PRODUCT MONOGRAPH

PrSYMBICORT® TURBUHALER®

budesonide/formoterol fumarate dihydrate dry powder for oral inhalation

PrSYMBICORT® ***100*** TURBUHALER®

100 mcg budesonide and 6 mcg formoterol fumarate dihydrate

PrSYMBICORT® ***200*** TURBUHALER®

200 mcg budesonide and 6 mcg formoterol fumarate dihydrate

PrSYMBICORT® ***FORTE*** TURBUHALER®

400 mcg budesonide and 12 mcg formoterol fumarate dihydrate

Corticosteroid and bronchodilator for oral inhalation

AstraZeneca Canada Inc.
1004 Middlegate Road
Mississauga, Ontario
L4Y 1M4
www.astrazeneca.ca

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Pr SYMBICORT® TURBUHALER®

budesonide/formoterol fumarate dihydrate

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral inhalation	Turbuhaler / 100 mcg budesonide / 6 mcg formoterol fumarate dihydrate 200 mcg budesonide / 6 mcg formoterol fumarate dihydrate 400 mcg budesonide / 12 mcg formoterol fumarate dihydrate	Lactose monohydrate (which may contain milk protein residue)

INDICATIONS AND CLINICAL USE

Asthma

SYMBICORT (budesonide and formoterol fumarate dihydrate) is indicated for the treatment of asthma in patients 12 years and older with reversible obstructive airways disease.

SYMBICORT should not be used in patients whose asthma can be managed by occasional use of a rapid onset, short duration, inhaled $beta_2$ agonist or in patients whose asthma can be managed by inhaled corticosteroids along with occasional use of a rapid onset, short duration, inhaled $beta_2$ agonist.

Long-acting $beta_2$ agonists (LABA), such as formoterol, one of the active ingredients in SYMBICORT, may increase the risk of asthma-related death. Available data from controlled clinical trials suggest that LABA may increase the risk of asthma-related hospitalization in pediatric and adolescent patients (see WARNINGS AND PRECAUTIONS). Therefore, when treating patients with asthma, physicians should only prescribe SYMBICORT for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid, or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA.

Once asthma control is achieved and maintained, assess the patient at regular intervals, and do not use SYMBICORT for patients whose asthma is adequately controlled on low- to medium-dose inhaled corticosteroids.

For SYMBICORT there are two treatment approaches:

A. **SYMBICORT Maintenance Therapy**: SYMBICORT is taken as regular maintenance treatment with a separate rapid-acting bronchodilator as rescue.

B. **SYMBICORT Maintenance and Reliever Therapy**: SYMBICORT is taken as regular maintenance treatment and as needed in response to symptoms.

See DOSAGE AND ADMINISTRATION and WARNINGS AND PRECAUTIONS.

Chronic Obstructive Pulmonary Disease (COPD)

SYMBICORT TURBUHALER is indicated for the maintenance treatment of moderate to severe COPD including chronic bronchitis and emphysema, in patients with persistent symptoms and a history of exacerbations, where the use of a combination product is considered appropriate.

SYMBICORT TURBUHALER is NOT indicated for the relief of acute bronchospasm in COPD patients.

See DOSAGE AND ADMINISTRATION and WARNINGS AND PRECAUTIONS.

Geriatrics:

No dosage adjustment is required in patients 65 years of age and older.

Pediatrics:

The safety and efficacy in pediatric patients younger than 12 years have not been established.

CONTRAINDICATIONS

SYMBICORT (budesonide/formoterol fumarate dihydrate) is contraindicated in patients with a known hypersensitivity to budesonide, formoterol or inhaled lactose.

WARNINGS AND PRECAUTIONS

WARNING FOR ASTHMA PATIENTS:

Asthma-Related Death: Long-acting beta$_2$ agonists (LABA), such as formoterol, one of the active ingredients in SYMBICORT, may increase the risk of asthma-related death. Data from a large placebo-controlled US study, which compared the safety of salmeterol, a LABA, with placebo when added to patients' usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a LABA class effect. Available data from controlled clinical trials suggest that LABA may increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA.

Therefore, when treating patients with asthma, SYMBICORT should only be used for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals, and do not use SYMBICORT for patients whose asthma is adequately controlled on low- to medium- dose inhaled corticosteroids (see DOSAGE AND ADMINISTRATION).

General

When beginning treatment with SYMBICORT (budesonide/formoterol fumarate dihydrate), patients who have been taking inhaled beta$_2$-agonist on a regular basis should be instructed to discontinue the regular use of these drugs.

It is crucial to inform patients with asthma to have medication for rescue use available at all times. Asthma patients should be clearly instructed to use medication for rescue (e.g., SYMBICORT, terbutaline, or salbutamol) if they develop asthma symptoms while taking SYMBICORT.

The reliever inhalations of SYMBICORT should be taken in response to symptoms but are not intended for regular prophylactic use before exercise.

Do not exceed recommended dosage of SYMBICORT.

Use in adolescents and asthma severity reassessment: In adolescents the severity of asthma may vary with age and periodic reassessment should be considered to determine if continued therapy with SYMBICORT is still indicated.

Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods; these effects are much less likely to occur than with oral

corticosteroids. Possible systemic effects include Cushing's syndrome, Cushingoid features, and adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density (BMD), cataract and glaucoma. It is important therefore, that the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control is maintained (see Monitoring and Laboratory Tests).

A reduction of growth velocity in children or teenagers may occur as a result of inadequate control of chronic diseases such as asthma or from use of corticosteroids for treatment. Physicians should closely follow the growth of adolescents taking long-term corticosteroids by any route, and weigh the benefits of the corticosteroid therapy and asthma control against the possible risk of growth suppression if any adolescent's growth appears slowed.

Discontinuance

Treatment with inhaled corticosteroids should not be stopped abruptly, but tapered gradually under the supervision of a physician.

Cardiovascular

Cardiovascular Effects: Although clinically not significant, a small increase in QTc interval has been reported with therapeutic doses of formoterol. It is not known if this becomes clinically significant when concomitant medications causing similar effects are prescribed and/or in the presence of heart diseases, hypokalemia, or hypoxia.

No clinically significant effect on the cardiovascular system is usually seen after the administration of inhaled formoterol in recommended doses, but the cardiovascular and central nervous system effects seen with all sympathomimetic drugs (e.g., increased blood pressure, heart rate, excitement) can occur after use of formoterol. Formoterol, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive disorders or thyrotoxicosis; diabetes mellitus, and in patients who are unusually responsive to sympathomimetic amines.

With beta-adrenergic agonist bronchodilators, changes in systolic and/or diastolic blood pressure, pulse rate, and electrocardiograms have been noted. No clinically important differences have been observed with SYMBICORT within the recommended dosages.

Ear/Nose/Throat

Candidiasis: Therapeutic dosages of budesonide may cause the appearance of Candida albicans (thrush) in the mouth and throat. The development of pharyngeal and laryngeal candidiasis is a cause for concern because the extent of its penetration into the respiratory tract is unknown. Symptomatic candidiasis can be treated with topical anti-fungal therapy while continuing to use SYMBICORT.

Endocrine and Metabolism

Metabolic Changes: In common with other beta-adrenergic agents, formoterol can induce reversible metabolic changes (hyperglycemia, hypokalemia).

Metabolic Effects: Due to reversible hyperglycemic effect of $beta_2$-agonists, additional blood glucose monitoring is recommended initially in diabetic patients.

Hypothyroidism: There is an enhanced effect of corticosteroids on patients with hypothyroidism.

Systemic steroid replacement by inhaled steroid: Particular care is needed in asthmatic patients who are transferred from systemically active corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have occurred during and after transfer. For the transfer of patients treated with oral corticosteroids, inhaled corticosteroids should first be added to the existing oral steroid therapy which is then gradually withdrawn.

Patients with adrenocortical suppression should be monitored regularly and the oral steroid reduced cautiously. Some depression of plasma cortisol may occur in a small number of patients on higher doses of inhaled budesonide (for example greater than 800 mcg/day). However, in most but not all patients on inhaled budesonide therapy, adrenal function and adrenal reserve remain within normal range. Some patients transferred from other inhaled steroids or oral steroids remain at risk of impaired adrenal reserve for a considerable time after transferring to inhaled budesonide.

After withdrawal from long-term treatment with systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery or infections, particularly gastroenteritis. Although inhaled budesonide may provide control of asthmatic symptoms during these episodes, it does not provide the systemic steroid which is necessary for coping with these emergencies. The physician may consider supplying oral steroids for use in times of stress (e.g. asthma exacerbations, chest infections, surgery).

During periods of stress or a severe asthmatic attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume systemic steroids immediately and to contact their physician for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic steroids during periods of stress or asthma exacerbation. To assess the risk of adrenal insufficiency in emergency situations, routine tests of adrenal cortical function, including measurement of early morning and evening cortisol levels, should be performed periodically in all patients. An early morning resting cortisol level may be accepted as normal only if it falls at or near the normal mean level.

Reduction in Bone Mineral Density: Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing inhaled corticosteroids. 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, chronic alcohol use, 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.

Hematologic

Eosinophilic Conditions: In rare cases, patients on inhaled corticosteroids may present with systemic eosinophilic conditions, with some patients presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of inhaled corticosteroid. Physicians should be alerted to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal relationship between inhaled corticosteroid and these underlying conditions has not been established.

Hepatic/Biliary/Pancreatic

Cirrhosis: There is an enhanced effect of corticosteroids on patients with cirrhosis. Reduced liver function may affect the elimination of corticosteroids. The intravenous pharmacokinetics of budesonide however, are similar in cirrhotic patients and in healthy subjects. The pharmacokinetics after oral ingestion of budesonide were affected by compromised liver function as evidenced by increased systemic availability. This is however, of little importance for budesonide, as after inhalation, the oral contribution to systemic availability is very small (see DOSAGE AND ADMINISTRATION, Special Populations, Hepatic/Renal Impairment and ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Excretion).

Immune

Effect on Infection: Patients who are on drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible children or adults on immunosuppressant corticosteroids. In such children or adults who have not had these diseases, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affect 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 to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intravenous immunoglobulin (IG) may be indicated. If chickenpox develops, treatment with antiviral agents may be considered.

Corticosteroids may mask some signs of infection and new infections may appear. A decreased resistance to localized infection has been observed during corticosteroid therapy;

this may require treatment with appropriate therapy or stopping the administration of SYMBICORT.

Ophthalmologic

Glaucoma, increased intraocular pressure, and cataracts have been reported in patients following the long-term administration of inhaled corticosteroids. Therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts.

Respiratory

Pneumonia (COPD patients): Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of pneumonia and exacerbations frequently overlap. Lower respiratory tract infections, including pneumonia, have been reported following the inhaled administration of corticosteroids. Clinical studies and meta-analyses indicate that treatment of COPD with inhaled corticosteroids may lead to an increased risk of pneumonia.

The incidence of pneumonia and lung infections other than pneumonia have been assessed in two 12-month studies of 1,834 patients with COPD. In these two studies, there was a slightly higher incidence of lung infections other than pneumonia (e.g., bronchitis, viral lower respiratory tract infections, etc.) in patients receiving SYMBICORT TURBUHALER 2 x 200/6 mcg bid (13.0%) in comparison with those receiving formoterol 2 x 6 mcg bid (11.4%), budesonide 2 x 200 mcg bid (9.9%), or placebo (8.2%). Pneumonia occurred in 4.1% of patients treated with SYMBICORT TURBUHALER compared with 2.4% treated with formoterol, 3.1% treated with budesonide, and 2.8% treated with placebo (see ADVERSE DRUG REACTIONS).

A pooled-analysis was carried out to specifically evaluate the risk of pneumonia in COPD patients treated with budesonide-containing products (i.e. SYMBICORT and PULMICORT). This pooled-analysis consisted of safety data from 11 randomized, double-blind, placebo or active-controlled, parallel-group clinical trials with a total 10,570 COPD patients, of whom 5,750 were exposed to a budesonide-containing treatment. The primary endpoint in the pooled analysis was time to first pneumonia treatment emergent serious adverse event and the primary comparison was budesonide-containing versus non-budesonide-containing treatment. The incidence rate of pneumonia reported as a serious adverse event was 1.9% per year on budesonide containing treatments and 1.5% per year on non-budesonide containing treatments. The overall pooled hazard ratio, comparing all patients that received budesonide with all patients that received non-budesonide-containing treatments, was 1.15 (95% CI: 0.83, 1.57).

Paradoxical Bronchospasm: As with other inhalation therapy, paradoxical bronchospasm may occur characterized by an immediate increase in wheezing after dosing. In this event, SYMBICORT should be discontinued immediately, the patient assessed, and if necessary, alternative therapy instituted.

Special Populations

Pregnant Women: In experimental animal studies, budesonide was found to cross the placental barrier. Like other glucocorticosteroids, budesonide is teratogenic to rodent species. High doses of budesonide administered subcutaneously produced fetal malformations, primarily skeletal defects, in rabbits, rats and mice. Results from world-wide post marketing experience indicate inhaled budesonide during pregnancy has no adverse effects on the health of the fetus/new born child. Review of published literature of orally inhaled budesonide, including results from a large case control study performed with cases identified from 3 Swedish health registers showed that there was no association between exposure to inhaled budesonide and overall congenital malformations. Results from a similar study performed with intranasal budesonide, using the same 3 Swedish health registers showed that the use of intranasal budesonide was associated with a subgroup "less severe cardiovascular defects"; however, there was no statistically significant association between the use of intranasal budesonide during pregnancy and overall congenital malformations, or overall frequency of cardiovascular defects in the offspring. The safety of formoterol during pregnancy has not yet been established. SYMBICORT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in Labour and Delivery: There are no well-controlled human studies that have investigated effects of formoterol on preterm labour or labour at term. Because of the potential for beta-agonist interference with uterine contractility, use of SYMBICORT during labour should be restricted to those patients in whom the benefits clearly outweigh the risks.

Nursing Women: A Clinical Pharmacology Study has shown that inhaled budesonide is excreted in breast milk. It is not known whether formoterol passes into human breast milk. In rats, small amounts of formoterol have been detected in maternal milk. Administration of SYMBICORT to women who are breastfeeding should only be considered if the expected benefit to the mother is greater than any possible risk to the child.

Pediatrics: SYMBICORT is not currently recommended in children younger than 18 years of age for the treatment of COPD or younger than 12 years of age for the treatment of asthma, due to limited clinical data in this age group.

Geriatrics: As with other beta$_2$-agonists, special caution should be observed when using formoterol in elderly patients who have concomitant cardiovascular disease that could be adversely affected by this class of drug. Based on available data, there is no need to adjust the dose in elderly patients.

Monitoring and Laboratory Tests

Monitoring Control of Asthma or COPD

With asthma, a persistent increase in the use of medication for rescue (e.g. SYMBICORT, terbutaline or salbutamol), indicates a deterioration of asthma control and the patient's condition should be re-evaluated (see DOSAGE AND ADMINISTRATION).

Asthma or COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If patients find the rescue medication less effective (e.g. increased or persistent use), or exceeds the highest recommended dose of SYMBICORT, medical attention must be sought as this could be indicative of disease deterioration.

Sudden and progressive deterioration in control of asthma or COPD (e.g. exacerbations) is potentially life threatening and the patient should undergo urgent medical assessment. It is recognized that exacerbations are the most frequent cause of medical visits, hospital admissions and mortality among patients with asthma or COPD. With asthma and COPD, consideration should be given to the need for increased therapy with corticosteroids, e.g. a course of oral corticosteroids. Antibiotic treatment should be considered if an infection is present. Treatment with SYMBICORT should not be initiated to treat a severe exacerbation.

During long-term therapy, HPA axis function and haematological status should be assessed periodically. For patients at risk, monitoring of bone and ocular effects (cataract and glaucoma) should also be considered in patients receiving maintenance therapy with SYMBICORT. It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroids is regularly monitored.

As with any asthma or COPD therapy, before introducing SYMBICORT, adequate education on how to use the drug and what to do during periods of worsening disease should be provided to the patient.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Since SYMBICORT (budesonide/formoterol fumarate dihydrate) contains both budesonide and formoterol, the same type and intensity of undesirable effects as reported for these substances may occur. No increased incidence of adverse reactions has been seen following concurrent administration of the two compounds. The most common drug related adverse reactions are pharmacologically predictable side-effects of $beta_2$-agonist therapy, such as headaches, tremor, palpitations and coughing. These tend to be mild and disappear within a few days of treatment.

Long-acting $beta_2$ agonists (LABA), such as formoterol, one of the active ingredients in SYMBICORT, may increase the risk of asthma-related death. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA may increase the risk of asthma-related hospitalization in pediatric and adolescent patients (see WARNINGS AND PRECAUTIONS).

Adverse reactions that have been associated with use of budesonide or formoterol, reported from either clinical trials for asthma or COPD, or SYMBICORT post-marketing use are noted in **Table 1** below.

Table 1 Adverse reactions associated with use of budesonide or formoterol

Frequency	System Organ Class (SOC) disorders	Reaction
Common 1% to 10%	Cardiac disorders:	Palpitations
(>1/100, <1/10)	Infections and infestations:	Candida infections in the oropharynx
	Nervous system disorders:	Headache, tremor
	Respiratory, thoracic and mediastinal disorders:	Mild irritation in the throat, coughing, hoarseness
Uncommon 0.1% to 1%	Cardiac disorders:	Tachycardia
(>1/1,000, </100)	Gastrointestinal disorders:	Nausea
	Musculoskeletal and connective tissue disorders:	Muscle cramps
	Nervous system disorders:	Dizziness
	Psychiatric disorders:	Agitation, restlessness, nervousness, sleep disturbances
Rare 0.01 to 0.1%	Cardiac disorders:	Cardiac arrhythmias, e.g. atrial fibrillation, supraventricular tachycardia, extrasystoles
(>1/10,000, <1/1,000)	Immune system disorders:	Immediate and delayed hypersensitivity reactions, e.g., dermatitis, exanthema, urticaria, pruritus, angioedema and anaphylactic reaction.
	Respiratory, thoracic and mediastinal disorders:	Bronchospasm
	Skin and subcutaneous tissue disorders:	Skin bruising
Very rare <0.01%	Cardiac disorders:	Angina pectoris
(<1/10,000)	Endocrine disorders:	Signs or symptoms of systemic glucocorticosteroid effects, e.g. hypofunction of the adrenal gland
	Metabolism and nutrition disorders:	Hyperglycemia
Very rare <0.01%	Psychiatric disorders:	Depression, behavioural disturbances

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

COPD

Clinical trial adverse event data is provided from two 12-month, randomised, double-blind, placebo-control multicentre trials comparing SYMBICORT (2 x 200/6 mcg) bid with placebo, budesonide 2 x 200 mcg bid, and formoterol 2 x 6 mcg bid. A total of 1,834 COPD patients were enrolled in these studies. The most frequently reported adverse events are presented in Table 2. These adverse reactions were mostly mild to moderate in severity.

Table 2 includes all events (whether considered drug-related or non-drug related by the investigator) that occurred at a rate of 3% or greater in the SYMBICORT treatment group, and were more common than in the placebo group.

Table 2 Overall adverse experiences with ≥3% and more common than placebo in the SYMBICORT group in controlled clinical trials (0629 and 0670) with SYMBICORT in patients with COPD

Adverse event	**Symbicort (n=462)**	**Budesonide (n=455)**	**Formoterol (n=456)**	**Placebo (n=461)**
System organ class **Preferred term**	**%**	**%**	**%**	**%**
% of patients reporting at least one adverse event	**63**	**64**	**67**	**61**
Infections and infestations				
Nasopharyngitis	9	7	7	6
Pneumonia	4	3	2	3
General disorders and administration site conditions				
Chest pain	3	2	2	2
Nervous system disorders				
Headache	3	2	3	2
Musculoskeletal and connective tissue disorders				
Muscle spasms	3	2	2	1

COPD Clinical Trial Adverse Drug Reactions (1-3%)

Gastrointestinal disorders: diarrhea, dyspepsia, constipation, abdominal pain, abdominal pain upper, vomiting

General disorders and administration site conditions: pyrexia

Infections and infestations: influenza, respiratory tract infection, upper respiratory tract infection, rhinitis, pharyngitis, cystitis, oral candidiasis

Musculoskeletal and connective tissue disorders: myalgia, arthralgia, pain in extremity

Nervous system disorders: tremor

Psychiatric disorders: insomnia, anxiety

Respiratory, thoracic and mediastinal disorders: dysphonia, oropharyngeal pain, nasal congestion

All cause mortality was assessed in COPD trials 0629 and 0670. Of the 1834 patients in the pooled data, there were 56 (3.1%) deaths: 20 (4.4%) in the formoterol group, 14 (3.0%) in the placebo group, 11 (2.4%) in the budesonide group, and 11 (2.4%) in the SYMBICORT group. The most common cause of death overall was COPD (formoterol=9, placebo=7, budesonide=3, and SYMBICORT=3 cases).

Post-market Adverse Drug Reactions

The following adverse reactions have been reported during post-approval use of SYMBICORT. 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. Some of these adverse reactions may also have been observed in clinical studies with SYMBICORT.

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

Endocrine disorders: hypercorticism, growth retardation

Eye disorders: cataract, glaucoma, increased intraocular pressure

Gastrointestinal disorders: oropharyngeal candidiasis, nausea

Immune system disorders: immediate and delayed hypersensitivity reactions, such as anaphylactic reaction, angioedema, brochospasm, uticaria, rash, dermatitis, pruritus

Metabolic and nutrition disorders: hyperglycemia, hypokalemia

Musculoskeletal, connective tissue, and bone disorders: muscle spasms

Nervous system disorders: tremor, dizziness, headache

Psychiatric disorders: behaviour disturbances, sleep disturbances, nervousness, agitation, depression, restlessness

Respiratory, thoracic, and mediastinal disorders: dysphonia, cough, throat irritation

Skin and subcutaneous tissue disorders: skin bruising

Vascular disorders: hypotension, hypertension

DRUG INTERACTIONS

Overview

Pharmacokinetic interactions: The metabolism of budesonide is primarily mediated by the enzyme CYP3A4. CYP3A4 inhibitors like ritonavir and azole antifungals (e.g. ketoconazole and itraconazole), increase the systemic exposure to budesonide. Therefore, concomitant use of budesonide and ritonavir or azole antifungals should be avoided unless the potential benefit outweighs the risk of systemic corticosteroid side-effects.

Pharmacodynamic interactions: Beta-adrenergic blockers (including eye drops) can weaken or inhibit the effect of formoterol.

Budesonide and formoterol have not been observed to interact with any other drug used in the treatment of asthma.

DOSAGE AND ADMINISTRATION

SYMBICORT (budesonide/formoterol fumarate dihydrate) is for oral inhalation only. Patients should be instructed in the correct method to use the TURBUHALER, which is described in the CONSUMER INFORMATION, Proper Use of This Medication. An instructional video is also available at Symbicort.ca/video. The medication from SYMBICORT is delivered to the lungs as the patient inhales, and, therefore, it is important to instruct the patient to breathe in forcefully and deeply through the mouthpiece. The patient may not taste or feel any medication when using SYMBICORT due to the small amount of drug dispensed.

Patients should never breathe out through the mouthpiece and should replace the cover of the SYMBICORT TURBUHALER after use. Patients should be instructed to rinse their mouths out with water after inhaling the maintenance dose. This will help prevent the occurrence of candidiasis. Cleansing dentures has the same effect.

Clinically equivalent doses of SYMBICORT and PULMICORT® plus OXEZE® TURBUHALER are defined as follows:

SYMBICORT TURBUHALER	PULMICORT TURBUHALER **plus** OXEZE TURBUHALER
SYMBICORT ***100*** TURBUHALER:	PULMICORT TURBUHALER: (100 mcg budesonide per metered dose) plus OXEZE TURBUHALER: (6 mcg formoterol per metered dose)
SYMBICORT ***200*** TURBUHALER:	PULMICORT TURBUHALER: (200 mcg budesonide per metered dose) plus OXEZE TURBUHALER: (6 mcg formoterol per metered dose)
SYMBICORT ***FORTE*** TURBUHALER:	PULMICORT TURBUHALER: (400 mcg budesonide per metered dose) plus OXEZE TURBUHALER: (12 mcg formoterol per metered dose)

Dosing Considerations for Asthma

Long-acting beta$_2$ agonists (LABA), such as formoterol, one of the active ingredients in SYMBICORT, may increase the risk of asthma-related death. Available data from controlled clinical trials suggest that LABA may increase the risk of asthma-related hospitalization in pediatric and adolescent patients (see WARNINGS AND PRECAUTIONS). Therefore, when treating patients with asthma, physicians should only prescribe SYMBICORT for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid, or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA.

It is crucial to inform patients to have a medication for rescue use (e.g., SYMBICORT, terbutaline or salbutamol) available at all times to relieve acute asthmatic symptoms. If the patient's medication for rescue becomes less effective medical attention should be sought.

The patients should be made aware that for optimum benefit, SYMBICORT should be taken regularly, even when they are asymptomatic. Rescue inhalations only need to be taken to relieve acute asthma symptoms (see WARNINGS AND PRECAUTIONS).

A reassessment of asthma therapy should be considered in patients using an increasing number of rescue inhalations for symptom relief without achieving improved asthma control.

SYMBICORT therapy should not be initiated to treat an asthma exacerbation.

Recommended Dose and Dosage Adjustment for Asthma

When starting a patient on SYMBICORT, the dose should first be selected so that effective symptom control is obtained. Subsequently, the dose should be adjusted to the lowest dose at which symptom control is maintained.

The dosage of SYMBICORT should be individualized according to disease severity. Once asthma control has been achieved and maintained, assess the patient at regular intervals so that the dosage of SYMBICORT they are receiving remains optimal, and do not use SYMBICORT for patients whose asthma can be adequately controlled on low- to medium-dose inhaled corticosteroids.

There are two strategies for the treatment of asthma with SYMBICORT:

A. SYMBICORT Maintenance Therapy (SMT)

With SYMBICORT maintenance therapy, patients use SYMBICORT TURBUHALER as a daily maintenance dose and a separate fast-acting inhaled bronchodilator (e.g., terbutaline or salbutamol) for symptom relief. Patients should be advised to have a fast-acting bronchodilator available at all times.

Adults and adolescents (12 years and older):

1 - 2 inhalations SYMBICORT ***100*** TURBUHALER once or twice daily. The maximum recommended daily **maintenance** dose is 4 inhalations.

or

1 - 2 inhalations SYMBICORT ***200*** TURBUHALER once or twice daily. The maximum recommended daily **maintenance** dose is 4 inhalations.

or

1 inhalation SYMBICORT ***FORTE*** TURBUHALER once or twice daily. The maximum recommended daily **maintenance** dose is 4 inhalations.

In adults and adolescents the recommended starting dose is one or two inhalations of SYMBICORT ***200*** TURBUHALER twice daily.

During periods of worsening of asthma, the dose may temporarily be increased up to a maximum of 4 inhalations of SYMBICORT ***100*** TURBUHALER or SYMBICORT ***200*** TURBUHALER twice daily or 2 inhalations of SYMBICORT ***FORTE*** TURBUHALER twice daily.

Missed Dose for Asthma

If a dose of SYMBICORT is missed, it should be taken as soon as possible; the patient should then resume their regular schedule. A double dose of SYMBICORT should not be taken to make up for doses that are missed.

B. SYMBICORT Maintenance and Reliever Therapy (SYMBICORT SMART®)

Patients use SYMBICORT TURBUHALER both as a daily maintenance dose plus additional inhalations as needed for rapid symptom relief and a timely increase in controller therapy for improved asthma control. Patients should be advised to always have SYMBICORT TURBUHALER available for rescue use. A persistent increase in the use of SYMBICORT as needed indicates a deterioration of asthma control, and the patient's condition should be re-evaluated.

Adults and adolescents (12 years and older):

1 – 2 inhalations SYMBICORT ***100*** TURBUHALER twice daily or 2 inhalations once daily. Additional doses can be used as needed to provide rapid symptom relief and improved asthma control as follows. Patients should take 1 additional inhalation as needed in response to symptoms. If symptoms persist after a few minutes, an additional inhalation should be taken. Not more than 6 inhalations should be taken on any single occasion. The maximum recommended total daily dose is 8 inhalations.

or

1 – 2 inhalations SYMBICORT ***200*** TURBUHALER twice daily or 2 inhalations once daily. Additional doses can be used as needed to provide rapid symptom relief and improved asthma control as follows. Patients should take 1 additional inhalation as needed in response to symptoms. If symptoms persist after a few minutes, an additional inhalation should be taken. Not more than 6 inhalations should be taken on any single occasion. The maximum recommended total daily dose is 8 inhalations.

SYMBICORT ***FORTE*** TURBUHALER should only be used as SYMBICORT Maintenance Therapy and not as Symbicort Maintenance and Reliever Therapy.

SYMBICORT Maintenance and Reliever Therapy and Symbicort Maintenance Therapy

SYMBICORT is not currently recommended for children younger than 12 years of age due to the limited clinical data in this age group.

Dosing Considerations for Chronic Obstructive Pulmonary Disease (COPD)

SYMBICORT therapy should not be initiated to treat acute symptoms of COPD.

Recommended Dose and Dosage Adjustment for COPD

Maintenance for Adults (18 years and older)

2 inhalations SYMBICORT ***200*** TURBUHALER twice daily. The maximum recommended daily dose is 4 inhalations.

or

1 inhalation SYMBICORT ***FORTE*** TURBUHALER twice daily. The maximum recommended daily dose is 2 inhalations.

Special Populations

Geriatrics: There are no special dosage requirements for elderly patients.

Hepatic/Renal Impairment: There are no data available for the use of SYMBICORT in patients with hepatic or renal impairment. As budesonide and formoterol are primarily eliminated via hepatic metabolism an increased exposure can be expected in patients with severe liver disease (see WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic and ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Excretion).

OVERDOSAGE

For management of suspected drug overdose, contact your regional Poison Control Centre.

There are no data available from clinical trials on overdose with SYMBICORT (budesonide/formoterol fumarate dihydrate). An overdose of formoterol would likely lead to effects that are typical for beta$_2$-adrenergic agonists: tremor, headache, palpitations, and tachycardia. Hypotension, metabolic acidosis, hypokalemia and hyperglycemia may also occur. Supportive and symptomatic treatment may be indicated. A metered dose of 120 mcg formoterol administered during three hours in patients with acute bronchial obstruction raised no safety concerns.

Acute overdosage with budesonide even in excessive doses, is not expected to be a clinical problem. When used chronically in excessive doses, systemic glucocorticosteroid effects, such as hypercorticism and adrenal suppression, may appear.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

SYMBICORT contains formoterol fumarate dihydrate and budesonide, which have different modes of action and show additive effects in terms of reduction of asthma and COPD exacerbations. In asthma, SYMBICORT can offer a more convenient regime for patients requiring concurrent long-acting beta$_2$-agonist and inhaled corticosteroid therapy - dosing with SYMBICORT may be adjusted to meet the condition of the patients' disease. SYMBICORT can be used both as a maintenance and reliever medication in asthma, due to the rapid bronchodilator effect of formoterol and the anti-inflammatory effects of budesonide.

Pharmacodynamics

The respective mechanisms of action of budesonide and formoterol are discussed below.

Budesonide: Budesonide is a potent synthetic glucocorticosteroid with strong topical and weak systemic effects. Budesonide has a high local anti-inflammatory potency and it is rapidly biotransformed in the liver. This favorable separation between topical anti-inflammatory activity and systemic effect is due to strong glucocorticosteroid receptor affinity and an effective first pass metabolism with a short half-life. The anti-anaphylactic and anti-inflammatory effects of budesonide manifest themselves as decreased bronchial obstruction in the early as well as the late phase allergic reactions. When administered by inhalation at therapeutic doses, it has a direct, potent anti-inflammatory action within the lungs, resulting in reduced symptoms and exacerbations of asthma, without the adverse effects observed when corticosteroids are administered systemically. Budesonide has also been shown to decrease airway reactivity to both direct and indirect challenge in hyperreactive patients. Therapy with inhaled budesonide has been effective when used for prevention of exercise-induced asthma.

Formoterol: Formoterol is a potent, selective, fast and long-acting beta$_2$-adrenergic stimulant used for the prevention and relief of asthma symptoms. Formoterol produces relaxation of bronchial smooth muscle in patients with reversible airways obstruction. The bronchodilating effect sets in as rapidly as short-acting bronchodilators (salbutamol, terbutaline), within 1-3 minutes after inhalation, and has a duration of 12 hours after a single dose. Formoterol offers more effective protection against carbachol, histamine- or methacholine-induced bronchoconstriction than other short (e.g., salbutamol) and long-acting (e.g., salmeterol) beta$_2$-agonists. Formoterol provides dose-related benefits in pulmonary function and in bronchoprotective effects against methacholine, histamine and AMP challenges, indicating a dose-related reduction in airways responsiveness to both direct and indirect stimuli and a greater protection against asthma triggers such as allergens and exercise.

SYMBICORT: In clinical trials in asthma and COPD, combination treatment with formoterol and budesonide improved symptoms and lung function, and reduced exacerbations.

In asthma, the effect on lung function of SYMBICORT was clinically equivalent to that of the free combination of budesonide and formoterol in separate inhalers in adults and exceeded that of budesonide alone in adults and adolescents. There was no sign of attenuation of the

anti-asthmatic effect over time. SYMBICORT and the short-acting bronchodilator salbutamol have been shown to have similarly rapid onsets of effect. The combination of budesonide and formoterol does not mask the onset or severity of exacerbations.

Pharmacokinetics

Absorption: After the administration of budesonide, formoterol or the fixed combination, pharmacokinetic parameters, for the respective substances, were comparable. Specifically, for budesonide, AUC was slightly higher, rate of absorption more rapid and maximal plasma concentration higher after administration of the fixed combination. For formoterol, maximal plasma concentration was slightly lower after administration of the fixed combination.

SYMBICORT and the monoproducts (PULMICORT TURBUHALER and OXEZE TURBUHALER) were bioequivalent with regard to systemic bioavailability of budesonide and formoterol.

Inhaled budesonide is rapidly absorbed and the maximum plasma concentration is reached within 30 minutes after inhalation. In studies, mean lung deposition of budesonide after inhalation via TURBUHALER ranged from 32 to 44% of the delivered dose (25 to 30% of the metered dose). The systemic bioavailability is about 49% of the delivered dose and 38% of the metered dose.

Inhaled formoterol is rapidly absorbed and the maximum plasma concentration is reached within 10 minutes after inhalation. In studies the mean lung deposition of formoterol after inhalation via TURBUHALER ranged from 28-49% of the delivered dose (21-37% of the metered dose). Because of the low therapeutic dose, systemic levels of formoterol are low or undetectable after inhalation.

Distribution: Plasma protein binding is approximately 50% for formoterol and 90% for budesonide. Volume of distribution is about 4 L/kg for formoterol and 3 L/kg for budesonide.

Metabolism: Formoterol is inactivated via conjugation reactions (active O-demethylated and deformylated metabolites are formed, but they are seen mainly as inactivated conjugates). Budesonide undergoes an extensive degree (≈90%) of biotransformation on first passage through the liver to metabolites of low glucocorticosteroid activity. The glucocorticosteroid activity of the major metabolites, 6β-hydroxy-budesonide and 16α-hydroxy-prednisolone, is less than 1% of that of budesonide. There are no indications of any metabolic interactions or any displacement reactions between formoterol and budesonide.

Excretion: The major part of a dose of formoterol is eliminated via hepatic metabolism followed by renal excretion. After inhalation 8-13% of the delivered dose of formoterol is excreted unmetabolised in the urine. Formoterol has a high systemic clearance (approximately 1.4 L/min) and the late elimination half-life averages 17 hours.

Budesonide is eliminated via metabolism mainly catalysed by the enzyme CYP3A4. The metabolites of budesonide are excreted in urine as such or in conjugated form. Only

negligible amounts of unchanged budesonide have been detected in the urine. Budesonide has a high systemic clearance (approximately 1.2 L/min) and the plasma elimination half-life after i.v. dosing averages 4 hours.

Special Populations and Conditions

Pediatrics: Budesonide has a systemic clearance of approximately 0.5 L/min in 4-6 year old asthmatic children. Per kg body weight children have a clearance which is approximately 50% greater than in adults. The terminal half-life of budesonide after inhalation is approximately 2.3 hours in asthmatic children. The pharmacokinetics of formoterol in children has not been studied.

STORAGE AND STABILITY

SYMBICORT TURBUHALER (budesonide/formoterol fumarate dihydrate) should be stored at room temperature between 15ºC and 30ºC with the cover tightened.

SPECIAL HANDLING INSTRUCTIONS

SYMBICORT TURBUHALER (budesonide/formoterol fumarate dihydrate) cannot be refilled and should be discarded when finished.

DOSAGE FORMS, COMPOSITION AND PACKAGING

SYMBICORT TURBUHALER (budesonide/formoterol fumarate dihydrate) is a dry powder inhalation device that contains 6 mcg of formoterol fumarate dihydrate, and 100 or 200 mcg of budesonide, or 12 mcg formoterol fumarate dihydrate and 400 mcg of budesonide per inhalation. SYMBICORT TURBUHALER also contains lactose (may contain milk protein residue) which acts as a "carrier". The amount added does not normally cause problems in lactose-intolerant people.

SYMBICORT TURBUHALER is supplied in three strengths: SYMBICORT ***100*** TURBUHALER (100/6 mcg budesonide/formoterol fumarate dihydrate per dose), SYMBICORT ***200*** TURBUHALER (200/6 mcg budesonide/formoterol fumarate dihydrate per dose) and SYMBICORT ***FORTE*** TURBUHALER (400/12 mcg budesonide/formoterol fumarate dihydrate per dose).

SYMBICORT ***100*** TURBUHALER is available in a 120 dose pack size, and SYMBICORT ***200*** TURBUHALER is available in 60 or 120 dose pack sizes. SYMBICORT ***FORTE*** TURBUHALER is available in a 60 dose pack size.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name Budesonide

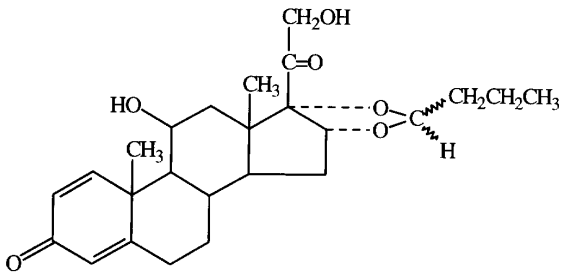
Chemical Name Budesonide is a mixture of two isomers:

1. Pregna-1,4-diene-3,20-dione,16,17-butylidenebis(oxy)-11,21-dihydroxy-,[11β,16α(R)] and

2. Pregna-1,4-diene-3,20-dione,16,17-butylidenebis(oxy)-11,21-dihydroxy-,[11β,16α(S)].

Molecular Formula and Molecular Mass $C_{25}H_{34}O_6$ 430.5

Structural Formula



Physiochemical Properties: Budesonide is a glucocorticosteroid and consists of a 1:1 mixture of two epimers, 22R and 22S. It is a white to off-white crystalline powder and is freely soluble in chloroform, sparingly soluble in ethanol, practically insoluble in water and in heptane. Budesonide melts at 224°C to 231.5°C, with decomposition.

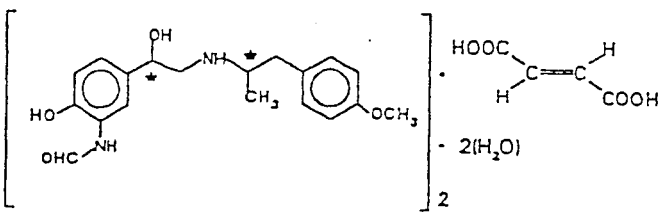
Drug Substance

Proper Name formoterol fumarate dihydrate

Chemical Name (R*,R*)-(±)-N-[2-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]formamide, (E)-2-butendioate(2:1), dihydrate

Molecular Formula and Molecular Mass $C_{42}H_{56}N_4O_{14}$ 840.9

Structural Formula:



Physiochemical Formoterol fumarate dihydrate is a white to off-white or slightly

Properties	yellow non-hygroscopic crystalline powder.
Dissociation Constant	The pKa of formoterol fumarate dihydrate at 25°C is 7.9 for the phenolic group and 9.2 for the amino group.
Partition Coefficient	The octanol-water partition coefficient at 25°C is 2.6.

CLINICAL TRIALS

Clinical Studies in Asthma

SYMBICORT Maintenance Therapy

Clinical studies in asthmatic adults and adolescents showed that SYMBICORT (budesonide/formoterol fumarate dihydrate) was significantly more effective than budesonide alone on all primary efficacy comparisons.

In studies comparing the safety of the combination product to concomitant treatment with budesonide and formoterol via separate inhalers, no differences were seen with respect to adverse events, laboratory measurements, vital signs or ECG.

Compared to treatment with budesonide alone, in mild asthmatics (≤ 500 mcg ICS daily) SYMBICORT increased the time to first mild exacerbation ($p=0.02$) and decreased the relative risk for mild exacerbations by 26% ($p=0.02$).

In a study of moderate to severe adult and adolescent asthmatics not well-controlled on inhaled glucocorticosteroids alone (≥ 750 mcg ICS daily), SYMBICORT dosed twice daily (total daily dose 1600/48 mcg) was more effective than budesonide dosed twice daily (total daily dose 1600 mcg) in increasing morning PEF over 12 weeks of treatment (mean difference was 32.9 L/min, $p<0.001$). Statistically significant improvements were also seen for evening PEF ($p<0.001$), total asthma symptom score ($p=0.005$), daytime asthma symptoms ($p<0.001$), symptom free days ($p<0.001$), use of rescue medication ($p<0.001$), rescue free days ($p<0.001$), asthma control days ($p<0.001$), time to first mild exacerbation ($p=0.003$) and FEV_1 ($p<0.001$).

In this 24-week study, no new safety concerns were identified and similar safety profiles were observed between the SYMBICORT and budesonide + formoterol treatment groups.

No clinically important differences with regards to s-potassium, s-glucose, vital signs, or ECG variables were identified between the SYMBICORT and budesonide + formoterol treatment groups or within these groups over time. There were no statistically significant differences between the SYMBICORT and budesonide + formoterol treatment groups regarding morning plasma cortisol or stimulated cortisol.

SYMBICORT Maintenance and Reliever Therapy (SYMBICORT SMART®)

SYMBICORT maintenance and reliever therapy is supported by 5 double-blind, randomized, parallel-group multicentre clinical studies that compared the safety and efficacy of SYMBICORT maintenance and reliever therapy with established treatments for persistent

asthma for 6 or 12 months. The studies included 12,076 patients, of which 4447 were randomized to SYMBICORT maintenance and reliever therapy, 1519 were adolescents (ages 12 to 17) and 842 were elderly (ages 65 to 80). Patients were required to be symptomatic despite daily use of inhaled glucocorticosteroids.

SYMBICORT maintenance and reliever therapy provided statistically significant and clinically meaningful reductions in severe exacerbations by prolonging time to first event and reducing the event rate (Table 3), as compared with all comparator treatments, including SYMBICORT at a higher maintenance dose (Study 735). Symptom control, lung function and reliever use were improved compared with SYMBICORT at the same maintenance dose or budesonide at a 2 to 4 times higher maintenance dose. This was generally achieved with a lower overall drug load, including reduced use of glucocorticosteroids (GCS) and less as-needed inhalations (see Table 3).

In Study 735, SYMBICORT maintenance and reliever therapy significantly prolonged the time to the first exacerbation compared to the other treatment groups. The rate of exacerbations was reduced by 28% compared to twice the maintenance dose of SYMBICORT with terbutaline as reliever (see Table 3).

In Study 734, SYMBICORT maintenance and reliever therapy prolonged the time to the first exacerbation compared to SYMBICORT at the same maintenance dose with either formoterol or terbutaline as reliever. The rate of exacerbations was reduced by 33% and 48%, respectively. Symptoms and reliever use were reduced and lung function improved, compared with both comparator treatments (see Table 3).

In Studies 673, 668 and 667, SYMBICORT maintenance and reliever therapy prolonged the time to the first exacerbation compared to SYMBICORT at the same maintenance dose with terbutaline as reliever and compared to a 2- to 4-fold higher maintenance dose of budesonide with terbutaline as reliever. Across the 3 studies, the rate of exacerbations was reduced by 45-54%. Symptoms and reliever use were reduced and lung function improved compared with all other treatments**.** The increases in symptoms, the increases in as-needed use, and the decreases in morning and evening peak expiratory flow (PEF) around severe exacerbations were similar between treatment groups, indicating exacerbations were no more severe in patients receiving SYMBICORT maintenance and reliever therapy.

In the 5 long-term studies, patients receiving SYMBICORT maintenance and reliever therapy used, on average, no reliever inhalations on 57% of treatment days and 0-2 reliever inhalations on 87% of treatment days and 0-6 reliever inhalations on 99% of treatment days. There was no sign of development of tolerance over time.

No new safety concerns were identified, based on the adverse event profile and the known class effects (GCS-related or $beta_2$-agonist-related).

Table 3 **Summary of pivotal clinical studies in support of SYMBICORT maintenance and reliever therapy (SYMBICORT SMART) - Baseline characteristics, dose, and effect on severe exacerbations in double-blind, long-term studies**

	Study 735[a] (COMPASS)		Study 734 (SMILE)			Study 673 (STAY)			Study 668 (STEP)		Study 667 (STEAM)	
Treatment group	**Symb + Symb**	**Symb + terb**	**Symb + Symb**	**Symb + form**	**Symb + terb**	**Symb + Symb**	**Symb + terb**	**Bud + terb**	**Symb + Symb**	**Bud + terb**	**Symb + Symb**	**Bud + terb**
N randomized	**1107**	**1105**	**1113**	**1140**	**1141**	**925**	**909**	**926**	**947**	**943**	**355**	**342**
Study duration	6 months		12 months			12 months			12 months		6 months	
Age, years	Mean: 37.9 Range: 11-83		Mean: 42 Range: 12-89			Mean: 36 Range: 4-79			Mean: 43 Range: 11-80		Mean: 38 Range: 11-79	
Gender, M/F	1411/1924		1345/2049			1231/1529			798/1092		270/427	
Race	2329 Caucasian, 33 black, 424 oriental, 549 other		2689 Caucasian, 12 black, 645 oriental, 48 other			2130 Caucasian, 29 black, 455 oriental, 146 other			1751 Caucasian, 9 black, 13 oriental, 117 other		361 Caucasian, 3 black, 332 oriental, 1 other	
Baseline characteristics indicative of asthma severity												
FEV_1 (%PN)	72	73	72	72	72	73	73	73	70	70	75	75
Reversibility (%)	24	25	24	24	24	21	21	21	24	24	17	17
GCS dose (mcg /day)	740	750	757	758	751	619	598	620	744	748	353	343
LABA use (%)[b]	45	46	59	58	59	28	28	27	44	43	22	18
Daily use of GCS/LABA during treatment (budesonide/formoterol for SYMBICORT. NB budesonide and formoterol as delivered dose)												
Maintenance dose (mcg)	320/9	640/18	320/9	320/9	320/9	160/9	160/9	640/0	320/9	640/0	160/9	320/0
Mean as-needed inh.	1.02	1.05	1.02	1.23	1.26	1.00	1.20	1.44	0.91	1.42	1.03	1.46
Mean total dose (mcg)	483/13.6	640/18	483/13.6	320/14.5	320/9	240/13.5[c]	160/9[c]	640/0[c]	466/13	640/0	242/16.7	320/0

Incidence of severe exacerbations (excluding exacerbations due to PEF falls).

Symb + Symb was statistically significantly superior to all comparators for time to first severe exacerbation and total number of severe exacerbations.

Table 3 **Summary of pivotal clinical studies in support of SYMBICORT maintenance and reliever therapy (SYMBICORT SMART) - Baseline characteristics, dose, and effect on severe exacerbations in double-blind, long-term studies**

	Study 735[a] (COMPASS)		Study 734 (SMILE)			Study 673 (STAY)			Study 668 (STEP)		Study 667 (STEAM)	
Treatment group	**Symb + Symb**	**Symb + terb**	**Symb + Symb**	**Symb + form**	**Symb + terb**	**Symb + Symb**	**Symb + terb**	**Bud + terb**	**Symb + Symb**	**Bud + terb**	**Symb + Symb**	**Bud + terb**
N randomized	**1107**	**1105**	**1113**	**1140**	**1141**	**925**	**909**	**926**	**947**	**943**	**355**	**342**
Patients with an exacerbation (%)	9	11	13	17	22	11	21	19	14	22	3	11
Number of severe exacerbations	125	173	194	296	377	160	330	294	197	349	14	57
Exacerbations per patient-year	0.23	0.32	0.19	0.29	0.37	0.19	0.40	0.35	0.23	0.42	0.08	0.35
Risk of 1st severe asthma exacerbation	Hazard ratio for the time to 1st severe exacerbation decreased with Symb + Symb versus Symb + terb by 26% (p=0.026)		Hazard ratio for the time to 1st severe exacerbation decreased with Symb + Symb versus Symb + form by 27% (p=0.0038) and versus Symb + terb by 45% (p<0.001)			Hazard ratio for the time to 1st severe exacerbation decreased with Symb + Symb versus Symb + terb by 50% (p<0.001) and versus Bud + terb by 45% (p<0.001)			Hazard ratio for the time to 1st severe exacerbation decreased with Symb + Symb versus Bud + terb by 39% (p<0.001)		Hazard ratio for the time to 1st severe exacerbation decreased with Symb + Symb versus Bud + terb by 70% (p<0.001)	
Number of days of systemic GCS use	694	1133	1295	2174	2930	1255	2918	2577	1776	3177	114	498

a The data from another inhaled corticosteroid/long-acting beta$_2$-agonist treatment arm are not shown.
b As monoproduct or in combination with inhaled GCS.
c Mean total daily dose is the sum of the maintenance dose for adults and adolescents and the mean as-needed dose for the whole population.

Table 4 Summary of results for key secondary efficacy variables in double-blind, long-term studies

Study	Treatment arm	N[a]	Morning PEF (L/min) [b]	Total symptom score (0-6)		Total daily as-needed inhalations		Nights with awakenings due to asthma symptoms (%)		Comments
			Change from baseline	Baseline	Treatment	Baseline	Treatment	Baseline	Treatment	
735[c]	Symb + Symb	1103	25.0	1.91	1.06	2.29	1.02	33.7	14.1	Despite lower daily dose in Symb + Symb group similar results were seen between Symb + Symb and Symb + terb for all variables.
	Symb + terb	1099	25.7	1.93	1.07	2.31	1.05	32.8	14.6	
734	Symb + Symb	1107	15.3	1.71	1.02	1.83	1.02	31.2	14.7	Symb + Symb stat. sig. superior to both comparators for all variables.
	Symb + form	1137	10.6	1.70	1.13	1.90	1.23	28.0	15.4	
	Symb + terb	1138	7.9	1.74	1.14	1.91	1.26	30.3	17.0	
673	Symb + Symb	922	29.9	1.48	0.79	2.45	1.01	21.8	8.6	Symb + Symb stat. sig. superior to both comparators for all variables.
	Symb + terb	906	22.0	1.44	0.86	2.41	1.21	20.2	11.9	
	Bud + terb	925	13.0	1.50	1.01	2.41	1.46	20.6	12.4	
668	Symb + Symb	947	34.2	1.84	1.08	1.85	0.90	22.6	9.4	Symb + Symb stat. sig. superior to budesonide for all variables
	Bud + terb	943	13.9	1.90	1.32	1.99	1.42	23.5	13.0	
667	Symb + Symb	354	34.5	1.25	0.73	1.64	1.04	13.3	6.5	Symb + Symb stat. sig. superior to budesonide for all variables except awakenings
	Bud + terb	342	9.5	1.33	0.94	1.77	1.48	18.6	10.7	

a Number refers to all patients analysed for efficacy; data were not available for every patient for every variable
b Primary efficacy parameter in study 667; time to 1st severe exacerbation was a secondary endpoint
c The data from another inhaled corticosteroid/long-acting beta$_2$-agonist treatment arm are not shown.

Clinical Studies in COPD

The use of SYMBICORT in the treatment of patients with moderate to severe COPD is supported by two 12-month, randomised, double-blind, placebo-controlled, parallel-group, multicentre clinical studies comparing efficacy and safety of SYMBICORT 2 x 200/6 mcg bid with placebo and with the individual components (budesonide 2 x 200 mcg bid or formoterol 2 x 6 mcg bid).

Patients with a clinical history of COPD, age 40 years or older, a pre-bronchodilator FEV_1 of ≤ 50% predicted normal, an FEV_1/VC ratio of ≤70%, a history of least one COPD exacerbation within 2-12 months period prior to enrolment, and a smoking history equivalent to 10 or more pack years were included in the studies. Patients with a history of asthma or seasonal allergic rhinitis prior to age 40, respiratory disorders other than COPD, relevant cardiac disorders, a requirement for the regular use of oxygen, or an exacerbation of COPD requiring hospitalisation, a course of antibiotics, and/or oral or systemic corticosteroids within 4 weeks prior to the study were excluded.

The co-primary efficacy endpoints in the SYMBICORT studies (0629 and 0670) were post-bronchodilator FEV_1 and moderate to severe COPD exacerbations, to demonstrate the benefit of the formoterol and budesonide components, respectively. A moderate to severe COPD exacerbation was defined as one or more of the following; use of oral steroids, antibiotics, or hospitalization due to respiratory symptoms. Specific respiratory symptoms or duration of symptoms were not pre-defined criteria for exacerbations and there was no criterion to distinguish between a new exacerbation and a relapse of a previous exacerbation. The statistical analyses did adjust for patient exposure and took into consideration heterogeneity caused by between-patient variation. While there is no consensus for the definition and classification of COPD exacerbations, a similar definition has been used in other COPD clinical studies.

A total of 1,834 COPD patients were randomised and received treatment. The average age of patients was 64 years, and 23% of those enrolled were female. The mean pre-bronchodilator FEV_1 at baseline was 0.99 L or 36% predicted in both studies. Inhaled corticosteroids were used by 26% (Study 0629) and 48% (Study 0670) of the patients prior to enrolment, with a mean daily dose of around 850 mcg.

Both trials showed that in COPD patients, the improvements with SYMBICORT were statistically significantly superior to placebo for the following variables: post-bronchodilator FEV_1, number of moderate to severe exacerbations, morning and evening PEF, total COPD symptom scores, night-time awakenings due to COPD symptoms, Health Related Quality of Life as measured by St. George's Respiratory Questionnaire (SGRQ), and the use of short-acting $beta_2$-agonists.

SYMBICORT was also statistically significantly superior to budesonide for post-bronchodilator FEV_1, morning and evening PEF, and use of short-acting $beta_2$-agonists.

In comparison to formoterol, SYMBICORT demonstrated a significant reduction in moderate to severe exacerbation rate of 23% (p=0.043) in Study 0629 and 26% (p=0.015) in Study 0670 (Table 5). In Study 0629, the mean number of moderate to severe exacerbations/patient-year was 1.42 for SYMBICORT, 1.84 for formoterol and 1.87 for placebo. Compared with

formoterol, the treatment of SYMBICORT reduced the rate of exacerbations by 0.42 exacerbations/patient-year. Similarly, in Study 0670, the mean number of moderate to severe exacerbations/patient-year was 1.38 for SYMBICORT, 1.85 for formoterol and 1.80 for placebo. The treatment of SYMBICORT reduced the exacerbation rate by 0.47 exacerbation/patient-year compared with formoterol. In comparison with formoterol, SYMBICORT statistically significantly improved post-bronchodilator FEV1 (p=0.002) in Study 0670 but not in Study 0629 (p=0.487). SYMBICORT also demonstrated a statistically significant improvement of -3.3 (p=0.014) units in the total score for SGRQ in Study 0670 when compared with formoterol, but not in Study 0629 (-0.34 units, p=0.816).

Table 5 Summary of Key Results for COPD Studies 0629 and 0670

		SYMBICORT vs placebo	SYMBICORT vs formoterol	Formoterol vs placebo
Improvements in post-dose FEV_1				
Study 0629	Mean ratio, %, (95% CI)	114.91 (110.96 – 119.06)	101.25 (97.76 – 104.86)	113.52 (109.54 –117.65)
	P-value	<0.001	0.487	<0.001
Study 0670	Mean ratio, %, (95% CI)	114.09 (110.45 – 117.84)	105.36 (101.99 – 108.84)	108.28 (104.75 –111.94)
	P-value	<0.001	0.002	<0.001
Reductions in Moderate to Severe Exacerbations				
Study 0629	Rate ratio[a] (95% CI)	0.758 (0.586 – 0.981)	0.771 (0.599 – 0.992)	0.984 (0.770 – 1.257)
	Reduction/patient-year	0.45	0.42	-
	P-value	0.035	0.043	0.895
Study 0670	Rate ratio[a] (95% CI)	0.764 (0.600 – 0.973)	0.745 (0.587 – 0.945)	1.026 (0.813 –1.295)
	Reduction/patient-year	0.42	0.47	-
	P-value	0.029	0.015	0.828
Improvements in Health-related Quality of Life: Change in total SGRQ score [b]				
Study 0629	Mean difference from baseline	-3.88	-0.34	-3.54
	P-value	0.009	0.816	0.018
Study 0670	Mean difference from baseline	-7.46	-3.33	-4.13
	P-value	<0.001	0.014	0.002

[a] From Poisson regression model
[b] St. George's Respiratory Questionnaire

In both studies, adverse reactions associated with SYMBICORT are described (see ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions, COPD).

DETAILED PHARMACOLOGY

Animal

Repeat dose pharmacokinetics of budesonide and formoterol fumarate dihydrate were determined by monitoring their plasma concentrations of each substance when inhaled individually and in combination during toxicity studies in the rat and dog. For both species, there was no evidence of altered exposure to or kinetics of budesonide and formoterol fumarate dihydrate, as a result of the combined administration of the substances.

Human

Pharmacokinetics and systemic pharmacodynamics of SYMBICORT were examined in healthy adult volunteers in repeat dose studies. Tolerability and systemic pharmacodynamics at doses exceeding the highest recommended dose were investigated in patients with asthma in repeat dose studies.

Pharmacodynamics: In these studies plasma cortisol, a marker of adaptation of the hypothalamic-pituitary-adrenal (HPA) axis was assessed as a single morning measurement. As well, 24 hour plasma cortisol AUC was measured. There was no difference in morning plasma cortisol between SYMBICORT and the free combination of budesonide and formoterol. The 24-hour plasma cortisol AUC detected differences in HPA axis adaptation that were not detected by the single morning measurement. Using this parameter, cortisol levels were 9% lower with SYMBICORT than with either budesonide alone or the free combination of budesonide and formoterol. As the difference was the same whether formoterol was present or not, greater systemic activity of SYMBICORT is not attributed to systemic interaction between budesonide and formoterol. The increased bioavailability of budesonide in SYMBICORT is considered to be of little clinical significance within the recommended dose.

In the tolerability study it was shown that the 12-hour average serum potassium concentration did not differ between SYMBICORT and formoterol alone at doses up to 2800/84 mcg budesonide/formoterol. Additionally, at this dose there were no differences in blood pressure, QT and QTc intervals and plasma lactate.

Pharmacokinetics: The systemic availabilities of budesonide and formoterol administered as SYMBICORT correspond to pulmonary availabilities of about 48% (budesonide) and 46% (formoterol) of the respective delivered dose. Absorption of budesonide and formoterol was rapid, both after administration of SYMBICORT and after administration of each drug alone. On average, peak plasma concentrations were reached within 10 minutes after drug inhalation.

TOXICOLOGY

For complete information on the toxicology of individual compounds, budesonide and formoterol fumarate dihydrate, please refer to the PULMICORT TURBUHALER and OXEZE TURBUHALER Product Monographs.

Long-term Toxicology

The general toxicity after repeated administration of the budesonide/formoterol combinations was studied in rats and dogs after inhalation.

Table 6 Summary of results of repeat dose toxicity studies

Species	Route Duration	Treatment	Dose (mcg/kg)	Results and Observations
Rat	inhalation 13 weeks	budesonide	72	- no mortalities or adverse clinical signs - decrease in body weight gain - increased hemoglobin (females) and red blood cells (males) - decreased white blood cells, lymphocytes and eosinophils - increased urea and alkaline phosphatase (males) - reduced thymus weights and increased kidney and heart weights - thymic atrophy - reduced incidence of extra medullary haemapoiesis in spleen (males)
		formoterol	2.25	- no mortalities or adverse clinical signs - slight increase in body weight gain - decreased white blood cells (females) - increased glucose (females) and alkaline phosphatase and phosphate (males) - increased weight of lung (males) and kidneys (females)
		budesonide/ formoterol	2.35/0.14 11.5/0.63 54/2.8	- no mortalities or adverse clinical signs - dose-related decrease in body weight gain (significant in high dose group) - food consumption slightly reduced (high dose group) - increased hemoglobin (high dose group) - dose-related decrease in white blood cells, lymphocytes and eosinophils (most pronounced in high dose females) - increased urea, potassium, alkaline phosphatase and phosphate (males) - increased urine pH (high dose females) - increased weight of kidney (females), lung (males) and heart (females) - dose-related decrease in thymus weights - thymic atrophy (high dose group) - reduced incidence of extramedullary haempoiesis in spleen (males)

Table 6 Summary of results of repeat dose toxicity studies

Species	Route Duration	Treatment	Dose (mcg/kg)	Results and Observations
Dog	Inhalation 13 weeks	budesonide	48.5	- no mortalities or adverse clinical signs - reduced body weight gain - slightly reduced lymphocyte counts - slight increase in total plasma protein, cholesterol and ALP levels - slightly decreased glucose levels - suppression of ACTH-mediated cortisol release - decreased adrenal and thymus weights and slight decrease in lung weight (males) - increased weight of spleen (males and females) and liver (females) - slightly decreased lung weights (males only) - marked or severe atrophy of the thymus - marked or severe atrophy of the Zona fasciculata of the adrenal cortex - minimal or slight lymphoid depletion in spleen (females)
		formoterol	2.65	- no mortalities or adverse clinical signs - mild to moderate transient tachycardia one hour after dosing - slightly raised neutrophil counts - slightly decreased plasma glucose levels (females) - slightly increased plasma cholesterol levels (females) - slightly decreased weights of adrenals, thymus and lungs (males) - increased weight of spleen (males and females) and liver (females)

Table 6 Summary of results of repeat dose toxicity studies

Species	Route Duration	Treatment	Dose (mcg/kg)	Results and Observations
		budesonide/ formoterol	2.05/0.105 9.8/0.5 49.5/2.7	- no mortalities or adverse clinical signs - reduced body weight gain (mid-dose males and both sexes at high dose) - mild to moderate transient tachycardia one hour after dosing (high dose group) - slightly reduced lymphocyte counts - slightly increased levels of total plasma protein, cholesterol and ALP - slightly decreased plasma glucose levels - dose-related suppression of ACTH mediated cortisol release (mid and high dose groups) - dose-related decrease in adrenal and thymus weights - increased weight of spleen (low and mid dose) and liver (females) - slightly decreased lung weights (males) - atrophy of the thymus (marked or severe at high dose, minimal or slight at low to mid dose, except in one animal where atrophy was marked) - dose-related atrophy of the Zona fasciculata of the adrenal cortex (marked or severe at high dose, minimal or slight at mid dose, minimal at low dose) - minimal or slight lymphoid depletion in spleen (males at mid and high dose)

In rats, daily nose only inhalation administration of budesonide, formoterol or budesonide + formoterol at total inhaled doses up to 73, 2.3 + 51 and 2.7 $mcg.kg^{-1}.day^{-1}$ respectively for 3 months produced a range of effects on body weight profiles, clinical pathology parameters, organ weights and histopathology findings. The changes observed were consistent with beta-agonist or glucocorticoid treatment and were considered to be mild in severity. Comparison of the effects of the high doses of budesonide and formoterol alone with the high dose of budesonide + formoterol revealed no obvious differences.

Daily inhalation dosing of a SYMBICORT powder formulation to dogs for 13 weeks at total inhaled doses of up to 50 $mcg.kg^{-1}.day^{-1}$ budesonide + 2.7 $mcg.kg^{-1}.day^{-1}$ formoterol produced no evidence of significant systemic toxicity. Changes seen were considered to represent the normal class effects expected from an inhaled glucocorticosteroid and beta-agonist. There was no evidence of any unexpected systemic toxicity and no evidence of local toxicity or irritation in the respiratory tract. Toxicokinetic data demonstrated that the animals had been systemically exposed to budesonide and/or formoterol and that the exposure was dose-related. Comparison of the effects of the high doses of budesonide and formoterol alone with the high dose of SYMBICORT revealed no significant differences.

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PART III:
CONSUMER INFORMATION

Pr SYMBICORT® TURBUHALER®
budesonide/formoterol fumarate dihydrate dry powder for oral inhalation

This leaflet is part III of a three-part "Product Monograph" published when SYMBICORT TURBUHALER was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about SYMBICORT TURBUHALER. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

This medicine is for you. Only a doctor can prescribe it for you. Never give it to someone else. It may harm them even if their symptoms are the same as yours.

WHAT THE MEDICATION IS USED FOR:
SYMBICORT TURBUHALER is used to treat:
- Asthma in adults and children (i.e. 12 years and older); and
- Chronic Obstructive Pulmonary Disease (COPD) in adults (i.e. 18 years and older).

WHAT IT DOES:
SYMBICORT TURBUHALER contains the medicines budesonide and formoterol.
- Budesonide is an inhaled corticosteroid (ICS). It reduces and prevents inflammation in the airways;
- Formoterol is a long-acting beta$_2$-agonist (LABA). It helps to widen and relax the muscles in your airways. This makes it easier for you to breathe. This effect starts within 1-3 minutes after you have inhaled the medicine and lasts for up to 12 hours.

Regular use of SYMBICORT TURBUHALER gives 24-hour relief or prevention of symptoms such as shortness of breath in patients with asthma, COPD and other similar conditions (see PROPER USE OF THIS MEDICATION).

WHEN IT SHOULD NOT BE USED:
- If you are allergic to budesonide, formoterol or inhaled lactose.
- **Asthma**: if you are under 12 years old.
- **COPD**: if you are under 18 years old.

WHAT THE MEDICINAL INGREDIENTS ARE:
Budesonide and formoterol fumarate dihydrate.

WHAT THE NONMEDICINAL INGREDIENTS ARE:
Lactose (may contain milk protein).

WHAT DOSAGE FORMS IT COMES IN:
Dry powder for oral inhalation:
- SYMBICORT ***100*** TURBUHALER (100 mcg/6 mcg);
- SYMBICORT ***200*** TURBUHALER (200 mcg/6 mcg);
- SYMBICORT ***FORTE*** TURBUHALER (400 mcg/12 mcg).

Your inhaler can contain either 60 or 120 doses.

WARNINGS AND PRECAUTIONS

Serious Warnings for Asthma Patients
Formoterol, one of the medicines in SYMBICORT TURBUHALER, may increase the risk of asthma-related death. It may increase the risk of asthma-related hospitalizations in pediatric and adolescent patients. Therefore,
- Your doctor will assess your asthma control at regular intervals. SYMBICORT TURBUHALER should only be used when your doctor decides that other asthma medications (e.g. inhaled glucocorticosteroids along with an as needed relief medication) are not helping you enough, or that you need two maintenance medications to control your asthma.
- SYMBICORT TURBUHALER should not be the first medication you use, unless advised by your doctor.

For any concerns regarding the use of SYMBICORT TURBUHALER, consult your doctor.

BEFORE you use SYMBICORT TURBUHALER talk to your doctor or pharmacist if you:
- Have health problems now or have had in the past
- Have heart problems;
- Have high blood sugar (diabetes);
- Have low blood potassium or any problems with your thyroid gland;
- Have seizures (epilepsy);
- Have severe liver problems (e.g. cirrhosis);
- Take, or have taken steroid medicines within the past several months;
- Have ever had a bad, unusual or allergic reaction to budesonide, formoterol or lactose or to other medicines for breathing problems;
- Are pregnant or planning to become pregnant;
- Are breast feeding;
- Have weak bones (osteoporosis).

Drugs like SYMBICORT can cause eye disorders:
- Cataracts: clouding of the lens in the eye, blurry vision, eye pain
- Glaucoma: an increased pressure in your eyes, eye pain. Untreated, it may lead to permanent vision loss;

You should therefore have regular eye exams.

You should avoid coming into contact with people who have measles or chicken pox while taking SYMBICORT TURBUHALER. If you are exposed, tell your doctor right away.

Special attention should be paid if you are an adolescent with asthma. Your growth should be monitored regularly by a doctor when being treated with corticosteroids. Studies have also shown that children whose asthma is not controlled do not grow as quickly as other children.

Patients with COPD:

Patients with COPD have a higher chance of getting pneumonia (a lung infection). Drugs like SYMBICORT TURBUHALER may increase the chance of getting pneumonia. It is very important that you tell your doctor immediately if you suspect an infection as even mild chest infections should be treated right away.

You should avoid close contact with people who have colds or the flu (influenza). Your doctor may also recommend that you receive a flu shot each year.

If you are using SYMBICORT TURBUHALER for COPD, tell your doctor if you have any of the following symptoms:
- Fever or chills;
- Increased mucus production or change in mucus colour;
- Increased cough;
- Increased breathing difficulties.

These all may be signs of pneumonia.

INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. Tell your doctor, nurse, or pharmacist about all the medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative medicines.

Drugs that may interact with SYMBICORT TURBUHALER are:
- Beta-blockers used to lower blood pressure (propranolol) or for other heart or eye problems (e.g. atenolol, timolol);
- Ketoconazole, itraconazole used to treat fungal infections;
- Ritonavir used to treat HIV or AIDS.

PROPER USE OF THIS MEDICATION

SYMBICORT TURBUHALER should be taken regularly (every day), even when you have no symptoms. Follow your doctor's instructions carefully. Asthma and COPD treatment will differ from person to person. Your prescribed treatment may be different from the information in this leaflet.

Do not stop taking SYMBICORT TURBUHALER without talking to your doctor. It is important that you do not suddenly stop taking SYMBICORT TURBUHALER as it may cause unwanted side effects.

DOSING

Patients with Asthma

Treatment with SYMBICORT should not be initiated to treat an asthma attack.

For the treatment of asthma, your doctor will instruct you to use SYMBICORT TURBUHALER in one of two ways:
1) SYMBICORT maintenance therapy; or
2) SYMBICORT maintenance and reliever therapy.

Each of these treatment plans is described below.

1) SYMBICORT Maintenance Therapy for Asthma

Using SYMBICORT TURBUHALER for maintenance therapy means:
i. you take a regular daily dose of SYMBICORT TURBUHALER, AND
ii. you use a separate inhaler, containing a fast-acting bronchodilator (airway-widening medicine) for relief of asthma symptoms.

This means that you need two separate inhalers.

Adults and adolescents (12 years and older)
- 1 - 2 inhalations SYMBICORT ***100*** TURBUHALER once or twice daily. The maximum recommended daily maintenance dose is 4 inhalations.
  or
- 1 - 2 inhalations SYMBICORT ***200*** TURBUHALER once or twice daily. The maximum recommended daily maintenance dose is 4 inhalations.
  or
- 1 inhalation SYMBICORT ***FORTE*** TURBUHALER once or twice daily. The maximum recommended daily maintenance dose is 4 inhalations.

Always carry your fast-acting bronchodilator (rescue medication) with you for relief of symptoms.

During periods of worsening asthma, the dose may temporarily be increased up to a maximum of 4 inhalations of SYMBICORT ***100*** TURBUHALER or SYMBICORT ***200*** TURBUHALER twice daily or 2 inhalations of SYMBICORT ***FORTE*** TURBUHALER twice daily.
Do NOT exceed the dose prescribed by your doctor.

2) SYMBICORT Maintenance and Reliever Therapy (SYMBICORT SMART®) for Asthma

Using SYMBICORT TURBUHALER for maintenance and reliever therapy means:
i. you take a regular daily maintenance dose of SYMBICORT TURBUHALER, AND
ii. you use SYMBICORT TURBUHALER if you need extra doses for relief of asthma symptoms.

This means that you use one inhaler (SYMBICORT TURBUHALER) for both daily maintenance and symptom relief.

Adults and adolescents (12 years and older)

- 1 - 2 inhalations SYMBICORT ***100*** TURBUHALER twice daily or 2 inhalations once daily. You should take 1 additional inhalation as-needed if you feel symptoms. If symptoms persist after a few minutes, an additional inhalation should be taken. Not more than 6 inhalations should be taken on any single occasion. The maximum recommended daily dose is 8 inhalations.
  or
- 1 - 2 inhalations SYMBICORT ***200*** TURBUHALER twice daily or 2 inhalations once daily. You should take 1 additional inhalation as-needed if you feel symptoms. If symptoms persist after a few minutes, an additional inhalation should be taken. Not more than 6 inhalations should be taken on any single occasion. The maximum recommended daily dose is 8 inhalations.

Always carry SYMBICORT TURBUHALER with you. You should use extra doses as needed to relieve your asthma symptoms, including periods when your asthma gets worse.

Do not exceed the maximum total number of daily inhalations (8 inhalations/day). If you exceed 8 inhalations/day please seek medical attention.

Patients with COPD

Adults (18 years and older)

- 2 inhalations SYMBICORT ***200*** TURBUHALER twice daily. The maximum recommended daily dose is 4 inhalations.
  or
- 1 inhalation SYMBICORT ***FORTE*** TURBUHALER twice daily. The maximum recommended daily dose is 2 inhalations.

Treatment with SYMBICORT should not be initiated to treat a COPD attack.

MISSED DOSE:
If you miss a dose, take it as soon as you remember and then go back to your regular schedule. Never take a double dose to make up for missed doses. If you are still unsure, check with your doctor or pharmacist to see what you should do.

OVERDOSE:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

The most common signs and symptoms of an overdose are:

- trembling
- headache
- rapid heartbeat.

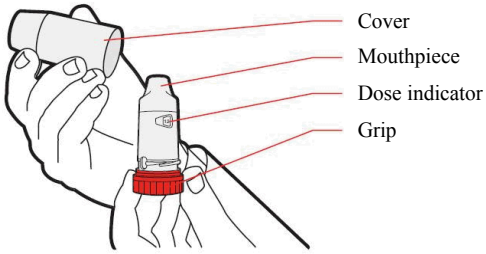
HOW TO USE YOUR SYMBICORT TURBUHALER INHALER

Before you start using SYMBICORT TURBUHALER for the first time it is important that you read the instructions below and follow them carefully.

Watch our video to make sure you use SYMBICORT TURBUHALER correctly.

Symbicort.ca/video

TURBUHALER is a multidose inhaler from which very small amounts of powder are administered. When you breathe in through the TURBUHALER, powder is delivered to the lungs. It is therefore important that you **inhale as deeply and strongly** as you can through the mouthpiece.



Before you use a **NEW** inhaler for the first time you must prepare the inhaler for use. Follow the steps under "**A. How to prepare a NEW inhaler for use:**".

For regular use of your inhaler follow the steps under "**B. How to take a dose:**".

A. How to prepare a NEW inhaler for use:
You only need to prepare your **NEW** inhaler for use **once.** You do not need to repeat these steps even if your inhaler is not used regularly.

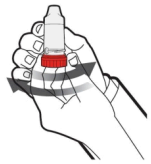
STEP 1 Unscrew and lift off the cover (Figure 1). You will hear a rattling sound when you unscrew the cover. This is normal.

Figure 1

STEP 2 Hold the inhaler upright. Do not hold the inhaler by the mouthpiece.

- Turn the **red grip** as far as it will go in one direction (clockwise or counter-clockwise, it does not matter

Figure 2



which way you turn it first).
- Then turn the red grip as far as it will go in the opposite direction (Figure 2).
- At some point when you are turning the grip, **you will hear a "click"**. This is part of the preparation process.

STEP 3 **Repeat STEP 2** one more time. Then follow the steps under "**B. How to take a dose:", starting at STEP 2.**

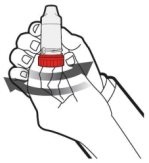
B. How to take a dose:
To properly take a dose, follow these 4 steps:

STEP 1 Unscrew and lift off the cover (Figure 1). You will hear a rattling sound when you unscrew the cover. This is normal.

Figure 1

STEP 2 Hold the inhaler upright. Do not hold the inhaler by the mouthpiece.
- Turn the **red grip** as far as it will go in one direction (clockwise or counter-clockwise, it does not matter which way you turn it first).
- Then turn the red grip as far as it will go in the opposite direction (Figure 2).

Figure 2



A dose has now been loaded.

- At some point when you are turning the grip, **you will hear a "click"**. This is part of the loading process.

NOTE: If you accidentally **drop**, **shake** or **breathe out** into SYMBICORT TURBUHALER after the dose has been loaded, you will lose your dose. If this happens, repeat STEP 2 to load a new dose.

STEP 3 **Breathe out**, with your mouth away from the mouthpiece (Figure 3). Then, place the mouthpiece gently between your teeth.

Figure 3

STEP 4 Now close your lips over the mouthpiece. Do not bite or chew the mouthpiece.
- **Inhale as deeply and strongly** as you can (Figure 4).
- You may not feel or taste the medication when inhaling. This is common.
- Before you exhale, remember to remove the inhaler from your mouth.

Figure 4

Repeat STEPS 2-4 if more than one dose has been prescribed. When you have taken the prescribed amount of doses, **replace the cover of the inhaler by screwing it back on**. Rinse your mouth with water, and do not swallow.

Note: Do not try to take off the mouthpiece or to twist it unnecessarily. The mouthpiece can be rotated but it is fixed to the inhaler and must not be taken off. Do not use the TURBUHALER if it has been damaged.

I cannot remember how many times I turned the red grip. What should I do?

The TURBUHALER is designed to load only one dose at a time. If you can't remember how many times you have turned the red grip, you can start the process again. Follow the steps below. You will not end up loading two doses.

If you are using a **NEW** inhaler for the first time, start at the beginning of STEP 2 under the section "**A. How to prepare a NEW inhaler for use:**".

If you are already regularly using your inhaler, start at the beginning of STEP 2 under the section "**B. How to take a dose:**".

How do I know my dose has been loaded?

By turning the red grip all the way in BOTH directions, you will properly load a dose of your medication. At some point when you are turning the grip you will hear a "click". This is part of the loading process. If you are not sure you heard the "click", repeat from the beginning of STEP 2 under the section "**B. How to take a dose:**". This will not result in two doses being loaded. The TURBUHALER is designed to load only one dose at a time.

How do I clean my inhaler?

Clean the outside of the mouthpiece once a week with a **dry** tissue. **Never** use water or any other fluid. If fluid enters the inhaler it may not work properly.

How do I know when to start a new inhaler?

SYMBICORT TURBUHALER has a dose indicator. The dose indicator tells you around how many doses are left in the inhaler. The dose indicator moves slowly each time you load a dose. Every 20th dose is marked with a number and every 10th dose is marked with a dash (Figure 5). When the "0" on the red background has reached the middle of the window, you should throw out your inhaler and start a new inhaler. The sound you hear if you shake the inhaler is made by a drying agent, not the

medication. SYMBICORT TURBUHALER cannot be refilled with drug and should be thrown away.

Figure 5

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Common side effects are:
- Headache;
- Trembling;
- Sensation of heart beat;
- Cough;
- Irritation of mouth and/or throat;
- Hoarseness.

Less common side effects are:
- Nausea;
- Sleep difficulties;
- Agitation;
- Restlessness or nervousness;
- Dizziness;
- Muscle cramps.

Rare side effects are:
- Skin bruising;
- Depression or behavioural disturbances.

If any of these side effects worry you, do not stop treatment, but tell your doctor about them.

If you had been taking oral corticosteroids to treat your asthma and you suddenly have a severe asthma attack when starting SYMBICORT TURBUHALER, contact your doctor right away.

In patients with asthma, you should TELL YOUR DOCTOR if:

- The relief of your asthma is not as good as usual or does not last as long as usual. A change from "usual" includes more wheezing, coughing, tightness or shortness of breath;
- You exceed the maximum total number of daily inhalations (8 inhalations/day);
- There is a constant increase in your use of fast-acting reliever medication;
- Your symptoms are waking you up at night;
- Measurement from your peak flow meter indicates a value between 60% and 80% of predicted or personal best.

These may be signs that your asthma is getting worse. Your doctor may adjust your treatment.

You should TELL YOUR DOCTOR RIGHT AWAY or go to the nearest hospital if you notice the following warning signs:

- **A sudden worsening of your shortness of breath and wheezing shortly after using your fast-acting medication;**
- **You do not feel relief from additional doses of your fast-acting reliever medication;**
- **Measurement from your peak flow meter indicates a value less than 60 percent of predicted or personal best;**
- **You are breathless at rest;**
- **Your pulse is more than 120 beats per minute.**

In patients with COPD, you should TELL YOUR DOCTOR RIGHT AWAY if you notice the following warning signs, which indicate your condition is worsening:

- **Unusual increase in the severity of the breathlessness, cough, tiredness or wheeze;**
- **Unusual colour, level, consistency or stickiness of phlegm;**
- **Symptoms of a chest cold and/or chest tightness (e.g. indicating a chest infection);**
- **Unexplained swelling;**
- **Unexplained fever.**

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

	Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and seek emergency medical attention
		Only if severe	In all cases	
Rare	**Bronchospasm:** Increased wheezing or tightness in the chest or difficulty in breathing immediately after inhalation of SYMBICORT.			√
	Hypersensitivity reactions: Skin rash, skin eruption or other effect on the skin or eyes, itching or fever.			√

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
	Allergic reactions: Swelling of the lips, face or neck, accompanied by difficulty in breathing, speaking or swallowing (angioedema) and anaphylactic reaction.			√
	Fast or irregular heartbeat.		√	
Very Rare	**Cushing's Syndrome** (*hypercorticism*): Rapid weight gain especially around the body and face; round "moon" face, excess sweating; thinning of the skin with easy bruising and dryness; muscle and bone weakness.		√	
	Increased blood sugar: Frequent urination, thirst and hunger.			√
Unknown	**Churg-Strauss syndrome:** A flu-like illness, rash, pins and needles or numbness of arms or legs, severe sinusitis and worsening lung or breathing problems.		√	
	Glaucoma: Increased pressure in your eyes, and/or eye pain.		√	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
	Cataract: Clouding of the lens in the eye, blurry vision, and/or eye pain.		√	
	Bone Fractures or Osteoporosis: In situations where healthy people would not normally break a bone you may have sudden pain in any location and especially in the wrist, spine or hip. This may be a fracture.		√	
	Pneumonia (*an infection of the lungs*): Fever, chills, increase in sputum production, change in sputum colour, increased cough or an increase in breathing difficulties.		√	

This is not a complete list of side effects. For any unexpected effects while taking SYMBICORT TURBUHALER, contact your doctor or pharmacist.

HOW TO STORE IT

Remember to keep SYMBICORT TURBUHALER out of the reach and sight of children.

Always replace the cover after using SYMBICORT TURBUHALER. Store the inhaler at room temperature (15-30°C).

IMPORTANT: PLEASE READ

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 1908C
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Forms and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

NOTE: This CONSUMER INFORMATION leaflet provides you with the most current information at the time of printing.

The Consumer Information Leaflet plus the full Product Monograph, prepared for health professionals can be found at: www.astrazeneca.ca
or by contacting the sponsor, AstraZeneca Canada Inc. at: 1-800-668-6000.

This leaflet was prepared by
AstraZeneca Canada Inc. Mississauga, Ontario L4Y 1M4

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