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

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 maintenance treatment of patients with chronic obstructive pulmonary disease (COPD). (1)

Limitations of Use: Not indicated for the relief of acute bronchospasm or for the treatment of asthma. (1, 5.1, 5.2)

DOSAGE AND ADMINISTRATION

- For oral inhalation only. (2)
- Maintenance treatment of COPD: 2 actuations of SYMBICORT AEROSPHERE (total dose of budesonide 320 mcg/formoterol fumarate 9.6 mcg) twice daily by oral inhalation. (2)

DOSAGE FORMS AND STRENGTHS

Inhalation aerosol: Pressurized metered dose inhaler that delivers a combination of budesonide (160 mcg), and formoterol fumarate (4.8 mcg) per actuation. (3)

CONTRAINDICATIONS

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 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)
- 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. (5.14)
- Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis. (5.15)
- Be alert to hypokalemia and hyperglycemia. (5.16)

ADVERSE REACTIONS

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: 04/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

Limitations of Use:

SYMBICORT AEROSPHERE is not indicated for the relief of acute bronchospasm or for the treatment of asthma *[see Warnings and Precautions (5.1, 5.2)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage and Administration

The recommended dosage of SYMBICORT AEROSPHERE is 2 actuations (containing total dose of budesonide 320 mcg and formoterol fumarate 9.6 mcg) twice daily in the morning and in the evening (approximately 12 hours apart) by oral inhalation. Do not take more than two inhalations twice daily.

After inhalation, rinse mouth with water without swallowing.

2.2 Priming Before Use

Prime SYMBICORT AEROSPHERE before using for the first time. Priming SYMBICORT AEROSPHERE is essential to ensure appropriate drug content in each actuation. Prime SYMBICORT AEROSPHERE by releasing 4 sprays into the air away from the face, shaking well before each spray.

If the inhaler has not been used for more than 7 days, is dropped, or after weekly cleaning, prime the inhaler again by releasing 2 sprays into the air away from the face, shaking well before each spray.

2.3 Dose Counter

SYMBICORT AEROSPHERE canister has an attached dose indicator, which indicates how many inhalations remain. The dose indicator display will move after every tenth actuation. When nearing the end of the usable inhalations, the color behind the number in the dose indicator display window changes to red. SYMBICORT AEROSPHERE should be discarded when the dose indicator display window shows zero.

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 red dust cap) that delivers a combination of budesonide 160 mcg and formoterol fumarate 4.8 mcg per actuation.

4 CONTRAINDICATIONS

SYMBICORT AEROSPHERE is contraindicated in patients who have demonstrated 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

The safety and effectiveness of SYMBICORT AEROSPHERE in patients with asthma have not been established. SYMBICORT AEROSPHERE is not indicated for the treatment of asthma.

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.

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

5.2 Deterioration of Disease and Acute Episodes

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

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 an inhaled short-acting beta$_2$-agonist.

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 an inhaled, short acting beta$_2$-agonist and instruct the patient on how it should be used. Increasing inhaled beta$_2$-agonist use is a signal of deteriorating disease for which prompt medical attention is indicated.

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 Risk Associated with Excessive Use of Long-Acting Beta$_2$-Agonists, Including SYMBICORT AEROSPHERE

As with other inhaled drugs containing beta$_2$-adrenergic agents, SYMBICORT AEROSPHERE should not be used more often than recommended *[see Dosage and Administration (2.1)]*, 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 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, 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, 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 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 Glaucoma and Cataracts

Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with 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.

5.15 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.

5.16 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)]*
- Glaucoma and Cataracts *[see Warnings and Precautions (5.14)]*

6.1 Clinical Trials Experience

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.

The safety of SYMBICORT AEROSPHERE is based on the safety data from two phase 3 trials, with durations of 24 weeks (TELOS) and 12-52 weeks (SOPHOS), respectively. In TELOS and SOPHOS, a total of 1274 COPD patients received at least 1 dose of SYMBICORT AEROSPHERE 320 mcg/9.6 mcg *[see Clinical Studies (14)]*.

In the two trials, 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)]*. The incidence of common adverse reactions in TELOS is shown in Table 1.

Table 1: Adverse Reactions Occurring at an Incidence of ≥ 2% and More Common in Patients 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 postapproval 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 COPD patients. Therefore, patients with 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 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 in a COPD population 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. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

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 not been established in pediatric patients.

8.5 Geriatric Use

There were 1229 patients and 999 patients 65 years of age and older in TELOS and SOPHOS, respectively *[see Clinical Studies (14)]*. 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.

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.

Budesonide

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

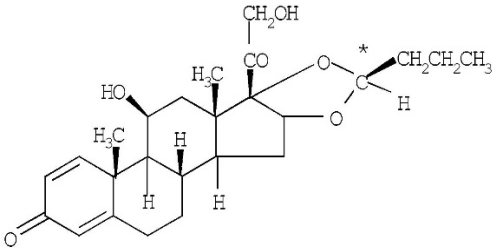
Formoterol Fumarate

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

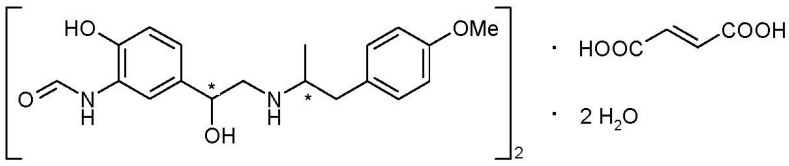
SYMBICORT AEROSPHERE (budesonide and formoterol fumarate) Inhalation Aerosol is a pressurized metered-dose inhaler that delivers a combination of micronized budesonide [an inhaled corticosteroid (ICS)], and micronized formoterol fumarate [an inhaled long-acting beta$_2$-adrenergic agonist (a LABA)] for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

After priming, each actuation of the inhaler meters 185 mcg of budesonide and 5.5 mcg of formoterol fumarate (equivalent to 4.7 mcg of formoterol) from the valve which delivers 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 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 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 9/4.8 mcg

and glycopyrrolate/formoterol fumarate 72/19.2 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 9/4.8 mcg and glycopyrrolate/formoterol fumarate 72/19.2 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

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

TELOS (NCT02766608) evaluated a patient population 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 320/9.6 mcg (budesonide/formoterol fumarate 320 mcg/9.6 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), all administered twice daily by oral inhalation. FF MDI and BD MDI used the same inhaler and excipients as SYMBICORT AEROSPHERE. Only the results of the approved dosage (SYMBICORT AEROSPHERE 320/9.6 mcg twice daily) are described below.

The population demographics across all treatments 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 compared to BD MDI and change from baseline in morning pre-dose trough FEV_1 for SYMBICORT AEROSPHERE compared to FF MDI at Week 24.

SOPHOS (NCT02727660) evaluated a patient population 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 320/9.6 mcg (budesonide/formoterol fumarate 320 mcg/9.6 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 across all treatments 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 compared to FF MDI at Week 12.

Lung Function

In TELOS, treatment with SYMBICORT AEROSPHERE resulted in a statistically significant increase in FEV_1 AUC_{0-4} relative to BD MDI and trough FEV_1 relative to FF MDI at Week 24 (Table 2). The effects on lung function (mean change from baseline in morning pre-dose trough FEV_1) of SYMBICORT AEROSPHERE compared with FF MDI were observed at all timepoints over the course of the study (Figure 1).

In SOPHOS, treatment with SYMBICORT AEROSPHERE resulted in a numerical increase in morning pre-dose trough FEV_1 at Week 12 compared with FF MDI (Table 2).

Table 2 provides results from TELOS and SOPHOS for effects on lung function, and Figure 1 provides results from TELOS for lung function over time.

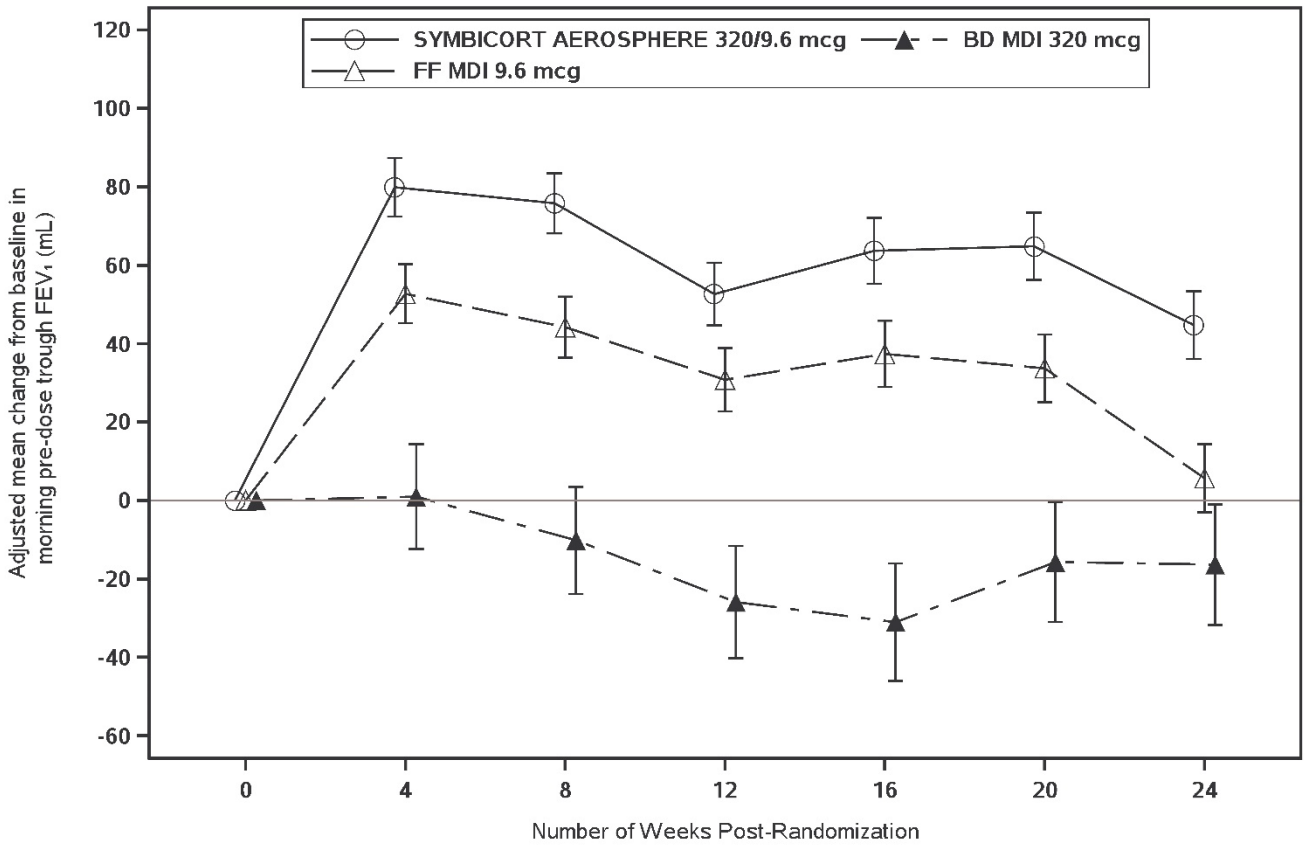
Table 2: Least Squares Mean Change from Baseline in FEV_1 AUC_{0-4} (mL) and Morning Pre-dose Trough FEV_1 (mL)

	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 320/9.6 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	-	18

SYMBICORT AEROSPHERE 320/9.6 mcg (N=619)		(-7, 43)

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

Figure 1: Adjusted Mean Change from Baseline in Morning Pre-dose Trough FEV_1 Over Time (TELOS)



In TELOS, treatment with SYMBICORT AEROSPHERE resulted in an improvement in LS mean peak change from baseline in FEV_1 at Week 24 compared with BD MDI (143 mL; 95% CI: 105, 180). The time to onset of action for SYMBICORT AEROSPHERE on Day 1 (defined as the first timepoint showing a statistically significant difference in change from baseline in FEV_1 from BD MDI) was 5 minutes. In TELOS and SOPHOS, treatment with SYMBICORT AEROSPHERE resulted in an improvement in LS mean change from baseline in average daily rescue medication use over 24 weeks compared with BD MDI (TELOS), and over 12 weeks compared with FF MDI (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 resulted in an improvement in time to first moderate or severe COPD exacerbation compared with FF MDI (hazard ratio 0.70; 95% CI: 0.55, 0.90).

In SOPHOS, treatment with SYMBICORT AEROSPHERE resulted in an improvement in time to first moderate or severe COPD exacerbation compared with FF MDI (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 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 (odds ratio 1.3; 95% CI: 1.0, 1.6) or 48% for BD MDI (odds ratio 1.1; 95% CI: 0.8, 1.5), and in SOPHOS, SYMBICORT AEROSPHERE had 53% responders at Week 12 compared with 49% for FF MDI (odds ratio 1.2; 95% CI: 0.9, 1.5).

16 HOW SUPPLIED/STORAGE AND HANDLING

SYMBICORT AEROSPHERE Inhalation Aerosol:

- budesonide 160 mcg and formoterol fumarate 4.8 mcg per actuation.
- is supplied as a pressurized aluminum canister with an attached dose indicator, a white plastic actuator and mouthpiece, and a red dust cap.
- contains 120 actuations per canister.
- each 120-actuation canister has a net fill weight of 10.7 grams (NDC 0310-2009-12).
- 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.

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.

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 display window shows zero, even though the canister may not feel completely empty. SYMBICORT AEROSPHERE should be discarded when the dose indicator display window shows 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").

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).

Not for Treatment of Acute Symptoms

Inform patients that SYMBICORT AEROSPHERE is not meant to relieve acute symptoms of 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 such as albuterol. Provide patients with such medication and instruct them in 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$_2$-agonists
- Need for more inhalations than usual of inhaled, short-acting beta$_2$-agonists
- Significant decrease in lung function as outlined by the health care practitioner

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)]*.

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 (5.14)]*.

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). COPD is a long term (chronic) lung disease that includes chronic bronchitis, emphysema, or both.
- SYMBICORT AEROSPHERE 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 for better breathing and to reduce the number of flare-ups (the worsening of your COPD symptoms for several days).
- **SYMBICORT AEROSPHERE is not for the treatment of asthma.** It is not known if SYMBICORT AEROSPHERE is safe and effective in people with asthma. 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.
- **SYMBICORT AEROSPHERE is not used to relieve sudden breathing problems** and will not replace a rescue inhaler**.** Always have a rescue inhaler (an inhaled, short-acting bronchodilator) 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.
- **SYMBICORT AEROSPHERE should not be used in children.** It is not known if SYMBICORT AEROSPHERE is safe and effective in children.

Do not use SYMBICORT AEROSPHERE 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 forgotten 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 fungus 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
  - increase 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).**
- **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

- 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. Issued: 04/2023

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 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.

Important Information:

- **For oral inhalation use only**.
- Use SYMBICORT AEROSPHERE exactly as your healthcare provider tells you to.
- If you have any questions about the use of your inhaler, ask your healthcare provider or pharmacist.
- Clean your inhaler 1 time each week. See Step 1 to Step 8, "**How to clean your SYMBICORT AEROSPHERE inhaler**".

Parts of your SYMBICORT AEROSPHERE inhaler (**See Figure 1**):

- SYMBICORT AEROSPHERE comes as a canister that fits into an actuator with a dose indicator.
  - **Do not** use the SYMBICORT AEROSPHERE actuator with a canister of medicine from any other inhaler.
  - **Do not** use the SYMBICORT AEROSPHERE canister with an actuator from any other inhaler.

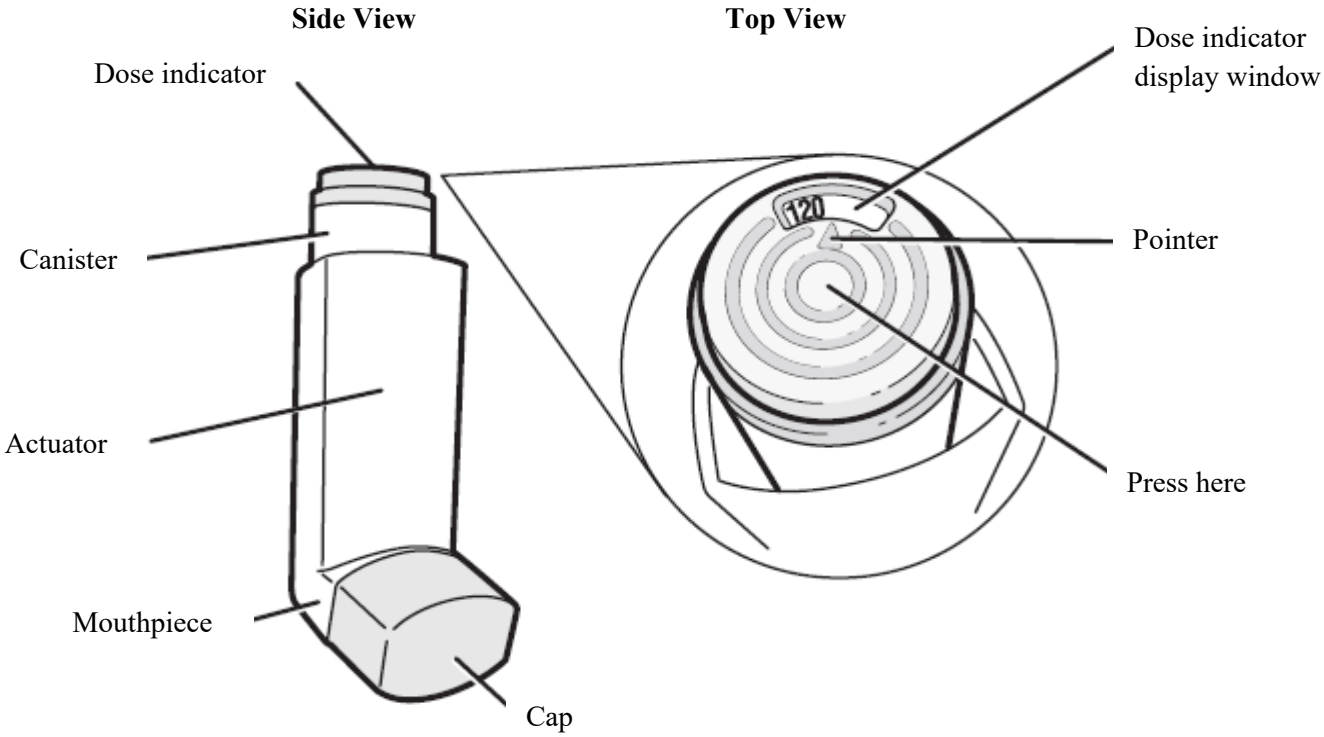


Figure 1

- SYMBICORT AEROSPHERE comes with a dose indicator located on the top of the canister (**See Figure 1**). The dose indicator display window will show you how many puffs of medicine you have left. A puff of medicine is released each time you press the center of the dose indicator.

Before you use SYMBICORT AEROSPHERE for the first time make sure that the pointer on the dose indicator is pointing to the right of the "120" inhalation mark in the dose indicator display window (**See Figure 1**). If you have a 7-day inhaler (28 inhalation canister), the pointer should point to the right of the "30" inhalation mark.

- The pointer will be pointing to 120 after 10 puffs are delivered from SYMBICORT AEROSPHERE. This means that there are 120 puffs of medicine left in the canister (**See Figure 2a**).
- The pointer will be pointing between 100 and 120 after you take 10 more puffs. This means that there are 110 puffs of medicine left in the canister (**See Figure 2b**).
- The pointer will be pointing to 100 after you take 10 more puffs. This means that there are 100 puffs of medicine left in the canister (**See Figure 2c)**.

Figure 2a
120 puffs

Figure 2b
110 puffs

Figure 2c
100 puffs

- The dose indicator display window will continue to move after every 10 puffs. The number in the dose indicator display window will continue to change after every 20 puffs.

Figure 2d

- The color in the dose indicator display window will change to red, as shown in the shaded area, when there are only 20 puffs of medicine left in your inhaler (**See Figure 2d**)**.**
- Throw away (discard) SYMBICORT AEROSPHERE when the dose indicator pointer reaches "0".

Preparing your SYMBICORT AEROSPHERE inhaler for use:

- Your SYMBICORT AEROSPHERE inhaler comes in a foil pouch that contains a drying packet (desiccant).
  - Take the SYMBICORT AEROSPHERE inhaler out of the foil pouch.
  - Throw away the foil pouch and the drying packet. Do not eat or breathe in the contents of the drying packet.
- SYMBICORT AEROSPHERE should be at room temperature before you use it.

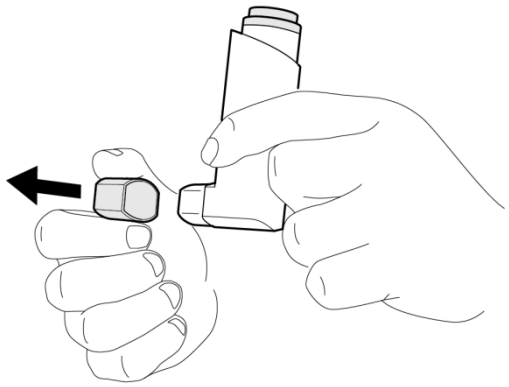


Figure 3

Priming your SYMBICORT AEROSPHERE inhaler:

Before you use SYMBICORT AEROSPHERE for the first time, you must prime the inhaler.

- Remove the cap from the mouthpiece (**See Figure 3**). Check inside the mouthpiece for objects before use.
- Hold the inhaler in the upright position away from your face and shake the inhaler well (**See Figure 4**).

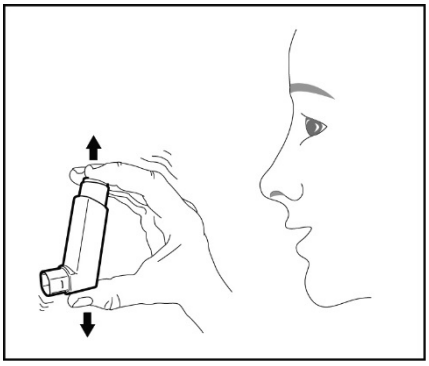


Figure 4

- Press down firmly on the center of the dose indicator until the canister stops moving in the actuator**,** to release a puff of medicine from the mouthpiece (**See Figure 5**). You may hear a soft click from the dose indicator as it counts down during use.

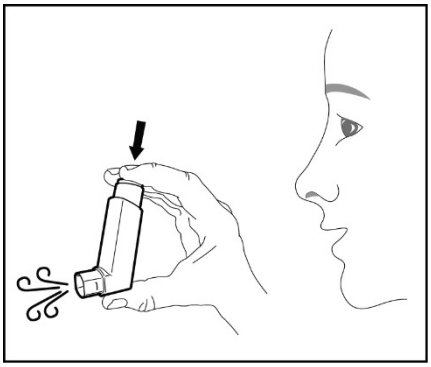


Figure 5

- **Repeat the priming steps 3 more times (See Figure 4 and Figure 5).** Shake the inhaler well before each priming puff.
- After priming 4 times, the dose indicator should be pointing to the right of "**120**" (**See Figure 1**) and your inhaler is now ready to use.
- Replace the cap until you are ready to use your SYMBICORT AEROSPHERE inhaler.

Using your SYMBICORT AEROSPHERE inhaler:

Step 1: Remove the cap from the mouthpiece (**See Figure 6**).

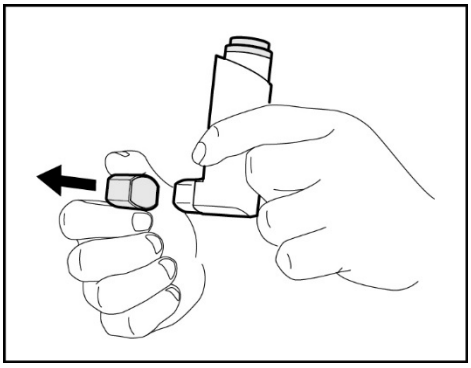


Figure 6

Step 2: Shake the inhaler well before each use (**See Figure 7**).

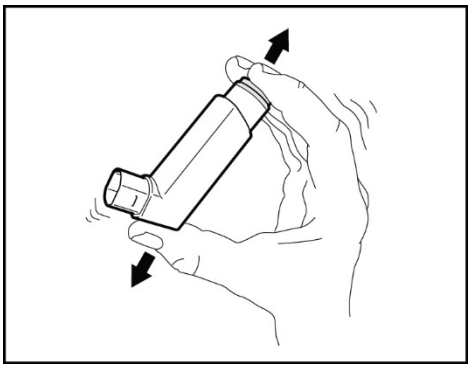


Figure 7

Step 3: Hold the inhaler with the mouthpiece pointing towards you and breathe out as fully as you can through your mouth (**See Figure 8**).

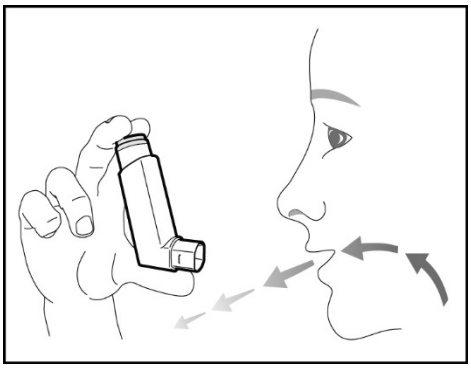


Figure 8

Step 4: Close your lips around the mouthpiece and tilt your head back, keeping your tongue below the mouthpiece (**See Figure 9**).

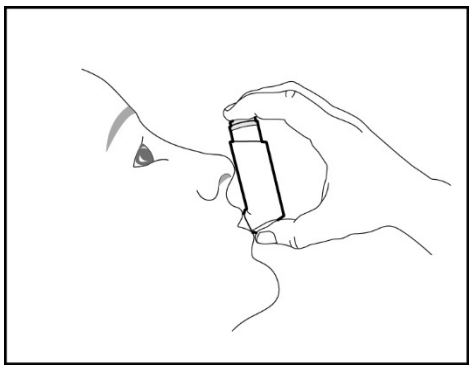


Figure 9

Step 5: While breathing in deeply and slowly, press down on the center of the dose indicator until the canister stops moving in the actuator and a puff of medicine has been released (**See Figure 10**). Then stop pressing the dose indicator.

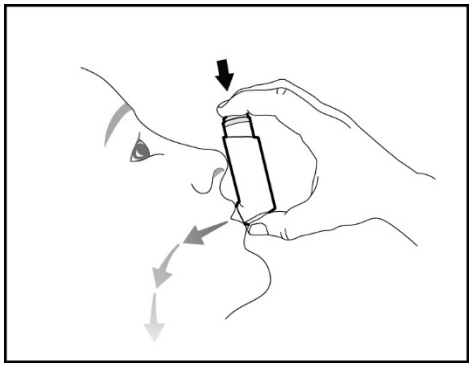


Figure 10

Step 6: When you have finished breathing in, remove the mouthpiece from your mouth. Hold your breath as long as you comfortably can, up to 10 seconds (**See Figure 11**).

Figure 11

Step 7: Breathe out gently (**See Figure 12**). **Repeat Step 2 through Step 7** to take your second puff of SYMBICORT AEROSPHERE.

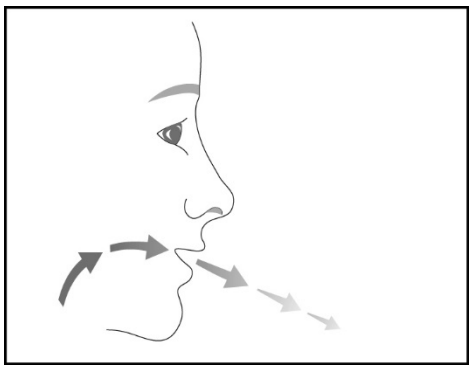


Figure 12

Step 8: Replace the cap over the mouthpiece right away after use (**See Figure 13**).

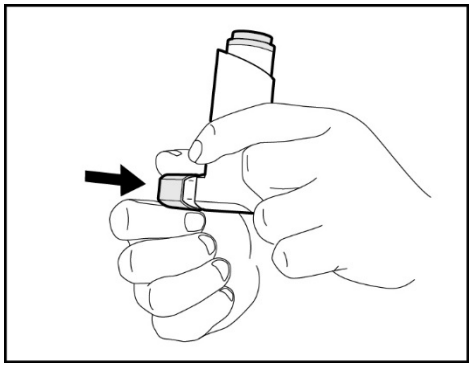


Figure 13

Step 9: Rinse your mouth with water and spit the water out to remove any extra medicine. Do not swallow the water.

It is important to store SYMBICORT AEROSPHERE in a dry place.

How to clean your SYMBICORT AEROSPHERE inhaler:

Clean the inhaler 1 time each week. It is very important to keep your inhaler clean so that medicine will not build-up and block the spray through the mouthpiece (**See Figure 14**).

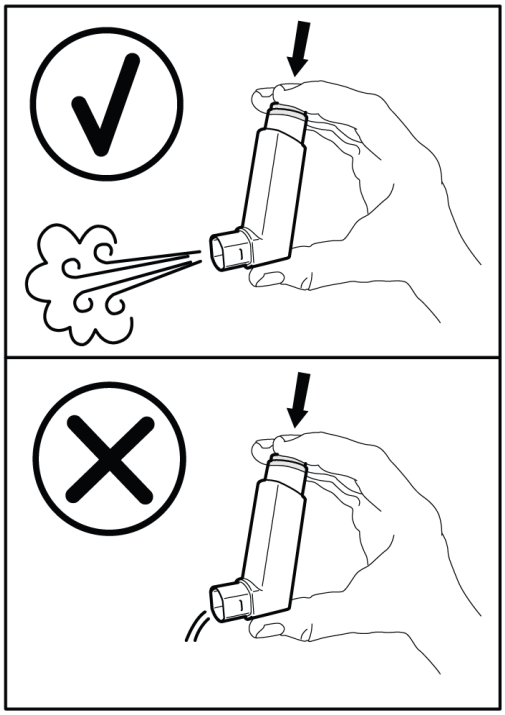


Figure 14

Step 1: Take the canister out of the actuator (**See Figure 15**). **Do not** clean the canister or let it get wet.

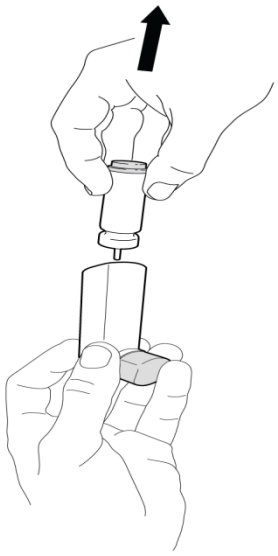


Figure 15

Step 2: Take the cap off the mouthpiece.

Step 3: Hold the actuator under the tap and run warm water through it for about 30 seconds. Turn the actuator upside down and run warm water through it again for about 30 seconds (**See Figure 16**).

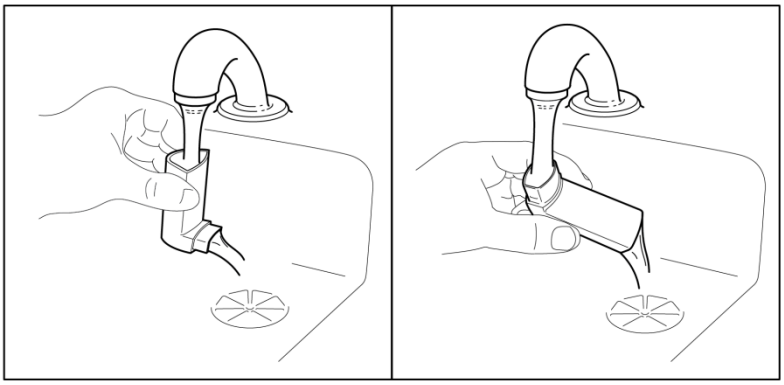


Figure 16

Step 4: Shake off as much water from the actuator as you can.

Step 5: Look into the actuator and the mouthpiece to make sure any medicine build-up has been completely washed away. If there is any build-up, repeat Step 3 through Step 5 in the section "**How to clean your SYMBICORT AEROSPHERE inhaler**".

Step 6: Let the actuator air-dry completely, such as overnight (**See Figure 17**). **Do not** put the canister back into the actuator if it is still wet.

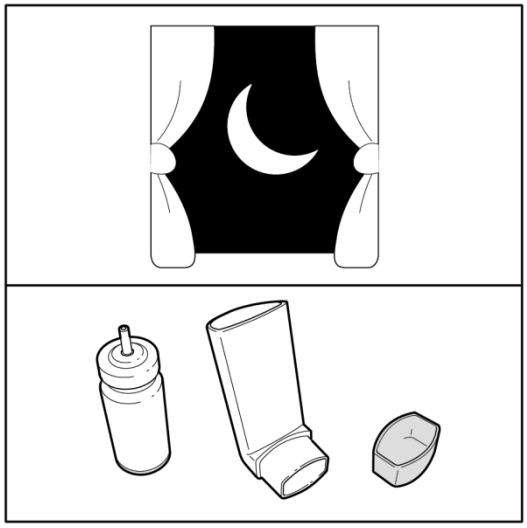


Figure 17

Step 7: When the actuator is dry, gently press the canister down in the actuator (**See Figure 18**). Do not press down too hard on the canister. This could cause a puff of medicine to be released.

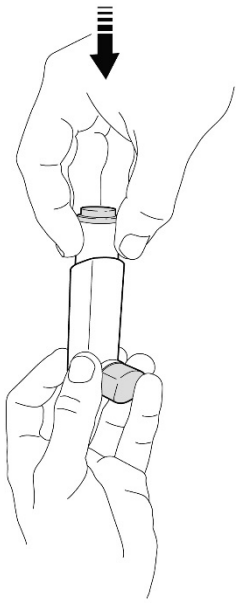


Figure 18

Step 8: Re-prime your **SYMBICORT AEROSPHERE** inhaler after each cleaning. To re-prime the inhaler, shake the inhaler well and press down on the center of the dose indicator 2 times to release a total of 2 puffs into the air away from your face. Your inhaler is now ready to use.

If SYMBICORT AEROSPHERE is not used for more than 7 days, or is dropped, you will need to re-prime it before use.

To re-prime the inhaler, shake the inhaler well and press down on the center of the dose indicator 2 times to release a total of 2 puffs into the air away from your face. Your inhaler is now ready to use again.

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

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