvement of respiratory function.

5.8 Hypercorticism and Adrenal Suppression

Inhaled budesonide is absorbed into the circulation and can be systemically active at higher doses. Effects of budesonide on the HPA axis are not observed with the therapeutic doses of budesonide in SYMBICORT AEROSPHERE. However, exceeding the recommended dosage or coadministration with a strong cytochrome P450 3A4 (CYP3A4) inhibitor may result in HPA axis dysfunction *[see Warnings and Precautions (5.9) and Drug Interactions (7.1)]*.

Because of the possibility of systemic absorption of ICS, patients treated with SYMBICORT AEROSPHERE should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response.

It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression (including adrenal crisis) may appear in a small number of patients who are sensitive to these effects. If such effects occur, appropriate therapy should be initiated as needed.

5.9 Drug Interactions with Strong Cytochrome P450 3A4 Inhibitors

Caution should be exercised when considering the coadministration of SYMBICORT AEROSPHERE with long-term ketoconazole, and other known strong CYP3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) because adverse effects related to increased systemic exposure to budesonide may occur *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*.

5.10 Paradoxical Bronchospasm

As with other inhaled therapies, SYMBICORT AEROSPHERE can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with SYMBICORT AEROSPHERE, it should be treated immediately with an inhaled, short-acting bronchodilator, SYMBICORT AEROSPHERE should be discontinued immediately, and alternative therapy should be instituted.

5.11 Hypersensitivity Reactions Including Anaphylaxis

Hypersensitivity reactions have been reported after administration of budesonide or formoterol fumarate, the components of SYMBICORT AEROSPHERE. If signs suggesting allergic reactions occur, in particular, angioedema (including difficulties in breathing or swallowing, swelling of tongue, lips, and face), urticaria, or skin rash, SYMBICORT AEROSPHERE should be stopped at once and alternative treatment should be considered *[see Contraindications (4)]*.

5.12 Cardiovascular Effects

SYMBICORT AEROSPHERE, like other drugs containing beta$_2$-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and also cardiac arrhythmias, such as supraventricular tachycardia and extrasystoles *[see Clinical Pharmacology (12.2)]*.

If such effects occur, SYMBICORT AEROSPHERE may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiographic changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression, although the clinical significance of these findings is unknown. Therefore, SYMBICORT AEROSPHERE should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

5.13 Reduction in Bone Mineral Density

Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing ICS. The clinical significance of small changes in BMD with regard to long-term consequences such as fracture is unknown. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, postmenopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care. Since patients with COPD often have multiple risk factors for reduced BMD, assessment of BMD is recommended prior to initiating SYMBICORT AEROSPHERE and periodically thereafter. If significant reductions in BMD are seen and SYMBICORT AEROSPHERE is still considered medically important for that patient's COPD therapy, use of medication to treat or prevent osteoporosis should be strongly considered.

5.14 Effect on Growth

Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to pediatric patients. Monitor the growth of pediatric patients receiving SYMBICORT AEROSPHERE routinely (e.g., via stadiometry). To minimize the systemic effects of orally inhaled corticosteroids, including SYMBICORT AEROSPHERE, titrate each patient's dose to the lowest dosage that effectively controls his/her symptoms *[see Dosage and Administration (2.2) and Use in Specific Populations (8.4)]*.

5.15 Glaucoma and Cataracts

Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with asthma and COPD following the long-term administration of ICS, including budesonide, a component of SYMBICORT AEROSPHERE. Therefore, close monitoring is warranted in patients with a change in vision or with history of increased intraocular pressure, glaucoma, and/or cataracts. Consider referral to an ophthalmologist in patients who develop ocular symptoms.

5.16 Risks of Using Sympathomimetic Amines in Certain Coexisting Conditions

SYMBICORT AEROSPHERE, like all therapies containing sympathomimetic amines, should be used with caution in patients with convulsive disorders, thyrotoxicosis, or diabetes mellitus and in those who are unusually responsive to sympathomimetic amines. Doses of the related beta$_2$-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

5.17 Hypokalemia and Hyperglycemia

Beta-adrenergic agonist drugs may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects *[see Clinical Pharmacology (12.2)]*. The decrease in serum potassium is usually transient, not requiring supplementation. Beta$_2$-agonist therapies may produce transient hyperglycemia in some patients.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling.

- Serious Asthma-Related Events – Hospitalizations, Intubations, Death *[see Warnings and Precautions (5.1)]*
- Oropharyngeal Candidiasis *[see Warnings and Precautions (5.4)]*
- Risk of Pneumonia *[see Warnings and Precautions (5.5)]*
- Immunosuppression and Risk of Infections *[see Warnings and Precautions (5.6)]*
- Hypercorticism and Adrenal Suppression *[see Warnings and Precautions (5.8)]*
- Paradoxical Bronchospasm *[see Warnings and Precautions (5.10)]*
- Hypersensitivity Reactions Including Anaphylaxis *[see Contraindications (4) and Warnings and Precautions (5.11)]*
- Cardiovascular Effects *[see Warnings and Precautions (5.12)]*
- Reduction in Bone Mineral Density *[see Warnings and Precautions (5.13)]*
- Effect on Growth *[see Warnings and Precautions (5.14)]*
- Glaucoma and Cataracts *[see Warnings and Precautions (5.15)]*

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.1 Clinical Trials Experience

Asthma

The safety of SYMBICORT AEROSPHERE in asthma is based on the safety data from two clinical trials, with durations of 12 weeks (LITHOS) and 24 weeks (VATHOS), respectively. In LITHOS, a total of 357 adult and pediatric patients aged 12 years and older with asthma were randomized; 179 patients received at least 1 dose of SYMBICORT AEROSPHERE 160 mcg/9.6 mcg. In VATHOS, a total of 585 adult and pediatric patients aged 13 years and older were

randomized; 88 patients received at least 1 dose of SYMBICORT AEROSPHERE 160 mcg/9.6 mcg and 163 patients received at least 1 dose of SYMBICORT AEROSPHERE 320 mcg/9.6 mcg *[see Clinical Studies (14.1)]*.

Table 2 includes adverse reactions that occurred at an incidence of ≥2% with SYMBICORT AEROSPHERE and more commonly than in the budesonide (BD MDI) group with twice-daily dosing in VATHOS.

Table 2: Adverse Reactions Occurring at an Incidence of ≥2% and More Common in Patients with Asthma Treated with SYMBICORT AEROSPHERE than with BD MDI* (VATHOS)

Adverse Reaction	SYMBICORT AEROSPHERE* 320 mcg/9.6 mcg N=163 (%)	SYMBICORT AEROSPHERE* 160 mcg/9.6 mcg N=88 (%)	BD MDI* 320 mcg N=168 (%)
Nasopharyngitis	15 (9.2)	12 (13.6)	15 (8.9)
COVID-19	15 (9.2)	3 (3.4)	8 (4.8)
Rhinitis allergic	4 (2.5)	1 (1.1)	0 (0.0)
Bronchitis bacterial	2 (1.2)	2.(2.3)	2 (1.2)
Arthralgia	1 (0.6)	3 (3.4)	1 (0.6)
Gout	1 (0.6)	2 (2.3)	0 (0.0)
Hypertension	1 (0.6)	3 (3.4)	3 (1.8)
Diarrhea	0 (0.0)	2 (2.3)	1 (0.6)
Influenza like illness	0 (0.0)	2 (2.3)	0 (0.0)

*SYMBICORT AEROSPHERE=budesonide/formoterol fumarate 320 mcg/9.6 mcg or 160 mcg/9.6 mcg; BD MDI=budesonide 320 mcg; all treatments were administered twice daily.

Adverse Reactions in LITHOS

In the LITHOS trial, an adverse reaction that occurred at an incidence of at least 2% and more frequently in patients treated with SYMBICORT AEROSPHERE 160 mcg/9.6 mcg compared to patients treated with BD MDI 160 mcg was upper respiratory tract infection at 3.4% and 2.9%, respectively.

Chronic Obstructive Pulmonary Disease

The safety of SYMBICORT AEROSPHERE in COPD is based on the safety data from two clinical trials, with durations of 24 weeks (TELOS) and 12-52 weeks (SOPHOS), respectively. In TELOS and SOPHOS, a total of 1274 patients with COPD received at least 1 dose of SYMBICORT AEROSPHERE 320 mcg/9.6 mcg *[see Clinical Studies (14.2)]*.

In the two trials, adult patients were treated with SYMBICORT AEROSPHERE 320 mcg/9.6 mcg twice daily (TELOS mean age: 64 years [range: 40 to 81 years], 97% White, 61% male; SOPHOS: mean age 65 years [range: 40 to 80 years], 83% White, 57% male) *[see Clinical Studies (14.2)]*. The incidence of common adverse reactions in TELOS is shown in Table 3.

Table 3: Adverse Reactions Occurring at an Incidence of ≥2% and More Common in Patients with COPD Treated with SYMBICORT AEROSPHERE than Any Comparator Arm (TELOS)

Adverse Reaction	SYMBICORT AEROSPHERE* 320 mcg/9.6 mcg N=655 (%)	FF MDI* 9.6 mcg N=644 (%)	BD MDI* 320 mcg N=206 (%)
Upper respiratory tract infection	25 (3.8)	20 (3.1)	5 (2.4)
Chronic obstructive pulmonary disease	16 (2.4)	30 (4.7)	2 (1)
Back pain	18 (2.7)	18 (2.8)	3 (1.5)
Headache	19 (2.9)	15 (2.3)	3 (1.5)
Bronchitis	16 (2.4)	10 (1.6)	4 (1.9)
Oral candidiasis	17 (2.6)	5 (0.8)	3 (1.5)
Dysphonia	16 (2.4)	3 (0.5)	2 (1)
Muscle spasms	14 (2.1)	6 (0.9)	0

*SYMBICORT AEROSPHERE=budesonide/formoterol fumarate 320 mcg/9.6 mcg; FF MDI=formoterol fumarate 9.6 mcg; BD MDI=budesonide 320 mcg; all treatments were administered twice daily.

In SOPHOS, the following adverse reactions occurred at an incidence of at least 2% and more frequently in SYMBICORT AEROSPHERE 320 mcg/9.6 mcg than in FF MDI 9.6 mcg: nasopharyngitis (6.6% vs. 5.9%), upper respiratory tract infection (4.5% vs. 4%), dyspnea (3.7% vs. 2.6%), hypertension (2.4% vs. 2.3%), back pain (2.4% vs. 1.8%), influenza (2.4% vs. 1.6%), cough (2.3% vs. 1.5%), diarrhea (2.1% vs. 1.6%), and oral candidiasis (2.1% vs. 1.2%).

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of budesonide or formoterol. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiovascular disorders: angina pectoris, cardiac arrhythmias (e.g., atrial fibrillation, supraventricular tachycardia, and extrasystoles), tachycardia, palpitations

Endocrine disorders: signs or symptoms of systemic glucocorticoid steroid effects (e.g., hypofunctional adrenal gland)

Immune system disorders: bronchospasm, immediate and delayed hypersensitivity reactions (e.g., dermatitis, rash, urticaria, pruritus, angioedema and anaphylactic reaction)

Gastrointestinal disorders: nausea

Infections: pneumonia

Metabolic disorders: hyperglycemia

Neurological or psychiatric system disorders: abnormal behavior, agitation, depression, dizziness, insomnia, nervousness, restlessness, tremor

Respiratory, thoracic, and mediastinal disorders: throat irritation

Skin and subcutaneous tissue disorders: bruising

7 DRUG INTERACTIONS

No formal drug interaction studies have been performed with SYMBICORT AEROSPHERE.

7.1 Inhibitors of Cytochrome P450 3A4

The main route of metabolism of corticosteroids, including budesonide, a component of SYMBICORT AEROSPHERE, is via CYP3A4. After oral administration of ketoconazole, a strong inhibitor of CYP3A4, the mean plasma concentration of orally administered budesonide increased. Concomitant administration of a CYP3A4 inhibitor may inhibit the metabolism of, and increase the systemic exposure to, budesonide. Caution should be exercised when considering the coadministration of SYMBICORT AEROSPHERE with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) *[see Warnings and Precautions (5.9)]*.

7.2 Adrenergic Drugs

If additional adrenergic drugs are to be administered by any route, they should be used with caution because the sympathetic effects of formoterol, a component of SYMBICORT AEROSPHERE, may be potentiated *[see Warnings and Precautions (5.3)]*.

7.3 Xanthine Derivatives, Steroids, or Diuretics

Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate the hypokalemic effect of $beta_2$-adrenergic agonists such as formoterol, a component of SYMBICORT AEROSPHERE.

7.4 Non-Potassium Sparing Diuretics

The ECG changes and/or hypokalemia that may result from the administration of non-potassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded.

7.5 Monoamine Oxidase Inhibitors, Tricyclic Antidepressants, QTc Prolonging Drugs

SYMBICORT AEROSPHERE, as with other $beta_2$-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants or other drugs known to prolong the QTc interval because the action of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval may be associated with an increased risk of ventricular arrhythmias.

7.6 Beta-Adrenergic Receptor Blocking Agents

Beta-adrenergic receptor antagonists (beta-blockers) and SYMBICORT AEROSPHERE may interfere with the effect of each other when administered concurrently. Beta-blockers (including eye drops) not only block the therapeutic effects of $beta_2$-agonists, but may produce severe bronchospasm in asthma and COPD patients. Therefore, patients with asthma or COPD should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-blockers in patients with asthma or

COPD. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data with SYMBICORT AEROSPHERE use during pregnancy to inform the drug-associated risk for major birth defects and miscarriage. Studies are available with its individual components. Available data from published case series, epidemiological studies and reviews of budesonide use during pregnancy have not identified a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. There are insufficient data with formoterol fumarate use during pregnancy to inform a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Beta-agonists may interfere with uterine contractility *(see Clinical Considerations).*

In a rat reproduction study, the combination of budesonide and formoterol fumarate, administered by the inhalation route, was teratogenic and embryocidal at less than the maximum recommended human daily inhalation dose (MRHDID) on a mcg/m^2 basis. Reduced fetal weights were noted at doses similar to or slightly higher than the MRHDID on a mcg/m^2.

Budesonide alone, administered by the subcutaneous route, caused structural abnormalities, was embryocidal, and reduced fetal weights in rats and rabbits at 0.3 and 0.75 times the MRHDID, respectively, but these effects were not seen in rats that received inhaled doses up to 4 times the MRHDID. Experience with oral corticosteroids suggests that rodents are more prone to teratogenic effects from corticosteroid exposure than humans.

Formoterol fumarate alone, administered by the oral route in rats and rabbits, caused structural abnormalities at 1500 and 61,000 times the MRHDID, respectively. Formoterol fumarate was also embryocidal, increased pup loss at birth and during lactation, and decreased pup weight in rats at 110 times the MRHDID. These adverse effects generally occurred at large multiples of the MRHDID when formoterol fumarate was administered by the oral route to achieve high systemic exposures. No structural abnormalities, embryocidal, or developmental effects were seen in rats that received inhalation doses up to 350 times the MRHDID.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

In women with poorly or moderately controlled asthma, there is an increased risk of several perinatal adverse outcomes such as preeclampsia in the mother and prematurity, low birth weight, and small for gestational age in the neonate. Pregnant women with asthma should be closely monitored and medication adjusted as necessary to maintain optimal asthma control.

Labor or Delivery: Because of the potential for beta-agonist interference with uterine contractility, use of SYMBICORT AEROSPHERE during labor should be restricted to those patients in whom the benefits clearly outweigh the risks.

Data

Animal Data

Budesonide and Formoterol Fumarate

In an embryo-fetal development study in pregnant rats dosed during the period of organogenesis from the gestation days 6-16, budesonide and formoterol fumarate administered by the inhalation route was associated with fetal loss and produced umbilical hernia in fetuses at doses less than the MRHDID (on a mcg/m^2 basis at maternal inhaled doses of 12/0.66 mcg/kg/day [budesonide/formoterol] and above, but not at 2.5/0.14 mcg/kg/day). Fetal weights were reduced at doses similar to, or slightly higher than the MRHDID (on an mcg/m^2 basis at a maternal inhaled dose of 80/4.4 mcg/kg).

Budesonide

In a fertility and reproduction study, male rats were subcutaneously dosed for 9 weeks and females for 2 weeks prior to pairing and throughout the mating period. Females were dosed up until weaning of their offspring. Budesonide caused a decrease in prenatal viability and viability of the offspring at birth and during lactation, along with a decrease in maternal body weight gain, at a dose 0.3 times the MRHDID (on a mcg/m^2 basis at maternal subcutaneous doses of 20 mcg/kg/day and above). No such effects were noted at a dose 0.08 times the MRHDID (on a mcg/m^2 basis at a maternal subcutaneous dose of 5 mcg/kg/day).

In an embryo-fetal development study in pregnant rabbits dosed during the period of organogenesis from gestation days 6 to 18, budesonide produced fetal loss, decreased fetal weight, and skeletal abnormalities at a dose 0.75 times the MRHDID (on a mcg/m^2 basis at a maternal subcutaneous dose of 25 mcg/kg/day). In an embryo-fetal development study in pregnant rats dosed during the period of organogenesis from gestation days 6-15, budesonide produced similar adverse fetal effects at doses approximately 8 times the MRHDID (on a mcg/m^2 basis at a maternal subcutaneous dose of 500 mcg/kg/day). In another embryo-fetal development study in pregnant rats, no structural abnormalities or embryocidal effects were seen at doses up to 4 times the MRHDID (on a mcg/m^2 basis at maternal inhalation doses up to 250 mcg/kg/day).

In a peri- and post-natal development study, rats dosed from gestation day 15 to postpartum day 21, budesonide had no effects on delivery, but did affect growth and development of offspring. Offspring survival was reduced, and surviving offspring had decreased mean body weights at birth and during lactation at doses 0.3 times the MRHDID and higher (on a mcg/m^2 basis at maternal subcutaneous doses of 20 mcg/kg/day and higher). These findings occurred in the presence of maternal toxicity.

Formoterol Fumarate

In a fertility and reproduction study, male rats were orally dosed for at least 9 weeks and females for 2 weeks prior to pairing and throughout the mating period. Females were either dosed up to gestation day 19 or up until weaning of their offspring. Males were dosed up to 25 weeks. Umbilical hernia was observed in rat fetuses at oral doses 1500 times the MRHDID (on a mcg/m^2 basis at maternal oral doses of 3000 mcg/kg/day and higher). Brachygnathia was observed in rat fetuses at a dose 8000 times the MRHDID (on a mcg/m^2 basis at a maternal oral dose of 15,000 mcg/kg/day). Pregnancy was prolonged at a dose 8000 times the MRHDID (on a mcg/m^2 basis at a maternal oral dose of 15,000 mcg/kg/day). Fetal and pup deaths occurred at doses approximately 1500 times the MRHDID and higher (on a mcg/m^2 basis at oral doses of 3000 mcg/kg/day and higher) during gestation.

In an embryo-fetal development study in pregnant rats dosed during the period of organogenesis from gestation days 6 to 15, no structural abnormalities, embryocidal effects, or developmental effects were seen at doses up to 350 times the MRHDID (on a mcg/m^2 basis with maternal inhalation doses up to 690 mcg/kg/day).

In an embryo-fetal development study in pregnant rabbits dosed during the period of organogenesis from gestation days 6 to 18, subcapsular cysts on the liver were observed in the fetuses at a dose 61,000 times the MRHDID (on a mcg/m^2 basis with a maternal oral dose of 60,000 mcg/kg/day). No teratogenic effects were observed at doses up to 3500 times the MRHDID (on a mcg/m^2 basis at maternal oral doses up to 3500 mcg/kg/day).

In a pre- and post-natal development study, pregnant female rats received formoterol at oral doses of 0, 210, 840, and 3400 mcg/kg/day from gestation day 6 (completion of implantation) through the lactation period. Pup survival was decreased from birth to postpartum day 26 at doses 110 times the MRHDID and higher (on a mcg/m^2 basis at maternal oral doses of 210 mcg/kg/day and higher), although there was no evidence of a dose-response relationship. There were no treatment-related effects on the physical, functional, and behavioral development of rat pups.

8.2 Lactation

Risk Summary

Budesonide, like other ICS, is present in human milk *(see Data).* There are no available data on the presence of formoterol fumarate in human milk. Formoterol fumarate has been detected in the plasma of undosed rat pups suckling from exposed dams *(see Data)*. There are no available data on the effects of SYMBICORT AEROSPHERE, budesonide or formoterol fumarate on the breastfed child or on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SYMBICORT AEROSPHERE and any potential adverse effects on the breast-fed child from SYMBICORT AEROSPHERE or from the underlying maternal condition.

Data

Human Data

Human data with budesonide delivered via dry powder inhaler indicates that the total daily oral dose of budesonide available in breast milk to the infant is approximately 0.3% to 1% of the dose inhaled by the mother. For SYMBICORT AEROSPHERE, the dose of budesonide available to the infant in breast milk, as a percentage of the maternal dose, would be expected to be similar.

Animal Data

In the fertility and reproduction study in rats, plasma levels of formoterol were measured in pups on post-natal day 15 *[see Use in Specific Populations (8.1)]*. It was estimated that the maximum plasma concentration that the pups received from the maternal animal, at the highest dose of 15 mg/kg, after nursing was 4.4% (0.24 nmol/L for a litter vs. 5.5 nmol/L for the mother).

8.4 Pediatric Use

The safety and effectiveness of SYMBICORT AEROSPHERE have been established for the treatment of asthma in pediatric patients 12 years of age and older. Use of SYMBICORT AEROSPHERE in this indication is supported by evidence from two adequate and well-controlled trials (LITHOS and VATHOS) in patients 12 years of age and older with asthma. In the LITHOS and VATHOS trials, 15 pediatric patients 12 to 17 years of age were treated with SYMBICORT AEROSPHERE twice daily *[see Adverse Reactions (6.1) and Clinical Studies (14.1)]*.

Controlled clinical studies have shown that ICS agents, including budesonide, one of the components of SYMBICORT AEROSPHERE, may cause a reduction in growth velocity in pediatric patients. The effects of long-term treatment of pediatric patients with ICS on final adult height are not known. The potential growth effects of prolonged treatment should be weighed against the clinical benefits obtained *[see Warnings and Precautions (5.14)]*.

The safety and effectiveness of SYMBICORT AEROSPHERE have not been established in pediatric patients younger than 12 years of age.

8.5 Geriatric Use

There were 66 patients and 112 patients 65 years of age and older in the asthma trials LITHOS and VATHOS, respectively *[see Clinical Studies (14.1)]*. Of the total number of SYMBICORT AEROSPHERE-treated patients in these trials, 32 (18%) in LITHOS and 50 (20%) in VATHOS were 65 years of age and older, while 9 (2.6%) patients in LITHOS and 10 (1.7%) patients in VATHOS were 75 years of age and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, but greater sensitivity in some older individuals cannot be ruled out.

There were 1229 patients and 999 patients 65 years of age and older in the COPD trials TELOS and SOPHOS, respectively *[see Clinical Studies (14.2)]*. Of the total number of SYMBICORT AEROSPHERE-treated patients in these trials, 333 (51%) in TELOS and 347 (56%) in SOPHOS were 65 years of age and older, while 65 (10%) patients in TELOS and 87 (14%) patients in SOPHOS were 75 years of age and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, but greater sensitivity in some older individuals cannot be ruled out.

Based on available data for SYMBICORT AEROSPHERE or its active components, no adjustment of dosage of SYMBICORT AEROSPHERE in geriatric patients is warranted.

8.6 Hepatic Impairment

Formal pharmacokinetic studies using SYMBICORT AEROSPHERE have not been conducted in patients with hepatic impairment. However, since budesonide and formoterol fumarate are predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of budesonide and formoterol fumarate in plasma. Therefore, patients with severe hepatic disease should be closely monitored.

8.7 Renal Impairment

Formal pharmacokinetic studies using SYMBICORT AEROSPHERE have not been conducted in patients with renal impairment.

10 OVERDOSAGE

SYMBICORT AEROSPHERE contains both budesonide and formoterol fumarate; therefore, the risks associated with overdosage for the individual components described below apply to SYMBICORT AEROSPHERE. Treatment of overdosage consists of discontinuation of SYMBICORT AEROSPHERE together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. Cardiac monitoring is recommended in cases of overdosage.

Consider contacting the Poison Help line (1-800-222-1222) or a medical toxicologist for additional overdose management recommendations.

Budesonide

If used at excessive doses for prolonged periods, systemic corticosteroid effects such as hypercorticism may occur *[see Warnings and Precautions (5.8)]*.

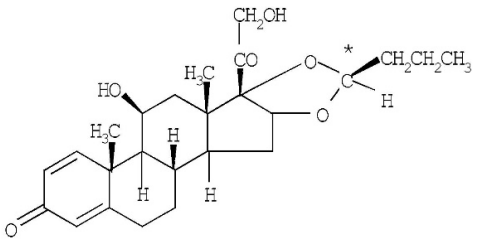
Formoterol Fumarate

An overdosage of formoterol would likely lead to an exaggeration of effects that are typical for beta$_2$-agonists: seizures, angina, hypertension, hypotension, tachycardia, atrial and ventricular tachyarrhythmias, nervousness, headache, tremor, palpitations, muscle cramps, nausea, dizziness, sleep disturbances, metabolic acidosis, hyperglycemia, hypokalemia. As with all sympathomimetic medications, cardiac arrest and even death may be associated with overdosage of formoterol fumarate.

11 DESCRIPTION

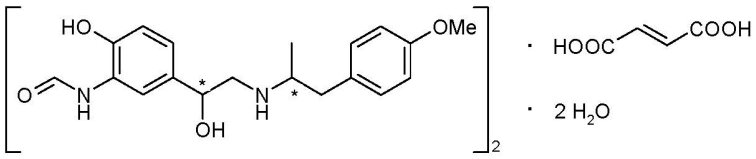
SYMBICORT AEROSPHERE (budesonide and formoterol fumarate) Inhalation Aerosol is a pressurized metered-dose inhaler that delivers a combination of micronized budesonide [an inhaled corticosteroid (ICS)], and micronized formoterol fumarate [an inhaled long-acting beta$_2$-adrenergic agonist (a LABA)] for oral inhalation.

Budesonide is a corticosteroid with the following chemical name: (RS)-11β, 16α, 17,21-Tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with butyraldehyde. Budesonide is a white to off-white, powder which is practically insoluble in water. The molecular formula is $C_{25}H_{34}O_6$ and the molecular weight is 430.54. The structural formula is as follows:



Budesonide contains nine chiral centers and is a mixture of the two epimers (22R and 22S).

Formoterol fumarate has the chemical name N-[2-Hydroxy-5-[(1RS)-1-hydroxy-2-[[(1RS)-2-(4-methoxyphenyl)-1-methylethyl]-amino] ethyl] phenyl] formamide, (E)-2-butenedioate dihydrate. Formoterol fumarate is a powder that is slightly soluble in water. The molecular formula is $(C_{19}H_{24}N_2O_4)_2 \cdot C_4H_4O_4 \cdot 2H_2O$ and the molecular weight is 840.91 g/mol. The structural formula is as follows:



Formoterol fumarate contains two chiral centers and consists of a single enantiomeric pair (a racemate of R,R and S,S).

SYMBICORT AEROSPHERE is formulated as a hydrofluoroalkane (HFA 134a) propelled pressurized metered dose inhaler containing 120 inhalations. The canister has an attached dose indicator and is supplied with a white plastic actuator body and mouthpiece with a grey dust cap.

After priming, each actuation of the inhaler meters 85 or 170 mcg of budesonide and 5.1 mcg of formoterol fumarate (equivalent to 4.4 mcg of formoterol) from the valve which delivers 80 or 160 mcg of budesonide and 4.8 mcg of formoterol fumarate (equivalent to 4.1 mcg of formoterol) from the actuator. The actual amount of drug delivered to the lung may depend on patient factors, such as the coordination between actuation of the device and inspiration through the

delivery system. SYMBICORT AEROSPHERE also contains porous particles that form a co-suspension with the drug crystals. The porous particles are comprised of the phospholipid, 1,2-distearoyl-*sn*-glycero-3-phosphocholine (DSPC), and calcium chloride. Porous particles and HFA 134a are excipients in the formulation.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

SYMBICORT AEROSPHERE

SYMBICORT AEROSPHERE contains budesonide and formoterol fumarate. The mechanism of action described below for the individual components applies to SYMBICORT AEROSPHERE. These drugs represent two different classes of medications (a synthetic corticosteroid and a long-acting selective $beta_2$-adrenoceptor agonist) that have different effects on clinical physiology and inflammatory indices of asthma and COPD.

Budesonide

Budesonide is an anti-inflammatory corticosteroid that exhibits potent glucocorticoid activity and weak mineralocorticoid activity. In standard *in vitro* and animal models, budesonide has approximately a 200-fold higher affinity for the glucocorticoid receptor and a 1000-fold higher topical anti-inflammatory potency than cortisol (rat croton oil ear edema assay). As a measure of systemic activity, budesonide is 40 times more potent than cortisol when administered subcutaneously and 25 times more potent when administered orally in the rat thymus involution assay.

In glucocorticoid receptor affinity studies, the 22R epimer of budesonide was two times as active as the 22S epimer. *In vitro* studies indicated that the two forms of budesonide do not interconvert.

Airway inflammation is an important component in the pathogenesis of asthma and COPD. Corticosteroids have a wide range of inhibitory activities against multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in allergic and non-allergic-mediated inflammation. These anti-inflammatory actions of corticosteroids may contribute to their efficacy.

Formoterol Fumarate

Formoterol fumarate is a long-acting selective $beta_2$-adrenergic agonist ($beta_2$-agonist) with a rapid onset of action. Inhaled formoterol fumarate acts locally in the lung as a bronchodilator. *In vitro* studies have shown that formoterol has more than 200-fold greater agonist activity at $beta_2$-receptors than at $beta_1$-receptors. The *in vitro* binding selectivity to $beta_2$- over $beta_1$-adrenoceptors is higher for formoterol than for albuterol (5 times), whereas salmeterol has a higher (3 times) $beta_2$-selectivity ratio than formoterol.

Although $beta_2$-receptors are the predominant adrenergic receptors in bronchial smooth muscle and $beta_1$-receptors are the predominant receptors in the heart, there are also $beta_2$-receptors in the human heart comprising 10% to 50% of the total beta-adrenergic receptors. The precise function of these receptors has not been established, but they raise the possibility that even highly selective $beta_2$-agonists may have cardiac effects.

The pharmacologic effects of $beta_2$-adrenoceptor agonist drugs, including formoterol fumarate, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

12.2 Pharmacodynamics

Cardiac Electrophysiology

A TQT study was not performed with SYMBICORT AEROSPHERE as budesonide is not known to affect the QT interval. However, the potential for QTc interval prolongation with formoterol fumarate was assessed in a double-blind, single-dose, placebo- and positive-controlled crossover trial in 69 healthy subjects treated with glycopyrrolate and formoterol fumarate. Although this was a study of a dose combination with glycopyrrolate, the dose of formoterol fumarate relevant to SYMBICORT AEROSPHERE was included. The largest mean (90% upper confidence bound) differences from placebo in baseline-corrected QTcI for 2 inhalations of glycopyrrolate/formoterol fumarate 9 mcg/4.8 mcg and glycopyrrolate/formoterol fumarate 72 mcg/19.2 mcg, were 3.1 (4.7) ms and 7.6 (9.2) ms, respectively, and excluded the clinically relevant threshold of 10 ms. A dose-dependent increase in heart rate was also observed. The largest mean (90% upper confidence bound) differences from placebo in baseline-corrected heart rate were 3.3 (4.9) beats/min and 7.6 (9.5) beats/min seen within 10 minutes of dosing with 2 inhalations of glycopyrrolate/formoterol fumarate 9 mcg/4.8 mcg and glycopyrrolate/formoterol fumarate 72 mcg/19.2 mcg, respectively.

Chronic Obstructive Pulmonary Disease

The effects of SYMBICORT AEROSPHERE on cardiac rhythm in subjects with COPD was assessed using 24-hour Holter monitoring at Week 16 in a 52-week trial. The Holter monitoring population included 183 subjects on SYMBICORT AEROSPHERE. No clinically meaningful effects on cardiac rhythm were observed.

HPA Axis Effects

Effects of SYMBICORT AEROSPHERE on the HPA axis were assessed by measurement of 24-hour serum cortisol at Baseline and Week 24 in subjects with COPD. The geometric mean ratio of Week 24 over Baseline (Co-efficient of variation [CV] %) was 0.73 (31%) (n=19) for SYMBICORT AEROSPHERE 320 mcg/9.6 mcg, 0.86 (38.8%) (n=44) for BGF (budesonide 320 mcg, glycopyrrolate 18 mcg, and formoterol fumarate 9.6 mcg) MDI , and 0.94 (36.6%) (n=33) for GFF (glycopyrrolate 18 mcg and formoterol fumarate 9.6 mcg) MDI. The cause of different ratios of 24-hour serum cortisol between SYMBICORT AEROSPHERE and BGF MDI is unclear. A smaller sample size and numerically higher baseline cortisol value were associated with SYMBICORT AEROSPHERE group compared with other groups in the study.

12.3 Pharmacokinetics

Absorption

Budesonide: Following inhaled administration of SYMBICORT AEROSPHERE in subjects with COPD, C_{max} occurred within 20 to 60 minutes. Steady state is estimated to be achieved after approximately 1 day of repeated dosing of SYMBICORT AEROSPHERE via population pharmacokinetic analysis and the AUC_{0-12} is approximately 1.3 times higher than after the first dose.

Formoterol Fumarate: Following inhaled administration of SYMBICORT AEROSPHERE in subjects with COPD, C_{max} occurred within 40 to 60 minutes. Steady state is estimated to be achieved after approximately 2 days of repeated dosing of SYMBICORT AEROSPHERE via population pharmacokinetic analysis and the AUC_{0-12} is approximately 1.4 times higher than after the first dose.

Distribution

Budesonide: The estimated budesonide apparent volume of distribution at steady-state in subjects with COPD is approximately 1200 L, via population pharmacokinetic analysis. Over the concentration range of 1-100 nmol/L, mean plasma protein binding of budesonide ranged from 86% to 87%.

Formoterol Fumarate: The estimated formoterol apparent volume of distribution at steady-state in subjects with COPD is approximately 2400 L, via population pharmacokinetic analysis. Over the concentration range of 10-500 nmol/L, plasma protein binding of formoterol ranged from 46% to 58%.

Elimination

Budesonide: Budesonide was excreted in urine and feces in the form of metabolites. Only negligible amounts of unchanged budesonide have been detected in the urine. The effective half-life of budesonide in subjects with COPD derived via population pharmacokinetic analysis was approximately 5 hours.

Formoterol Fumarate: The excretion of formoterol was studied in six healthy subjects following simultaneous administration of radiolabeled formoterol via the oral and IV routes. In that study, 62% of the drug related radioactivity of formoterol was excreted in the urine while 24% was eliminated in the feces. The effective half-life of formoterol in subjects with COPD derived via population pharmacokinetics analysis was approximately 10 hours.

Metabolism

Budesonide: In vitro studies with human liver homogenates have shown that budesonide was rapidly and extensively metabolized. Two major metabolites formed via CYP3A4-catalyzed biotransformation have been isolated and identified as 16α-hydroxyprednisolone and 6ß-hydroxybudesonide. The corticosteroid activity of each of these two metabolites was less than 1% of that of the parent compound. No qualitative differences between the *in vitro* and *in vivo* metabolic patterns were detected. Negligible metabolic inactivation was observed in human lung and serum preparations.

Formoterol Fumarate: The primary metabolism of formoterol is by direct glucuronidation and by O-demethylation followed by conjugation to inactive metabolites. Secondary metabolic pathways include deformylation and sulfate conjugation. CYP2D6 and CYP2C have been identified as being primarily responsible for O-demethylation.

Specific Populations

Population pharmacokinetic analysis showed no evidence of a clinically significant effect of age, sex, race/ethnicity, or body weight on the pharmacokinetics of budesonide or formoterol.

Patients with Hepatic Impairment

Dedicated studies of SYMBICORT AEROSPHERE evaluating effect of hepatic impairment on the pharmacokinetics of budesonide and formoterol were not conducted.

Reduced liver function may affect the elimination of corticosteroids. Budesonide pharmacokinetics was affected by compromised liver function as evidenced by a doubled systemic availability after oral ingestion. The intravenous budesonide pharmacokinetics were, however, similar in cirrhotic patients and in healthy subjects.

As budesonide and formoterol are primarily eliminated via hepatic metabolism, an increased systemic exposure can be expected in patients with severe hepatic impairment.

Patients with Renal Impairment

Studies with SYMBICORT AEROSPHERE evaluating the effect of renal impairment on the pharmacokinetics of budesonide and formoterol were not conducted.

The effect of renal impairment on the systemic exposure to budesonide and formoterol for up to 24 weeks was evaluated in a population pharmacokinetic analysis. Renal function was found not to significantly affect exposure to budesonide or formoterol after drug clearance adjusted by age or body weight in a population pharmacokinetic analysis.

Drug Interaction Studies

No pharmacokinetic interaction has been observed between budesonide and formoterol fumarate when administered in combination by the inhaled route. Specific drug interaction studies of SYMBICORT AEROSPHERE with other co-administered drugs have not been performed.

Ketoconazole and Itraconazole: Ketoconazole and itraconazole, strong inhibitors of CYP3A4, the main metabolic enzyme for corticosteroids, increased plasma levels of orally ingested budesonide and orally inhaled budesonide, respectively.

Cimetidine: At recommended doses, cimetidine, a non-specific inhibitor of CYP enzymes, had a slight but clinically insignificant effect on the pharmacokinetics of oral budesonide.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies of carcinogenicity, mutagenicity, or impairment of fertility were conducted with SYMBICORT AEROSPHERE; however, separate studies of budesonide and formoterol fumarate are described below.

Budesonide

Long-term studies were conducted in rats and mice using oral administration to evaluate the carcinogenic potential of budesonide.

In a 2-year study in Sprague-Dawley rats, budesonide caused a statistically significant increase in the incidence of gliomas in male rats at an oral dose of 50 mcg/kg (approximately equivalent to the MRHDID on a mcg/m^2 basis). No tumorigenicity was seen in male and female rats at respective oral doses up to 25 and 50 mcg/kg (approximately equivalent to the MRHDID on a mcg/m^2 basis). In two additional 2-year studies in male Fischer and Sprague-Dawley rats, budesonide caused no gliomas at an oral dose of 50 mcg/kg (approximately equivalent to the MRHDID on a mcg/m^2 basis). However, in the male Sprague-Dawley rats, budesonide caused a statistically significant increase in the incidence of hepatocellular tumors at an oral dose of 50 mcg/kg (approximately equivalent to the MRHDID on a mcg/m^2 basis). The concurrent reference corticosteroids (prednisolone and triamcinolone acetonide) in these two studies showed similar findings.

In a 91-week carcinogenicity study in mice, budesonide produced no treatment-related increases in the incidence of tumors at oral doses up to 200 mcg/kg (approximately 2 times the MRHDID on a mcg/m^2 basis).

Budesonide was not mutagenic or clastogenic in the Ames *Salmonella*/microsome plate test, mouse micronucleus test, mouse lymphoma test, chromosome aberration test in human lymphocytes, sex-linked recessive lethal test in *Drosophila melanogaster*, and DNA repair analysis in rat hepatocyte culture.

Fertility and reproductive performance were unaffected in rats at subcutaneous doses up to 80 mcg/kg (approximately equal to the MRHDID on a mcg/m^2 basis). However, it caused a decrease in prenatal viability and viability in the pups at birth and during lactation, along with a decrease in maternal body-weight gain, at subcutaneous doses of 20 mcg/kg and above (0.3 times the MRHDID on a mcg/m^2 basis). No such effects were noted at 5 mcg/kg (0.08 times the MRHDID on a mcg/m^2 basis).

Formoterol Fumarate

Long-term studies were conducted in mice using oral administration and rats using inhalation administration to evaluate the carcinogenic potential of formoterol fumarate.

In a 24-month carcinogenicity study in CD-1 mice, formoterol fumarate at oral doses of 100 mcg/kg and above (approximately 25 times MRHDID on a mcg/m^2 basis) caused a dose-related increase in the incidence of uterine leiomyomas.

In a 24-month carcinogenicity study in Sprague-Dawley rats, an increased incidence of mesovarian leiomyoma and uterine leiomyosarcoma were observed at the inhaled dose of 130 mcg/kg (approximately 65 times the MRHDID on a mcg/m^2 basis). No tumors were seen at 22 mcg/kg (approximately 10 times the MRHDID on a mcg/m^2 basis).

Other beta-agonist drugs have similarly demonstrated increases in leiomyomas of the genital tract in female rodents. The relevance of these findings to human use is unknown.

Formoterol fumarate was not mutagenic or clastogenic in Ames *Salmonella*/microsome plate test, mouse lymphoma test, chromosome aberration test in human lymphocytes, or rat micronucleus test.

A reduction in fertility and/or reproductive performance was identified in male rats treated with formoterol at an oral dose of 15,000 mcg/kg, (approximately 2600 times the MRHDID on an AUC basis). No such effect was seen at 3000 mcg/kg (approximately 1500 times the MRHDID on a mcg/m^2 basis). In a separate study with male rats treated with an oral dose of 15,000 mcg/kg (approximately 8000 times the MRHDID on a mcg/m^2 basis), there were findings of testicular tubular atrophy and spermatic debris in the testes and oligospermia in the epididymides. No effect on fertility was detected in female rats at doses up to 15,000 mcg/kg (approximately 1400 times the MRHDID on an AUC basis).

14 CLINICAL STUDIES

14.1 Asthma

The efficacy of SYMBICORT AEROSPHERE for treatment of asthma in adult and pediatric patients 12 years of age and older with mild to severe asthma was evaluated in two randomized, double-blind, multicenter, parallel group trials, LITHOS [NCT05755906] and VATHOS [NCT05202262], for 12 weeks and 24 weeks.

The LITHOS trial evaluated SYMBICORT AEROSPHERE in a patient population with asthma inadequately controlled (Asthma Control Questionnaire (ACQ-7) score ≥1.5) despite treatment with low dose inhaled corticosteroid (ICS) or ICS/long-acting beta$_2$-agonist (LABA) and with a screening pre-bronchodilator FEV_1 of 50 to ≤90% predicted normal value.

In the LITHOS trial, a total of 357 adult and pediatric patients aged 12 years and older were randomized (1:1) to receive SYMBICORT AEROSPHERE 160 mcg/9.6 mcg (2 actuations of SYMBICORT AEROSPHERE 80 mcg/4.8 mcg [budesonide/formoterol fumarate 160 mcg/9.6 mcg]) or budesonide 160 mcg (BD MDI) administered by oral inhalation twice daily. BD MDI used the same inhaler and excipients as SYMBICORT AEROSPHERE. Of those randomized, efficacy of SYMBICORT AEROSPHERE is based on 346 patients in the LITHOS trial.

The demographics of the study population in LITHOS had a mean age of 48 years (range: 12 to 79 years), 30% male, 67% White, 10% Black, 17% Asian, and 6% Other, and 23% of Hispanic or Latino ethnicity. At baseline, the mean pre-bronchodilator percent predicted FEV_1 was 70% (range 50% to 90%) and the mean ACQ-7 score was 2.4 (range 0.6 to 5.3).

The VATHOS trial evaluated SYMBICORT AEROSPHERE in a patient population with asthma inadequately controlled (ACQ-7 score ≥1.5) despite treatment with medium dose ICS or ICS/ LABA and with a screening pre-bronchodilator FEV_1 of 50 to ≤90% predicted normal value.

In the VATHOS trial, a total of 585 adult and pediatric patients aged 13 years and older were randomized (2:1:2:2) to receive SYMBICORT AEROSPHERE 320 mcg/9.6 mcg (2 actuations of SYMBICORT AEROSPHERE 160 mcg/4.8 mcg [budesonide/formoterol fumarate 320 mcg/9.6 mcg]), SYMBICORT AEROSPHERE 160 mcg/9.6 mcg (2 actuations of SYMBICORT AEROSPHERE 80 mcg/4.8 mcg [budesonide/formoterol fumarate 160 mcg/9.6 mcg]), budesonide 320 mcg (BD MDI), or open label budesonide and formoterol fumarate 320 mcg/9 mcg (inhalation powder), administered by oral inhalation twice daily. BD MDI used the same inhaler and excipients as SYMBICORT AEROSPHERE. Of those randomized, efficacy of SYMBICORT AEROSPHERE is based on 575 patients in the VATHOS trial.

The demographics of the study population in VATHOS had a mean age of 50 years (range: 13 to 78 years), 38% male, 73% White, 11% Black, 12% Asian, and 4% Other, and 21% of Hispanic or Latino ethnicity. At baseline, the mean pre-bronchodilator percent predicted FEV_1 was 71% (range 50% to 89%) and the mean ACQ-7 score was 2.3 (range 1.3 to 4.7).

Lung Function

The primary endpoint for the LITHOS and VATHOS trials was FEV_1 area under the curve from 0-3 hours (FEV_1 AUC_{0-3}) for SYMBICORT AEROSPHERE compared to BD MDI at Week 12 or Week 24, respectively. The key secondary endpoint for LITHOS and VATHOS was the trough FEV_1 at Week 12 and Week 24, respectively. LITHOS and VATHOS also evaluated whether onset of action occurred within 5 minutes, as defined by absolute change in FEV_1 at 5 minutes post-dose at Day 1 compared to BD MDI 320 mcg.

In LITHOS, treatment with SYMBICORT AEROSPHERE 160 mcg/9.6 mcg resulted in a significant increase in FEV_1 AUC_{0-3} and trough FEV_1 relative to BD MDI 160 mcg at Week 12 (Table 4). The effects on lung function (mean change from baseline in morning pre-dose trough FEV_1) of SYMBICORT AEROSPHERE 160 mcg/9.6 mcg compared with BD MDI 160 mcg were observed over the course of the trial (Figure 1). SYMBICORT AEROSPHERE 160 mcg/9.6 mcg demonstrated a difference of 153 mL in absolute change in FEV_1 at 5 minutes post-dose at Day 1 compared to BD MDI 160 mcg (95% CI: 114, 192).

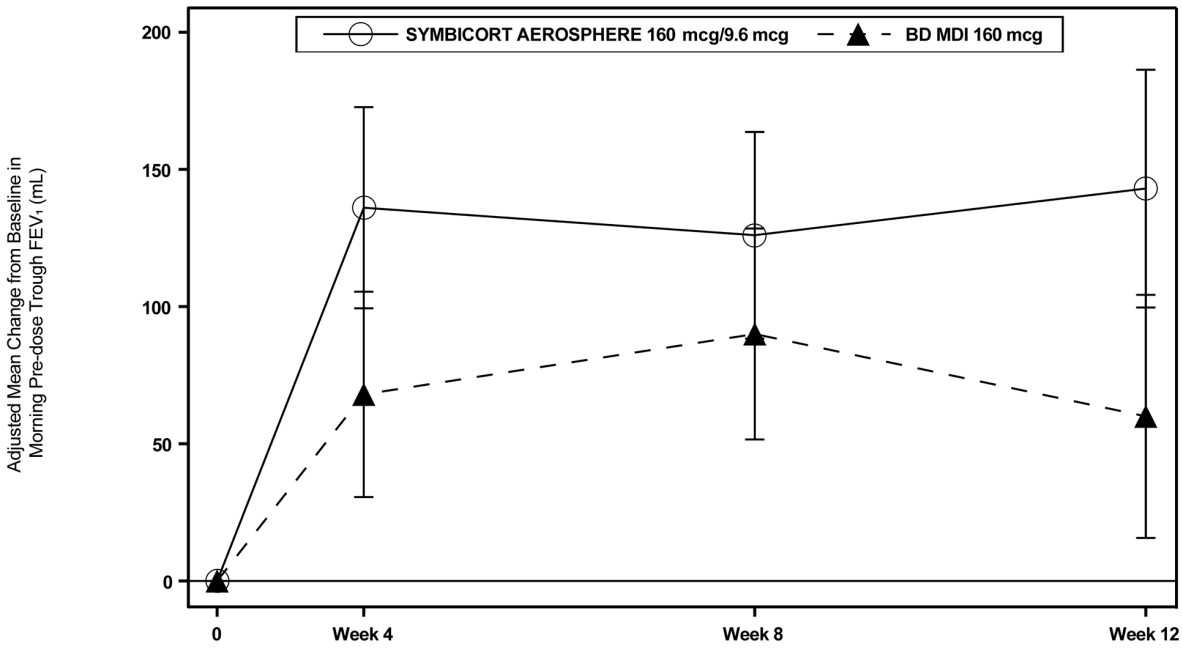
In VATHOS, treatment with SYMBICORT AEROSPHERE 320 mcg/9.6 mcg resulted in a significant increase in FEV_1 AUC_{0-3} and trough FEV_1 relative to BD MDI 320 mcg at Week 24 (Table 4). The effects on lung function (mean change from baseline in morning pre-dose trough FEV_1) of SYMBICORT AEROSPHERE 320 mcg/9.6 mcg compared with BD MDI 320 mcg were observed over the course of the trial (Figure 2). SYMBICORT AEROSPHERE 320 mcg/9.6 mcg demonstrated a difference of 144 mL in absolute change in FEV_1 at 5 minutes post-dose at Day 1 compared to BD MDI 320 mcg (95% CI: 110, 177).

Table 4: Least Squares Mean Change from Baseline in FEV_1 AUC_{0-3} (mL) and Morning Pre-dose Trough FEV_1 (mL) in Patients Aged 12 Years and Older with Asthma at Week 12 (LITHOS) and Week 24 (VATHOS)

LITHOS		
	Difference in FEV_1 AUC_{0-3} at Week 12 (95% CI)	**Difference in Trough FEV_1 at Week 12 (95% CI)**
SYMBICORT AEROSPHERE 160 mcg/9.6 mcg twice daily (N=177)* **vs** **BD MDI 160 mcg twice daily (N=169)***	200 (134, 267)	82 (20, 144)
VATHOS†		
	Difference in FEV_1 AUC_{0-3} at Week 24 (95% CI)	**Difference in Trough FEV_1 at Week 24 (95% CI)**
SYMBICORT AEROSPHERE 320 mcg/9.6 mcg twice daily (N=161)* **vs** **BD MDI 320 mcg twice daily (N=166)***	173 (112, 233)	61 (1, 120)

*Number of patients per treatment group contributing to the efficacy analysis with at least 1 change from baseline value.
†VATHOS included four treatment groups but efficacy results are provided for SYMBICORT AEROSPHERE 320 mcg/9.6 mcg compared to BD MDI 320 mcg.

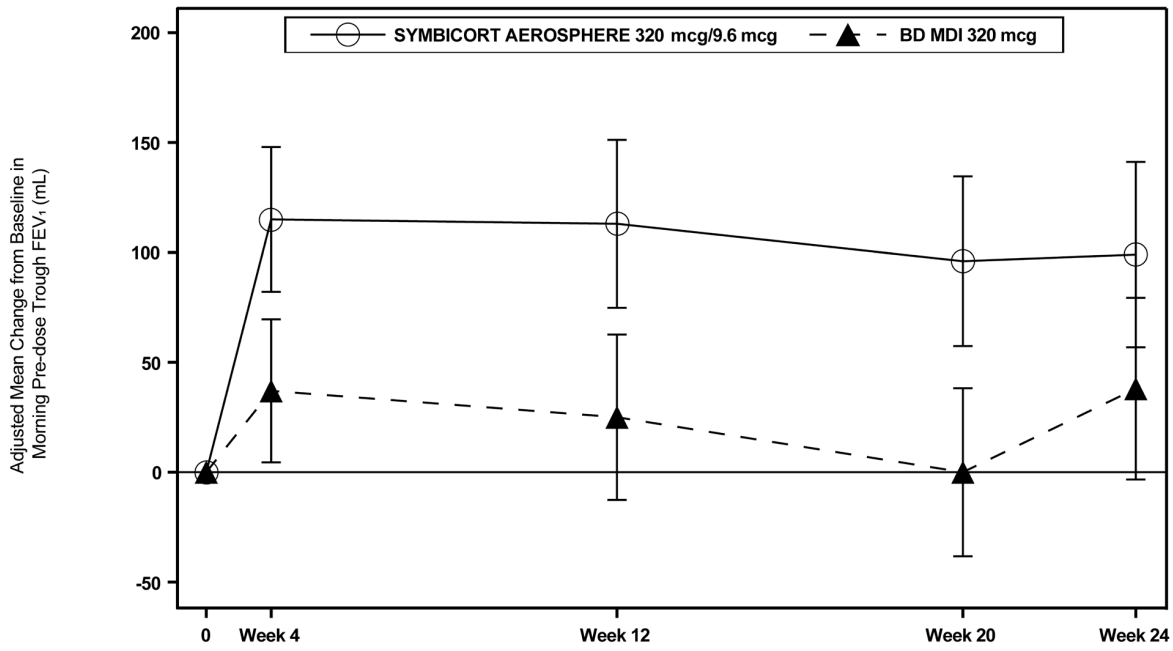
Figure 1: Adjusted Mean Change from Baseline in Morning Pre-dose Trough FEV_1 Over Time in Patients Aged 12 Years and Older with Asthma (LITHOS)



Number of Patients				
SYMBICORT AEROSPHERE 160 mcg/9.6 mcg	177	173	171	175
BD MDI 160 mcg	169	167	166	168

Error bars represent the 95% Confidence Intervals for Adjusted Mean Change from Baseline at each timepoint.

Figure 2: Adjusted Mean Change from Baseline in Morning Pre-dose Trough FEV_1 Over Time in Patients Aged 12 Years and Older with Asthma (VATHOS)



Number of Patients					
SYMBICORT AEROSPHERE 320 mcg/9.6 mcg	161	160	155	158	155
BD MDI 320 mcg	166	165	160	160	161

Error bars represent the 95% Confidence Intervals for Adjusted Mean Change from Baseline at each timepoint.

Exacerbations

In the clinical trials, mean annual rate of severe exacerbations in LITHOS was 0.25 for SYMBICORT AEROSPHERE 160 mcg/9.6 mcg and 0.52 for BD MDI 160 mcg (rate ratio: 0.48; 95% CI: 0.23, 0.97), and in VATHOS 0.36 for SYMBICORT AEROSPHERE 320 mcg/9.6 mcg and 0.35 for BD MDI 320 mcg (rate ratio 1.02; 95% CI: 0.61,1.70).

Use of Rescue Medication

In both LITHOS and VATHOS, SYMBICORT AEROSPHERE significantly reduced the use of rescue medication (measured as mean change from baseline in puffs per day) compared with BD MDI. In LITHOS, comparing SYMBICORT AEROSPHERE 160 mcg/9.6 mcg with BD MDI 160 mcg, the difference was -0.28 puffs/day (95% CI: -0.48, -0.08) over 12 weeks and in VATHOS, comparing SYMBICORT AEROSPHERE 320 mcg/9.6 mcg with BD MDI 320 mcg, a similar trend was observed (difference was -0.27 puffs/day over 24 weeks).

Health-Related Quality of Life

The subjective impact of asthma on patients' health-related quality of life was evaluated through the use of the standardized Asthma Quality of Life Questionnaire (AQLQ(s)+12; based on a 7-point scale where 1 = severe impairment and 7 = no impairment). Patients receiving SYMBICORT AEROSPHERE had clinically meaningful improvements in overall asthma-specific quality of life using a responder analysis, responders were defined as those with an improvement of 0.5 or more in AQLQ score at Week 12 (LITHOS) or Week 24 (VATHOS) compared to baseline. In LITHOS, treatment with SYMBICORT AEROSPHERE 160 mcg/9.6 mcg significantly increased the percentage of AQLQ(s)+12

responders (62%) compared with BD MDI 160 mcg (48%) at Week 12 (odds ratio 1.9; 95% CI: 1.2, 3.0). In VATHOS, the AQLQ(s)+12 responder rate at Week 24 also favored SYMBICORT AEROSPHERE 320 mcg/9.6 mcg (58%) when compared to BD MDI 320 mcg (47%) at Week 24.

14.2 Chronic Obstructive Pulmonary Disease

The efficacy of SYMBICORT AEROSPHERE for maintenance treatment of COPD was evaluated in two randomized, double-blind, multicenter, parallel-group trials (TELOS [NCT02766608] and SOPHOS [NCT02727660]) in patients with COPD who remained symptomatic despite maintenance treatment for COPD.

TELOS included patients with moderate to very severe COPD who had airflow limitation and remained symptomatic despite treatment with at least 1 inhaled maintenance bronchodilator. Patients had a screening post-bronchodilator FEV_1/FVC ratio of less than 0.70 and a post-bronchodilator FEV_1 of less than 80% predicted normal value, and were not required to have a history of moderate or severe exacerbations in the year prior to screening.

TELOS was conducted over 24 weeks in a total of 2389 patients randomized (3:3:3:1:1) to receive SYMBICORT AEROSPHERE 320 mcg/9.6 mcg (2 actuations of SYMBICORT AEROSPHERE 160 mcg/4.8 mcg [budesonide/formoterol fumarate 160 mcg/4.8 mcg]), budesonide and formoterol fumarate 160 mcg/9.6 mcg, formoterol fumarate 9.6 mcg (FF MDI), budesonide 320 mcg (BD MDI), or open label budesonide and formoterol fumarate 320 mcg/9 mcg (inhalation powder), administered by oral inhalation twice daily. FF MDI and BD MDI used the same inhaler and excipients as SYMBICORT AEROSPHERE. Only the results of the approved dosage for COPD (SYMBICORT AEROSPHERE 320 mcg/9.6 mcg twice daily) are described in this section.

The population demographics in TELOS were: mean age of 64 years (range: 40 to 81 years), 61% male, 97% White, 3% Black and <1% Other, and an average smoking history of 45 pack-years, with 53% identified as current smokers. The mean post-bronchodilator percent predicted FEV_1 was 53% (range 19% to 83%). At study entry, the most common COPD treatments were ICS + LABA (41%), LAMA + LABA (18%), and LAMA (12%). Most patients (51%) were not taking ICS as part of a COPD treatment regimen.

In TELOS, the primary endpoints were FEV_1 area under the curve from 0-4 hours (FEV_1 AUC_{0-4}) for SYMBICORT AEROSPHERE 320 mcg/9.6 mcg compared to BD MDI 320 mcg and change from baseline in morning pre-dose trough FEV_1 for SYMBICORT AEROSPHERE 320 mcg/9.6 mcg compared to FF MDI 9.6 mcg at Week 24.

SOPHOS included patients with moderate to very severe COPD who remained symptomatic while receiving at least 1 inhaled maintenance bronchodilator. Patients had a screening post-bronchodilator FEV_1/FVC ratio of less than 0.7 and a post-bronchodilator FEV_1 of less than 80% predicted normal value, and a history of 1 or more moderate or severe COPD exacerbation in the year prior to screening.

SOPHOS was conducted over 12-52 weeks in a total of 1876 patients randomized (1:1:1) to receive SYMBICORT AEROSPHERE 320 mcg/9.6 mcg (2 actuations of SYMBICORT AEROSPHERE 160 mcg/4.8 mcg [budesonide/formoterol fumarate 160 mcg/4.8 mcg]), budesonide and formoterol fumarate 160 mcg/9.6 mcg, or formoterol fumarate 9.6 mcg (FF MDI), all administered twice daily. FF MDI used the same inhaler and excipients as SYMBICORT AEROSPHERE.

The population demographics in SOPHOS were: mean age of 65 years (range: 40 to 80 years), 57% male, 83% White, 4% Black, 4% American Indian or Alaska Native, and 8% Other (including native Hawaiian and Pacific Islander) and an average smoking history of 45 pack-years, with 39% identified as current smokers. The mean post-bronchodilator percent predicted FEV_1 was 51% (range 25% to 87%). At study entry, the most common COPD treatments were ICS + LABA (42%), ICS + LAMA + LABA (23%), and LAMA + LABA (10%). Most patients (76%) were taking ICS as part of a COPD treatment regimen.

In SOPHOS, the primary endpoint was change from baseline in morning pre-dose trough FEV_1 for SYMBICORT AEROSPHERE 320 mcg/9.6 mcg compared to FF MDI 9.6 mcg at Week 12.

Lung Function

In TELOS, treatment with SYMBICORT AEROSPHERE 320 mcg/9.6 mcg resulted in a statistically significant increase in FEV_1 AUC_{0-4} relative to BD MDI 320 mcg and trough FEV_1 relative to FF MDI 9.6 mcg at Week 24 (Table 5). The effects on lung function (mean change from baseline in morning pre-dose trough FEV_1) of SYMBICORT AEROSPHERE 320 mcg/9.6 mcg compared with FF MDI 9.6 mcg were observed at all timepoints over the course of the study (Figure 3).

In SOPHOS, treatment with SYMBICORT AEROSPHERE 320 mcg/9.6 mcg resulted in a numerical increase in morning pre-dose trough FEV_1 at Week 12 compared with FF MDI 9.6 mcg (Table 5).

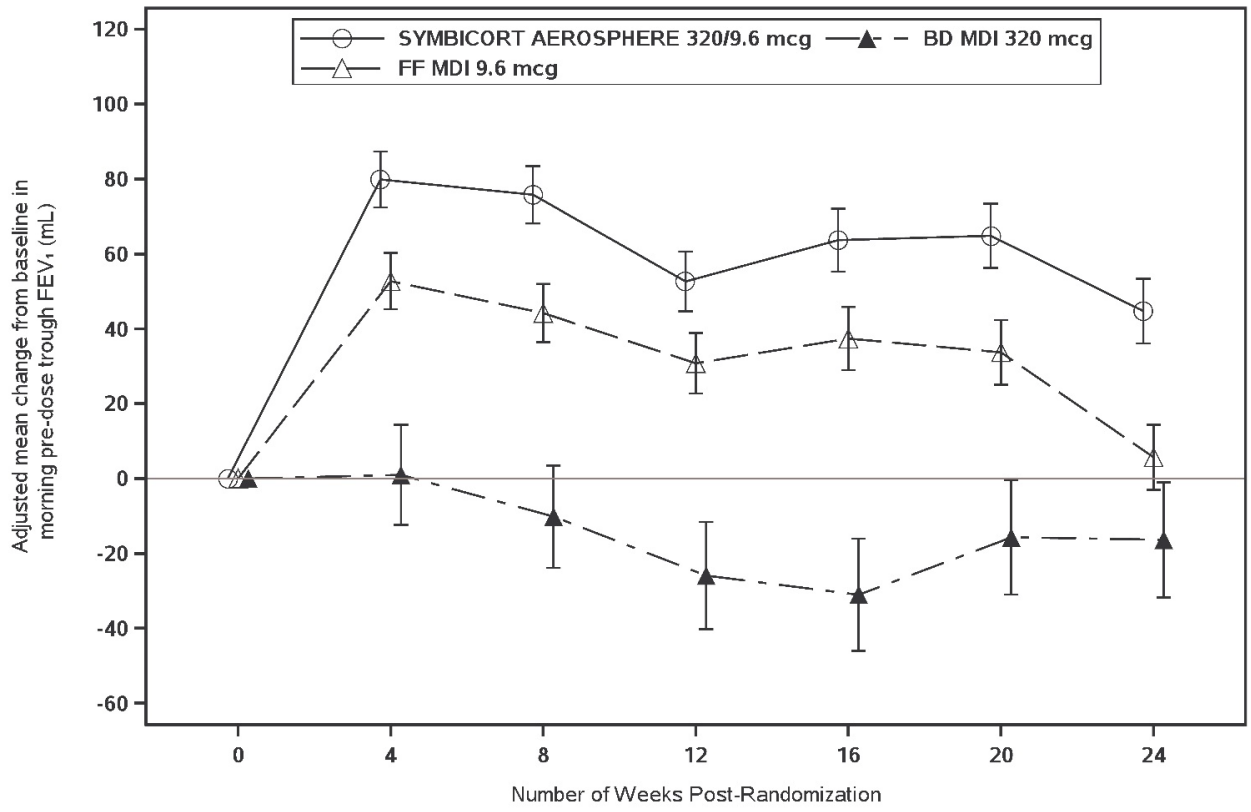
Table 5 provides results from TELOS and SOPHOS for effects on lung function, and Figure 3 provides results from TELOS for lung function over time.

Table 5: Least Squares Mean Change from Baseline in FEV_1 AUC_{0-4} (mL) and Morning Pre-dose Trough FEV_1 (mL) in Patients with COPD (TELOS and SOPHOS)

	BD MDI 320 mcg (N=206)	**FF MDI 9.6 mcg (N=644)**
Trial Treatment	**Difference in FEV_1 AUC_{0-4} at Week 24* (95% CI)**	**Difference in Trough FEV_1 at Week 24* (95% CI)**
TELOS SYMBICORT AEROSPHERE 320 mcg/9.6 mcg (N=655)	157 (121, 193)	39 (15, 63)
		FF MDI 9.6 mcg (N=607)
		Difference in Trough FEV_1 at Week 12* (95% CI)
SOPHOS SYMBICORT AEROSPHERE 320 mcg/9.6 mcg (N=619)	-	18 (-7, 43)

*Difference presented is SYMBICORT AEROSPHERE 320 mcg/9.6 mcg - comparator arm.

Figure 3: Adjusted Mean Change from Baseline in Morning Pre-dose Trough FEV_1 Over Time in Patients with COPD (TELOS)



In TELOS, treatment with SYMBICORT AEROSPHERE 320 mcg/9.6 mcg resulted in an improvement in LS mean peak change from baseline in FEV_1 at Week 24 compared with BD MDI 320 mcg (143 mL; 95% CI: 105, 180). The time to onset of action for SYMBICORT AEROSPHERE 320 mcg/9.6 mcg on Day 1 (defined as the first timepoint showing a statistically significant difference in change from baseline in FEV_1 from BD MDI 320 mcg) was 5 minutes. In TELOS and SOPHOS, treatment with SYMBICORT AEROSPHERE 320 mcg/9.6 mcg resulted in an improvement in LS mean change from baseline in average daily rescue medication use over 24 weeks compared with BD MDI 320 mcg (TELOS), and over 12 weeks compared with FF MDI 9.6 mcg (SOPHOS).

Exacerbations

COPD exacerbations were defined as worsening of 2 or more major symptoms (dyspnea, sputum volume, and sputum color) or worsening of any 1 major symptom together with any 1 of the following minor symptoms: cough, wheeze, sore throat, colds (nasal discharge and/or nasal congestion), and fever without other cause for at least 2 consecutive days. Exacerbations were considered to be moderate severity if treatment with systemic corticosteroids and/or antibiotics were required or severe if they resulted in hospitalization or death.

In TELOS, treatment with SYMBICORT AEROSPHERE 320 mcg/9.6 mcg resulted in an improvement in time to first moderate or severe COPD exacerbation compared with FF MDI 9.6 mcg (hazard ratio 0.70; 95% CI: 0.55, 0.90).

In SOPHOS, treatment with SYMBICORT AEROSPHERE 320 mcg/9.6 mcg resulted in an improvement in time to first moderate or severe COPD exacerbation compared with FF MDI 9.6 mcg (hazard ratio 0.82; 95% CI: 0.69, 0.98).

Health-Related Quality of Life

In both trials, health-related quality of life was assessed using the St. George's Respiratory Questionnaire (SGRQ) responder analysis which was defined as an improvement in SGRQ score from baseline of 4 or more.

Treatment with SYMBICORT AEROSPHERE 320 mcg/9.6 mcg resulted in a greater percentage of SGRQ responders in both TELOS and SOPHOS. In TELOS, SYMBICORT AEROSPHERE had 51% responders at week 24 compared with 45% for FF MDI 9.6 mcg (odds ratio 1.3; 95% CI: 1.0, 1.6) or 48% for BD MDI 9.6 mcg (odds ratio 1.1; 95% CI: 0.8, 1.5), and in SOPHOS, SYMBICORT AEROSPHERE 320 mcg/9.6 mcg had 53% responders at Week 12 compared with 49% for FF MDI 9.6 mcg (odds ratio 1.2; 95% CI: 0.9, 1.5).

16 HOW SUPPLIED/STORAGE AND HANDLING

SYMBICORT AEROSPHERE (budesonide/formoterol fumarate) Inhalation Aerosol:

- is supplied as a pressurized aluminum canister with an attached dose indicator, a white plastic actuator and mouthpiece, and a grey dust cap.
- each canister of SYMBICORT AEROSPHERE is packaged in a foil pouch with desiccant sachet and is placed into a carton.
- each carton contains one canister.

SYMBICORT AEROSPHERE is available as presented in Table 6.

Table 6: Package Information for SYMBICORT AEROSPHERE

Strength (budesonide/formoterol fumarate)	Number of Inhalations per Canister	Net Fill Weight	NDC
80 mcg/4.8 mcg	120	10.7	0310-2010-12
160 mcg/4.8 mcg	120	10.7	0310-2009-12

The SYMBICORT AEROSPHERE canister should only be used with the SYMBICORT AEROSPHERE actuator, and the SYMBICORT AEROSPHERE actuator should not be used with any other inhalation drug product.

Counter

The correct amount of medication in each inhalation cannot be assured after the label number of inhalations from the canister have been used, when the dose indicator pointer is at zero, even though the canister may not feel completely empty. SYMBICORT AEROSPHERE should be discarded when the dose indicator pointer is at zero or 3 months after removal from the foil pouch, whichever comes first. Never immerse the canister into water to determine the amount remaining in the canister ("float test").

Storage

Store at controlled room temperature 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP]. Keep in a dry place away from heat and sunlight.

The canister should be at room temperature before use. Shake well before using. Keep out of reach of children.

Contents under pressure. Do not puncture. Do not use or store near heat or open flames. Exposure to temperatures above 120°F (49°C) may cause bursting. Never throw canister into fire or incinerator. Avoid spraying in eyes.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Serious Asthma-Related Events

Inform patients with asthma that LABA when used alone increases the risk of asthma-related hospitalization or asthma-related death. Available data show that when ICS and LABA are used together, such as with SYMBICORT AEROSPHERE, there is not a significant increase in risk of these events.

Not for Treatment of Acute Symptoms

Inform patients that SYMBICORT AEROSPHERE is not used to relieve acute symptoms of asthma or COPD and extra doses should not be used for that purpose *[see Warnings and Precautions (5.2)]*. Advise patients to treat acute symptoms with an inhaled, short-acting beta$_2$-agonist/corticosteroid for asthma or, an inhaled, short-acting beta$_2$-agonist for asthma or COPD. Provide patients with such medication and instruct them on how it should be used.

Instruct patients to seek medical attention immediately if they experience any of the following:

- Decreasing effectiveness of inhaled, short-acting beta$_2$-agonist/corticosteroid combination, or inhaled, short-acting beta$_2$-agonists.
- Need for more inhalations than usual of inhaled, short-acting beta$_2$-agonist/corticosteroid combination, or inhaled, short-acting beta$_2$-agonists.
- Significant decrease in lung function as outlined by the health care practitioner.

Tell patients they should not stop therapy with SYMBICORT AEROSPHERE without physician/provider guidance since symptoms may recur after discontinuation.

Do Not Use Additional Long-Acting Beta$_2$-Agonists

Instruct patients not to use other LABA drugs *[see Warnings and Precautions (5.3)]*.

Oropharyngeal Candidiasis

Inform patients that localized infections with *Candida albicans* occurred in the mouth and pharynx in some patients. Advise patients to rinse the mouth with water without swallowing after inhalation to help reduce the risk of thrush *[see Warnings and Precautions (5.4)]*.

Risk of Pneumonia

Patients with COPD have a higher risk of pneumonia; instruct them to contact their healthcare providers if they develop symptoms of pneumonia *[see Warnings and Precautions (5.5)]*.

Immunosuppression and Risk of Infections

Warn patients who are on immunosuppressant doses of corticosteroids to avoid exposure to chickenpox or measles and, if exposed, to consult their healthcare providers without delay. Inform patients of potential worsening of existing

tuberculosis, fungal, bacterial, viral, or parasitic infections, or ocular herpes simplex *[see Warnings and Precautions (5.6)]*.

Hypercorticism and Adrenal Suppression

Advise patients that SYMBICORT AEROSPHERE may cause systemic corticosteroid effects of hypercorticism and adrenal suppression. Additionally, inform patients that deaths due to adrenal insufficiency have occurred during and after transfer from systemic corticosteroids *[see Warnings and Precautions (5.8)]*.

Paradoxical Bronchospasm

Instruct patients to discontinue SYMBICORT AEROSPHERE and contact their healthcare provider right away if they develop paradoxical bronchospasm *[see Warnings and Precautions (5.10)]*.

Hypersensitivity Reactions

Advise patients to contact their healthcare provider and discontinue SYMBICORT AEROSPHERE if hypersensitivity reactions (e.g., anaphylaxis, angioedema, rash, urticaria) occur with SYMBICORT AEROSPHERE use *[see Warnings and Precautions (5.11)]*.

Risks Associated with Beta-agonist Therapy

Instruct patients to contact their healthcare provider immediately if they experience adverse reactions associated with $beta_2$-agonists; such as palpitations, chest pain, rapid heart rate, tremor, or nervousness *[see Warnings and Precautions (5.12)]*.

Reduction in Bone Mineral Density

Advise patients who are at an increased risk for decreased BMD that the use of corticosteroids may pose an additional risk *[see Warnings and Precautions (5.13)]*.

Effect on Growth

Inform patients that orally inhaled corticosteroids, a component of SYMBICORT AEROSPHERE, may cause a reduction in growth velocity when administered to pediatric patients. Healthcare providers should closely follow the growth of pediatric patients taking corticosteroids by any route *[see Warnings and Precautions (5.14)]*.

Ocular Effects such as Cataracts or Glaucoma

Inform patients that long-term use of ICS may increase the risk of some eye problems (cataracts or glaucoma); consider regular eye examinations *[see Warnings and Precautions (5.15)]*.

Manufactured for: AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850

Manufactured by: AstraZeneca Dunkerque Production (AZDP), Dunkerque, France

PATIENT INFORMATION

SYMBICORT AEROSPHERE® (SIM-bi-kort AIR-oh-sfeer)

(budesonide and formoterol fumarate)

inhalation aerosol, for oral inhalation use

What is SYMBICORT AEROSPHERE?

SYMBICORT AEROSPHERE combines an inhaled corticosteroid (ICS) medicine (budesonide) and a long-acting beta$_2$-adrenergic agonist (LABA) medicine (formoterol fumarate).

- ICS medicines such as budesonide help to decrease inflammation in the lungs. Inflammation in the lungs can lead to breathing problems.
- LABA medicines help the muscles around the airways in your lungs stay relaxed to prevent symptoms, such as wheezing, cough, chest tightness, and shortness of breath. These symptoms can happen when the muscles around the airways tighten. This makes it hard to breathe.
- SYMBICORT AEROSPHERE is a prescription medicine used long term to treat people with chronic obstructive pulmonary disease (COPD) or asthma as follows:
  - **Asthma:** SYMBICORT AEROSPHERE, either 80 mcg/4.8 mcg or 160 mcg/4.8 mcg, is used as 2 inhalations, 2 times each day (2 puffs in the morning and 2 puffs in the evening) to control and prevent symptoms of asthma, such as wheezing in people 12 years of age and older.
    SYMBICORT AEROSPHERE contains formoterol fumarate. LABA medicines such as formoterol fumarate when used alone increase the risk of hospitalizations and death from asthma problems. SYMBICORT AEROSPHERE contains an ICS and a LABA. When an ICS and LABA are used together, there is not a significant risk in hospitalizations and deaths from asthma problems.
    It is not known if SYMBICORT AEROSPHERE is safe and effective in children less than 12 years of age.
  - **COPD:** COPD is a long term (chronic) lung disease that includes chronic bronchitis, emphysema, or both. SYMBICORT AEROSPHERE 160 mcg/4.8 mcg is used as 2 inhalations, 2 times each day (2 puffs in the morning and 2 puffs in the evening) to improve symptoms of COPD in adults for better breathing and to reduce the number of flare-ups (the worsening of your COPD symptoms for several days).
- **SYMBICORT AEROSPHERE is not used to relieve sudden breathing problems** and will not replace a rescue inhaler. Always have a rescue inhaler with you to treat sudden breathing problems. If you do not have a rescue inhaler, contact your healthcare provider to have one prescribed for you.

Do not use SYMBICORT AEROSPHERE:

- to treat sudden severe symptoms of asthma or COPD.
- if you are allergic to budesonide, formoterol, or any of the ingredients in SYMBICORT AEROSPHERE. See the end of this Patient Information leaflet below for a complete list of ingredients in SYMBICORT AEROSPHERE.

Before using SYMBICORT AEROSPHERE, tell your healthcare provider about all of your medical conditions, including if you:

- have heart problems.
- have high blood pressure.
- have seizures.
- have thyroid problems.
- have diabetes.
- have liver problems.
- have weak bones (osteoporosis).
- have an immune system problem.
- have eye problems such as glaucoma or cataracts. SYMBICORT AEROSPHERE may make your glaucoma worse.
- have any type of viral, bacterial, parasitic, or fungal infection.
- are exposed to chickenpox or measles.
- are pregnant or plan to become pregnant. It is not known if SYMBICORT AEROSPHERE may harm your unborn baby.
- are breastfeeding. It is not known if the medicines budesonide and formoterol fumarate in SYMBICORT AEROSPHERE pass into your breast milk and if they can harm your baby. You and your healthcare provider should decide if you will use SYMBICORT AEROSPHERE while breastfeeding.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. SYMBICORT AEROSPHERE and certain other medicines may interact with each other. This may cause serious side effects.

Especially tell your healthcare provider if you take:

- other LABAs (including salmeterol, arformoterol tartrate, vilanterol, olodaterol, and indacaterol)
- atropine
- antifungal or anti-HIV medicines

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist each time you get a new medicine.

How should I use SYMBICORT AEROSPHERE?

Read the step-by-step instructions for using SYMBICORT AEROSPHERE that come with this Patient Information leaflet.

- Before using SYMBICORT AEROSPHERE, make sure your healthcare provider has taught you how to use the inhaler and you understand how to use it correctly.
- Use SYMBICORT AEROSPHERE exactly as your healthcare provider tells you to use it. **Do not** use SYMBICORT AEROSPHERE more often than prescribed.
- Use 2 inhalations of SYMBICORT AEROSPHERE, 2 times each day (2 puffs in the morning and 2 puffs in the evening) about 12 hours apart.
- **Do not** use more than 2 inhalations of SYMBICORT AEROSPHERE 2 times each day.
- If a dose (2 puffs) of SYMBICORT AEROSPHERE is missed, it should be taken as soon as possible and the next dose should be taken at the usual time. Do not take more than one dose to make up for a missed dose.
- Rinse your mouth with water and spit the water out after each dose (2 puffs) of SYMBICORT AEROSPHERE. Do not swallow the water. This will help to reduce the chance of getting a fungal infection (thrush) in the mouth and throat.
- If you use too much SYMBICORT AEROSPHERE, call your healthcare provider or go to the nearest hospital emergency room right away if you have any unusual symptoms, such as worsening shortness of breath, chest pain, increased heart rate, or shakiness.
- **Do not** spray SYMBICORT AEROSPHERE in your eyes. If SYMBICORT AEROSPHERE gets in your eyes, rinse them well with water. If redness continues, call your healthcare provider.
- Do not change or stop any medicines used to control or treat your breathing problems because your symptoms might get worse. Your healthcare provider will change your medicines as needed.
- **While you are using SYMBICORT AEROSPHERE 2 times each day, do not use other medicines that contain a LABA for any reason. Ask your healthcare provider or pharmacist if any of your other medicines are LABA medicines.**
- **SYMBICORT AEROSPHERE does not relieve sudden breathing problems and you should not use extra doses of SYMBICORT AEROSPHERE to relieve sudden symptoms.** Always have a rescue inhaler with you to treat sudden symptoms. If you do not have a rescue inhaler, call your healthcare provider to have one prescribed for you.
- **Call your healthcare provider or get emergency medical care right away if:**
  - your breathing problems get worse.
  - you need to use your rescue inhaler more often than usual.
  - your rescue inhaler does not work as well to relieve your symptoms.

What are the possible side effects of SYMBICORT AEROSPHERE?
SYMBICORT AEROSPHERE can cause serious side effects, including:

- **using too much of a LABA medicine may cause**:
  - chest pain
  - fast and irregular heartbeat
  - tremor
  - increased blood pressure
  - headache
  - nervousness
- **fungal infection in your mouth or throat (thrush).** Rinse your mouth with water without swallowing after using SYMBICORT AEROSPHERE to help reduce your chance of getting thrush.
- **pneumonia.** People with COPD have a higher chance of getting pneumonia. SYMBICORT AEROSPHERE may increase your chance of getting pneumonia. Call your healthcare provider if you notice any of the following symptoms:
  - increase in mucus (sputum) production
  - chills

- change in mucus color
- fever
- increased cough
- increased breathing problems

- **weakened immune system and increased chance of getting infections (immunosuppression).**
- **reduced adrenal function (adrenal insufficiency).** Adrenal insufficiency is a condition where the adrenal glands do not make enough steroid hormones. This can happen when you stop taking oral corticosteroid medicines (such as prednisone) and start taking a medicine containing an ICS (such as SYMBICORT AEROSPHERE). 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 (hypotension)
- **sudden breathing problems right after using SYMBICORT AEROSPHERE.** If you have sudden breathing problems right after inhaling your medicine, stop using SYMBICORT AEROSPHERE and call your healthcare provider right away.
- **serious allergic reactions.** Call your healthcare provider or get emergency medical care if you get any of the following symptoms of a serious allergic reaction:
  - rash
  - hives
  - swelling of your face, mouth, and tongue
  - breathing problems
- **effects on your heart.**
  - increased blood pressure
  - a fast or irregular heartbeat
  - chest pain
- **effects on your nervous system.**
  - tremor
  - nervousness
- **bone thinning or weakness (osteoporosis).**
- **slowed growth in children.** A child's growth should be checked regularly while using SYMBICORT AEROSPHERE.
- **new or worsened eye problems including glaucoma and cataracts.** You should have regular eye exams while using SYMBICORT AEROSPHERE.
- **changes in laboratory blood values,** including high levels of blood sugar (hyperglycemia) and low levels of potassium (hypokalemia). Low levels of potassium may cause symptoms of muscle spasm, muscle weakness, or abnormal heart rhythm.

The most common side effects of SYMBICORT AEROSPHERE include:
People with asthma:

- pain or swelling of your nose or throat (nasopharyngitis)
- COVID-19
- hay fever (allergic rhinitis)
- bronchitis
- upper respiratory tract infection
- joint pain (arthralgia)
- gout
- high blood pressure
- diarrhea
- influenza like illness

People with COPD:

- upper respiratory tract infection
- symptoms of chronic obstructive pulmonary disease
- back pain
- headache
- bronchitis
- thrush in your mouth and throat. Rinse your mouth with water without swallowing after use to help prevent this.
- hoarseness
- muscle spasms

Tell your healthcare provider about any side effect that bothers you or that does not go away.
These are not all the possible side effects of SYMBICORT AEROSPHERE. Ask your healthcare provider or pharmacist for more information.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. You may also report side effects to AstraZeneca at 1-800-236-9933.

How should I store SYMBICORT AEROSPHERE?

- Store SYMBICORT AEROSPHERE at room temperature between 68ºF to 77ºF (20ºC to 25ºC). Keep in a dry place away from heat and sunlight.
- Store SYMBICORT AEROSPHERE in the unopened foil pouch and only open when ready for use.
- **Do not** put a hole in the SYMBICORT AEROSPHERE canister.

- **Do not** use or store SYMBICORT AEROSPHERE near heat or a flame. Temperatures above 120ºF (49ºC) may cause the canister to burst.
- **Do not** throw the SYMBICORT AEROSPHERE canister into a fire or an incinerator.
- Throw away SYMBICORT AEROSPHERE 3 months after you open the foil pouch, or when the puff indicator reaches zero “0”, whichever comes first.
- Keep SYMBICORT AEROSPHERE and all medicines out of the reach of children.

General information about the safe and effective use of SYMBICORT AEROSPHERE.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use SYMBICORT AEROSPHERE for a condition for which it was not prescribed. Do not give your SYMBICORT AEROSPHERE to other people, even if they have the same condition that you have. It may harm them.

You can ask your healthcare provider or pharmacist for information about SYMBICORT AEROSPHERE that is written for health professionals.

What are the ingredients in SYMBICORT AEROSPHERE?

Active ingredients: micronized budesonide and micronized formoterol fumarate

Inactive ingredients: hydrofluoroalkane (HFA 134a) and porous particles (comprised of DSPC [1,2-Distearoyl-*sn*-glycero-3-phosphocholine] and calcium chloride)

Manufactured for: AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850; Manufactured by: AstraZeneca Dunkerque Production (AZDP), Dunkerque, France

For more information call 1-800-236-9933.

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: April 2026

Instructions for Use
SYMBICORT AEROSPHERE® (SIM-bi-kort AIR-oh-sfeer)
(budesonide and formoterol fumarate)
inhalation aerosol, for oral inhalation use

Read this Instructions for Use before you start using SYMBICORT AEROSPHERE and each time you get a new refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment. Your SYMBICORT AEROSPHERE inhaler may be different from inhalers you have used before.

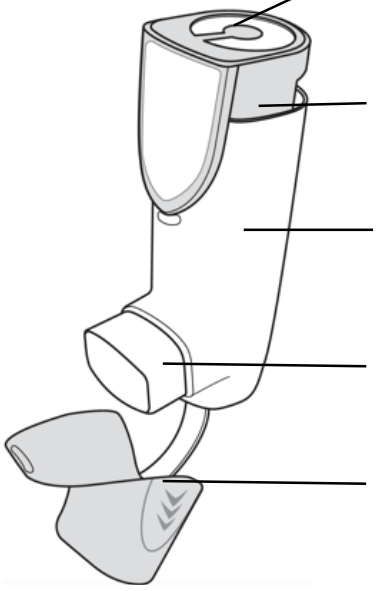
Important information

- **For oral inhalation use only.**
- Prime your SYMBICORT AEROSPHERE inhaler before using it for the first time.
- Rinse the white actuator 1-time each week so that medicine does not build up and block the spray through the mouthpiece.
- Take 2 puffs of medicine in the morning and 2 puffs of medicine in the evening.
- Rinse mouth with water after the 2 puffs to reduce your chance of getting a fungal infection (thrush) in the mouth and throat.

Storing your inhaler

- Store your inhaler at room temperature between 68°F to 77°F (20°C to 25°C).
- **Do not store in a humid environment, such as a bathroom.**
- Keep your inhaler and all medicines out of the reach of children.

Parts of your SYMBICORT AEROSPHERE inhaler



Puff indicator
Attached to the top of the pressurized canister.

Pressurized canister (inside)
Holds the medicine.

Actuator (white)
Contains the pressurized canister.

Mouthpiece
Sprays the medicine.

Mouthpiece cover
Protects the mouthpiece when the inhaler is not in use.

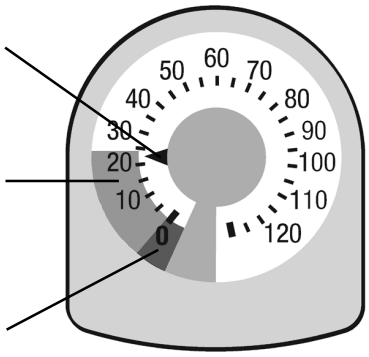
Reading the puff indicator

The puff indicator will count down by 1 each time you spray a puff of medicine.

Pointer
Points to number of puffs remaining.

Yellow zone
Order a new inhaler when the pointer is in the yellow zone.

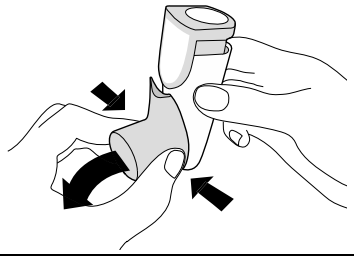
Red zone
Throw away your inhaler when the pointer is at 0 in the red zone.



Do not try to take a puff of medicine when the pointer is at **0** because you will not receive a full dose.

BEFORE FIRST USE – Prime your inhaler 4 times before first use

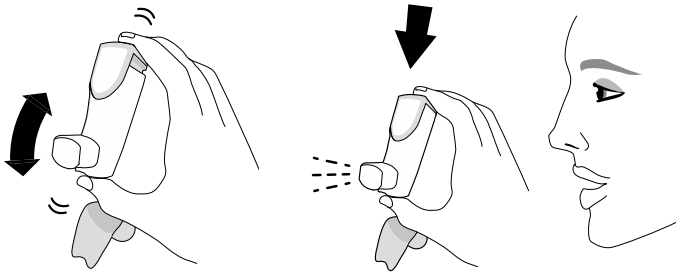
- Before you use your SYMBICORT AEROSPHERE inhaler for the first time, prime it so that you will get the right amount of medicine when you use it.

Prime 1
Remove mouthpiece cover by squeezing both sides and pulling out. 

Prime 2

Shake the inhaler well and spray **1 test-puff** into the air facing away from you. Repeat Prime 2 for a total of **4 test-puffs**, shaking the SYMBICORT AEROSPHERE inhaler before each test-puff.

4 total shake and test-puffs



Do not skip priming. Extra puffs are provided for priming.

Re-prime your inhaler:

- after rinsing the white actuator
- if dropped
- if not used for more than 7 days

To re-prime, spray **2 test-puffs**, shaking the inhaler before each test-puff.

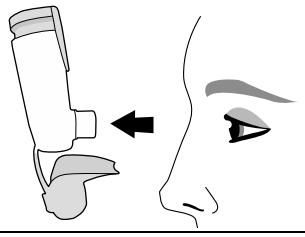
2 total shake and test-puffs

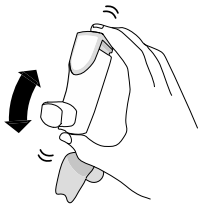
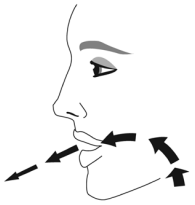
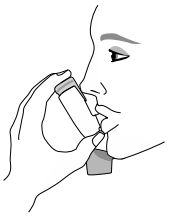
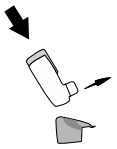
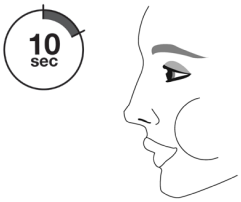
DAILY USE - Using your SYMBICORT AEROSPHERE inhaler

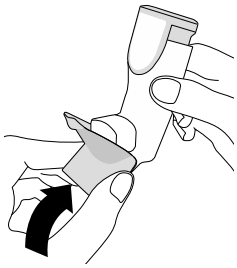
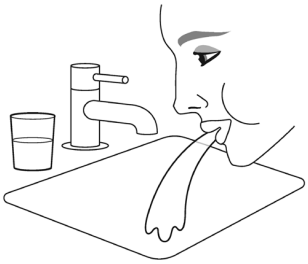
- **Dose: 2 puffs in the morning and 2 puffs in the evening.**
- Rinse mouth with water after the 2 puffs to reduce your chance of getting a fungal infection (thrush) in your mouth and throat.

Step 1

Remove mouthpiece cover. Check the mouthpiece for foreign objects and remove objects before use.

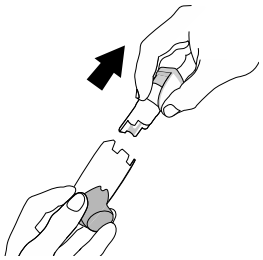
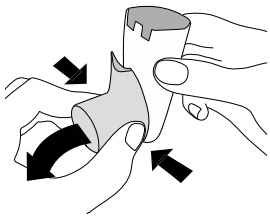


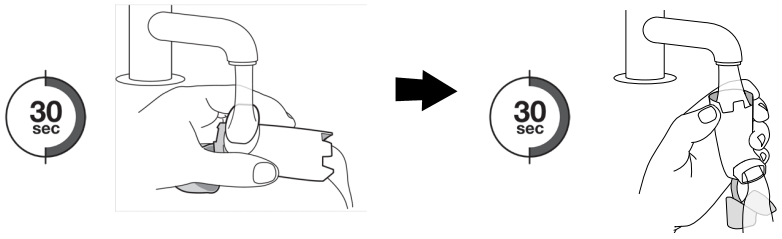
Step 2				
2.1 Shake the inhaler well before each puff. 	**2.2** Breathe out fully. 	**2.3** Place mouthpiece into mouth and close lips around the mouthpiece. 	**2.4** Start to breathe in deeply and slowly while spraying **1 puff**. Continue breathing in until you cannot anymore. 	**2.5** Hold breath for as long as you can, up to **10 seconds.** 

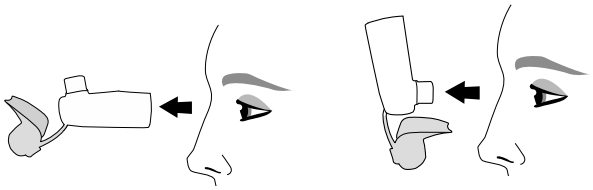
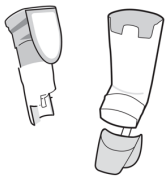
Step 3	Step 4	Step 5
Repeat all parts in Step 2 for the second puff.	Put mouthpiece cover back on. 	Rinse your mouth with water. Spit out the water. Do not swallow the water. 

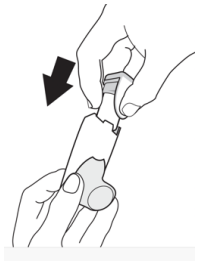
WEEKLY RINSE – Rinse your actuator 1-time each week

- Rinse the white actuator 1-time each week so that the medicine does not build up and block the spray through the mouthpiece.
- Keep canister dry.
- Re-prime after rinsing.

Rinse 1	Rinse 2
Remove canister and set aside. **Keep canister dry.** 	Remove the mouthpiece cover. 

Rinse 3	Rinse 4
Run warm water through the mouthpiece for 30 seconds and then through the top of the actuator for 30 seconds. Rinse for 60 seconds in total. 	Shake off as much water as you can.  Do not dry the actuator with a towel or tissue.

Rinse 5	Rinse 6
Look into the actuator and mouthpiece for medicine build-up. If there is any build-up, repeat Rinse 3, 4, and 5. 	Let the actuator air-dry, such as overnight. **Do not** put the canister back into the actuator if it is still wet. 

Rinse 7	Rinse 8
When completely dry, **replace the mouthpiece cover first,** then gently press the canister down into the actuator. 	Re-prime the inhaler by spraying **2 test-puffs,** shaking the inhaler before each test-puff. **2 total shake and test-puffs**

Throwing away your SYMBICORT AEROSPHERE inhaler

Throw away your inhaler in a household trash when:

- puff indicator shows **0**

or

- **3 months** after your inhaler has been removed from the foil pouch.

Do not reuse or use the actuator with medicine canisters from other inhalers.
Do not puncture or throw the canister into a fire or incinerator.

Ordering a new SYMBICORT AEROSPHERE inhaler

- Order a new SYMBICORT AEROSPHERE inhaler when the pointer on the puff indicator is in the yellow zone.

Distributed by: AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Issued: April 2026