

## PRODUCT MONOGRAPH

### SYMBICORT® TURBUHALER®

budesonide/formoterol fumarate dihydrate dry powder for oral inhalation

### SYMBICORT® **100** TURBUHALER®

100 mcg budesonide and 6 mcg formoterol fumarate dihydrate

### SYMBICORT® **200** TURBUHALER®

200 mcg budesonide and 6 mcg formoterol fumarate dihydrate

### SYMBICORT® **FORTE** TURBUHALER®

400 mcg budesonide and 12 mcg formoterol fumarate dihydrate

Corticosteroid and bronchodilator for oral inhalation

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**Pr** SYMBICORT® TURBUHALER®

budesonide/formoterol fumarate dihydrate

**PART I: HEALTH PROFESSIONAL INFORMATION**

**SUMMARY PRODUCT INFORMATION**

<b>Route of Administration</b>	<b>Dosage Form / Strength</b>	<b>Non-medicinal Ingredients</b>
Oral inhalation	Dry powder for 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 TURBUHALER (budesonide and formoterol fumarate dihydrate) is indicated for the treatment of asthma in patients 12 years and older with reversible obstructive airways disease.

SYMBICORT TURBUHALER can be used according to three different treatment approaches:

- A. SYMBICORT TURBUHALER Anti-inflammatory Reliever Therapy:** in patients with mild persistent asthma, SYMBICORT **200** TURBUHALER is taken as needed for relief of asthma symptoms when they occur.  
SYMBICORT TURBUHALER has not been evaluated in patients whose asthma can be managed by occasional use of a rapid onset, short duration, inhaled beta<sub>2</sub>-agonist.
- B. SYMBICORT TURBUHALER Anti-inflammatory Reliever plus Maintenance Therapy:** in patients with moderate or severe asthma, SYMBICORT **100** TURBUHALER or SYMBICORT **200** TURBUHALER are taken both as daily maintenance therapy and as needed for relief of asthma symptoms when they occur.
- C. SYMBICORT TURBUHALER Maintenance Therapy:** in patients with moderate or severe asthma, SYMBICORT TURBUHALER is taken as a fixed-dose daily

treatment with a separate short-acting bronchodilator for relief of symptoms when they occur.

Once asthma control is achieved and maintained, the patient should be assessed at regular intervals.

### **Chronic Obstructive Pulmonary Disease (COPD)**

SYMBICORT **200** TURBUHALER and SYMBICORT **FORTE** TURBUHALER are 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:**

In the treatment of asthma, safety and efficacy in pediatric patients younger than 12 years have not been established. In the treatment of COPD, safety and efficacy in patients younger than 18 years have not been established.

## **CONTRAINDICATIONS**

SYMBICORT TURBUHALER is contraindicated in patients with a known hypersensitivity to budesonide, formoterol or inhaled lactose.

## **WARNINGS AND PRECAUTIONS**

### **General**

#### ***Serious Asthma-Related Events – Hospitalizations, Intubations, Death***

Use of long-acting beta<sub>2</sub>-agonists (LABA) as monotherapy (without inhaled corticosteroids [ICS]) for asthma is associated with an increased risk of asthma-related death (see Salmeterol Multicenter Asthma Research Trial). Available data from controlled clinical trials also suggest that the use of LABA as monotherapy increases the risk of asthma-related hospitalization in pediatric and adolescent patients. These findings are considered a class effect of LABA monotherapy.

When LABA are used in fixed-dose combination with ICS, data from large clinical trials do not show a significant increase in the risk of serious asthma-related events (hospitalizations,

intubations, death) compared with ICS alone (see Serious Asthma-Related Events with Inhaled Corticosteroid/Long-acting Beta<sub>2</sub>-adrenergic Agonist Combination Products).

#### Serious Asthma-Related Events with Inhaled Corticosteroid/Long-acting Beta<sub>2</sub>-adrenergic Agonist Combination Products

Four (4) large, 26-week, randomized, double-blind, active-controlled clinical safety trials were conducted to evaluate the risk of serious asthma-related events when LABA were used in fixed-dose combination with ICS compared with ICS alone in subjects with asthma. Three (3) trials included adult and adolescent subjects aged 12 years and older: 1 trial compared budesonide/formoterol with budesonide, 1 trial compared fluticasone propionate/salmeterol with fluticasone propionate, and 1 trial compared mometasone furoate/formoterol with mometasone furoate. The fourth trial included pediatric subjects aged 4 to 11 years and compared fluticasone propionate/salmeterol with fluticasone propionate. The primary safety endpoint for all 4 trials was serious asthma-related events (hospitalizations, intubations, death). A single, blinded, independent, joint adjudication committee determined whether events were asthma related.

The 3 adult and adolescent trials were designed to rule out a 2.0-fold increase in relative risk for ICS/LABA compared with ICS, and the pediatric trial was designed to rule out a 2.7-fold increase in this relative risk. Each individual trial met its pre-specified objective and demonstrated non-inferiority of ICS/LABA to ICS alone. A meta-analysis of the 3 adult and adolescent trials did not show a significant increase in risk of a serious asthma-related event with ICS/LABA fixed-dose combination compared with ICS alone (Table 1). These trials were not designed to rule out all risk for serious asthma-related events with ICS/LABA compared with ICS.

**Table 1**                      **Meta-analysis of serious asthma-related events in subjects with asthma aged 12 years and older**

	<b>ICS/LABA (n=17,537)<sup>a</sup></b>	<b>ICS (n=17,552)<sup>a</sup></b>	<b>ICS/LABA vs. ICS Hazard Ratio (95% CI)<sup>b</sup></b>
Serious asthma-related event <sup>c</sup>	116	105	1.10 (0.85, 1.44)
Asthma-related death	2	0	
Asthma-related intubation (endotracheal)	1	2	
Asthma-related hospitalization (≥24-hour stay)	115	105	

ICS = Inhaled corticosteroid; LABA = Long-acting beta<sub>2</sub>-adrenergic agonist.

<sup>a</sup> Randomized subjects who had taken at least 1 dose of study drug. Planned treatment used for analysis.

<sup>b</sup> Estimated using a Cox proportional hazards model for time to first event with baseline hazards stratified by each of the 3 trials.

<sup>c</sup> Number of subjects with an event that occurred within 6 months after the first use of study drug or 7 days after the last date of study drug, whichever date was later. Subjects may have had one or more events, but only the first event was counted for analysis. A single, blinded, independent, joint adjudication committee determined whether events were asthma related.

The pediatric safety trial included 6208 pediatric subjects aged 4 to 11 years who received ICS/LABA (fluticasone propionate/salmeterol inhalation powder) or ICS (fluticasone propionate inhalation powder). In this trial, 27/3107 (0.9%) subjects randomized to ICS/LABA and 21/3101 (0.7%) subjects randomized to ICS experienced a serious asthma-related event. There were no asthma-related deaths or intubations. ICS/LABA did not show a significant increase in risk of serious asthma-related events compared with ICS based on the pre-specified risk margin (2.7), with an estimated hazard ratio of time to first event of 1.28 (95% CI: 0.73, 2.27). SYMBICORT TURBUHALER is not indicated in children younger than 12 years of age.

#### Salmeterol Multicenter Asthma Research Trial

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

#### ***Excessive Use and Use with Other LABA Products***

When beginning treatment with SYMBICORT TURBUHALER, patients who have been taking inhaled beta<sub>2</sub>-agonist on a regular basis should be instructed to discontinue the regular

use of these drugs. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients should be informed not to exceed the prescribed dose of SYMBICORT TURBUHALER.

### ***Asthma Reliever Medication***

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

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

### ***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 TURBUHALER is still indicated.

### ***Systemic Effects of Corticosteroids***

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***

Maintenance treatment with inhaled corticosteroids should not be stopped abruptly, but tapered gradually under the supervision of a physician. Complete withdrawal of inhaled corticosteroids should not be considered unless it is temporarily required to confirm the diagnosis of asthma.

## **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 TURBUHALER 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 TURBUHALER.

## **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<sub>2</sub>-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 eosinophilic granulomatosis with polyangiitis (EGPA) (formerly 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 TURBUHALER.

## **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 maintenance treatment of COPD with inhaled corticosteroids may lead to an increased risk of pneumonia. However, the absolute risk for budesonide is small.

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 **200** TURBUHALER compared with 2.4% treated with formoterol, 3.1% treated with budesonide, and 2.8% treated with placebo (see ADVERSE DRUG REACTIONS).

**Paradoxical Bronchospasm:** As with other inhalation therapy, paradoxical bronchospasm may occur characterized by an immediate increase in wheezing after dosing. In this event, SYMBICORT TURBUHALER 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 TURBUHALER 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 TURBUHALER 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 TURBUHALER 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 TURBUHALER 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<sub>2</sub>-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 relief of symptoms (e.g. SYMBICORT TURBUHALER, 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 their medication for relief of symptoms less effective (e.g. increased or persistent use), or exceeds the prescribed dose of SYMBICORT

TURBUHALER, 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. For treatment of severe exacerbations, SYMBICORT TURBUHALER alone is not sufficient.

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 TURBUHALER. 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 TURBUHALER, 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 TURBUHALER 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<sub>2</sub>-agonist therapy, such as headaches, tremor, palpitations and coughing. These tend to be mild and disappear within a few days of treatment.

Use of LABA monotherapy increases the risk of serious asthma-related events (death, hospitalizations, and intubations) (see WARNINGS AND PRECAUTIONS, General).

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 2 below.

**Table 2 Adverse reactions associated with use of budesonide or formoterol**

Frequency	System Organ Class (SOC) disorders	Reaction
<p><b>Common</b> 1% to 10% (&gt;1/100, &lt;1/10)</p>	<p>Cardiac disorders: Infections and infestations: Nervous system disorders: Respiratory, thoracic and mediastinal disorders:</p>	<p>Palpitations Candida infections in the oropharynx, Pneumonia (in COPD patients) Headache, tremor Mild irritation in the throat, coughing, hoarseness</p>
<p><b>Uncommon</b> 0.1% to 1% (&gt;1/1,000, &lt;/100)</p>	<p>Cardiac disorders: Gastrointestinal disorders: Musculoskeletal and connective tissue disorders: Nervous system disorders: Psychiatric disorders:</p>	<p>Tachycardia Nausea Muscle cramps Dizziness Agitation, restlessness, nervousness, sleep disturbances</p>

Frequency	System Organ Class (SOC) disorders	Reaction
<b>Rare</b> 0.01 to 0.1% (>1/10,000, <1/1,000)	Cardiac disorders:  Immune system disorders:  Respiratory, thoracic and mediastinal disorders:  Skin and subcutaneous tissue disorders:	Cardiac arrhythmias, e.g. atrial fibrillation, supraventricular tachycardia, extrasystoles  Immediate and delayed hypersensitivity reactions, e.g., dermatitis, exanthema, urticaria, pruritus, angioedema and anaphylactic reaction.  Bronchospasm  Skin bruising
<b>Very rare</b> <0.01% (<1/10,000)	Cardiac disorders:  Endocrine disorders:  Metabolism and nutrition disorders:  Psychiatric disorders:	Angina pectoris  Signs or symptoms of systemic glucocorticosteroid effects, e.g. hypofunction of the adrenal gland  Hyperglycemia  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, randomized, double-blind, placebo-control multicentre trials comparing SYMBICORT TURBUHALER (2 x 200/6 mcg) bid with placebo, budesonide 2 x 200 mcg bid, and formoterol 2 x 6 mcg bid. A total of 1834 COPD patients were enrolled in these studies. The most frequently reported adverse events are presented in Table 3. These adverse reactions were mostly mild to moderate in severity.

Table 3 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 TURBUHALER treatment group, and were more common than in the placebo group.

**Table 3 Overall adverse experiences with  $\geq 3\%$  and more common than placebo in the SYMBICORT TURBUHALER group in controlled clinical trials (0629 and 0670) with SYMBICORT TURBUHALER in patients with COPD**

Adverse event  <i>System organ class</i> <b>Preferred term</b>	<b>SYMBICORT TURBUHALER (n=462) %</b>	<b>Budesonide (n=455) %</b>	<b>Formoterol (n=456) %</b>	<b>Placebo (n=461) %</b>
% of patients reporting at least one adverse event	63	64	67	61
<i>Infections and infestations</i>				
Nasopharyngitis	9	7	7	6
Pneumonia	4	3	2	3
<i>General disorders and administration site conditions</i>				
Chest pain	3	2	2	2
<i>Nervous system disorders</i>				
Headache	3	2	3	2
<i>Musculoskeletal and connective tissue disorders</i>				
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 TURBUHALER group. The most common cause of death overall was COPD (formoterol=9, placebo=7, budesonide=3, and SYMBICORT TURBUHALER=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, bronchospasm, urticaria, 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**

#### **Inhibitors of cytochrome P450 3A4 (CYP3A4)**

The metabolism of budesonide is primarily mediated by CYP3A4. Strong CYP3A4 inhibitors like ritonavir and azole antifungals (e.g. ketoconazole and itraconazole) increase the systemic exposure to budesonide. If a patient requires long-term concomitant treatment with SYMBICORT TURBUHALER and a strong CYP3A4 inhibitor, the benefit should be weighed against the increased risk of systemic corticosteroid side effects, patients should be monitored for corticosteroid side effects and/or a reduction of the inhaled corticosteroid dose could be considered.

#### **Beta-adrenergic receptor blocking agents**

Beta-adrenergic blockers (including eye drops) can weaken or inhibit the effect of formoterol, a beta-adrenergic agonist. Beta-blockers not only block the therapeutic effects of beta-agonists, such as formoterol, but may produce severe bronchospasm in asthmatic patients. Therefore, patients with asthma should not normally be treated with beta-blockers. If concomitant treatment is necessary, patients should be monitored carefully for possible deterioration in pulmonary function and the need to adjust the dosage of either drug.

#### **Drugs known to prolong the QTc interval**

As with other beta<sub>2</sub>-adrenergic agonists, SYMBICORT TURBUHALER should be administered with caution to patients treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QT interval, as any effect of these on the QT interval may be potentiated. Drugs known to prolong the QT-interval may increase the risk of ventricular arrhythmia.

#### **Treatments Leading to Hypokalemia**

Concomitant treatment with xanthine derivatives, steroids or non-potassium sparing diuretics may potentiate a possible hypokalemic effect of beta<sub>2</sub>-agonists. Hypokalemia may increase the disposition towards arrhythmias in patients who are treated with digitalis glycosides.

#### **Other drugs**

L-Dopa, L-thyroxine, oxytocin and alcohol can impair cardiac tolerance towards beta<sub>2</sub>-sympathomimetics.

Concomitant treatment with monoamine oxidase inhibitors including agents with similar properties such as furazolidone and procarbazine may precipitate hypertensive reactions.

There is elevated risk of arrhythmias in patients receiving concomitant anaesthesia with halogenated hydrocarbons.

## **DOSAGE AND ADMINISTRATION**

SYMBICORT TURBUHALER is for oral inhalation only. Patients should be instructed in the correct method to use the TURBUHALER, which is described in CONSUMER INFORMATION, Proper Use of This Medication. An instructional video is also available at [Symbicort.ca/video](http://Symbicort.ca/video). The medication from SYMBICORT TURBUHALER 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 TURBUHALER 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 dose. This will help prevent the occurrence of candidiasis. Cleansing dentures has the same effect.

### **Dosing Considerations for Asthma**

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

If patients take SYMBICORT TURBUHALER as a maintenance therapy, they should be made aware that for optimum benefit, SYMBICORT TURBUHALER should be taken daily, even when they are asymptomatic. Inhalations for the rapid relief of symptoms 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 inhalations for rapid symptom relief without achieving improved asthma control.

For treatment of severe exacerbations, SYMBICORT TURBUHALER alone is not sufficient.

### **Recommended Dose and Dosage Adjustment for Asthma**

When starting a patient on SYMBICORT TURBUHALER, the most appropriate treatment approach should be selected on an individualized basis according to disease severity.

Patients should be assessed at regular intervals so that the treatment approach and dosage of SYMBICORT TURBUHALER they are receiving remains optimal.

SYMBICORT TURBUHALER can be used according to three different treatment approaches:

- A. SYMBICORT TURBUHALER anti-inflammatory reliever therapy.
- B. SYMBICORT TURBUHALER anti-inflammatory reliever plus maintenance therapy.
- C. SYMBICORT TURBUHALER maintenance therapy.

**A. SYMBICORT TURBUHALER Anti-Inflammatory Reliever Therapy (patients with mild persistent asthma)**

When the use of inhaled corticosteroids is appropriate, patients use SYMBICORT **200** TURBUHALER as needed for the rapid relief of asthma symptoms when they occur and for a timely increase in anti-inflammatory therapy.

Patients should be advised to always have SYMBICORT **200** TURBUHALER available for rapid relief of symptoms. A persistent increase in the use of SYMBICORT **200** TURBUHALER as needed indicates a deterioration of asthma control and the patient's condition should be re-evaluated to determine the appropriate treatment.

Adults and adolescents (12 years and older):

1 inhalation of SYMBICORT **200** TURBUHALER as needed in response to symptoms to control asthma. If symptoms persist after a few minutes, 1 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 **100** TURBUHALER and SYMBICORT **FORTE** TURBUHALER should **NOT** be used as SYMBICORT Anti-inflammatory Reliever Therapy.

**B. SYMBICORT TURBUHALER Anti-inflammatory Reliever plus Maintenance Therapy (SYMBICORT SMART®) (patients with moderate or severe asthma)**

When maintenance treatment with a combination of inhaled corticosteroid and long-acting beta<sub>2</sub>-agonist is required, patients use SYMBICORT TURBUHALER as an anti-inflammatory reliever as needed for rapid symptom relief and a timely increase in anti-inflammatory therapy, and take a daily maintenance dose of SYMBICORT TURBUHALER for improved asthma control. Patients should be advised to always have SYMBICORT TURBUHALER available for the rapid relief of symptoms when they occur. A separate inhaler for rapid symptom relief is not necessary.

When control has been achieved, the dose should be titrated to the lowest dose at which effective control of symptoms is maintained.

A persistent increase in the use of SYMBICORT TURBUHALER 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 or 2 inhalations of 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 to control asthma. If symptoms persist after a few minutes, 1 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 or 2 inhalations of 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 to control asthma. If symptoms persist after a few minutes, 1 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 **NOT** be used as SYMBICORT TURBUHALER Anti-inflammatory Reliever plus Maintenance Therapy.

**C. SYMBICORT TURBUHALER Maintenance Therapy (SMT) (patients with moderate or severe asthma)**

When maintenance treatment with a combination of inhaled corticosteroid and long-acting beta<sub>2</sub>-agonist is required, patients use SYMBICORT TURBUHALER as a fixed daily treatment with a separate short-acting inhaled bronchodilator (e.g., terbutaline or salbutamol) for rapid relief of symptoms. Patients should be advised to have their separate short-acting bronchodilator available at all times for rapid relief of symptoms.

Adults and adolescents (12 years and older):

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

or

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

or

1 inhalation of 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.

When control has been achieved, the dose should be titrated to the lowest dose at which effective control of symptoms is maintained.

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**

For SYMBICORT TURBUHALER Anti-inflammatory Reliever plus Maintenance Therapy and SYMBICORT TURBUHALER Maintenance Therapy:

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

### **Dosing Considerations for Chronic Obstructive Pulmonary Disease (COPD)**

SYMBICORT TURBUHALER should not be initiated to treat acute symptoms of COPD. For optimal benefit, patients should be instructed to take their daily maintenance dose of SYMBICORT TURBUHALER even when asymptomatic.

### **Recommended Dose and Dosage Adjustment for COPD**

#### **Maintenance for Adults (18 years and older)**

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

or

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

### **Special Populations**

**Pediatrics:** SYMBICORT TURBUHALER 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:** There are no special dosage requirements for elderly patients.

**Hepatic/Renal Impairment:** There are no data available for the use of SYMBICORT TURBUHALER 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.
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There are no data available from clinical trials on overdose with SYMBICORT TURBUHALER. An overdose of formoterol would likely lead to effects that are typical for beta<sub>2</sub>-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 and when given three times daily as a total of 54 mcg/day for 3 days to stable asthmatics 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 TURBUHALER contains budesonide and formoterol fumarate dihydrate, which have different modes of action and show additive effects in terms of the reduction of asthma and COPD exacerbations. In the treatment of asthma, SYMBICORT TURBUHALER can be used as an anti-inflammatory reliever, or anti-inflammatory reliever plus maintenance

therapy, 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<sub>2</sub>-adrenergic stimulant used for the prevention and rapid relief of asthma and COPD 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<sub>2</sub>-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 TURBUHALER:** 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 TURBUHALER 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 TURBUHALER 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 TURBUHALER 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 deformedylated metabolites are formed, but they are seen mainly as inactivated conjugates). Budesonide undergoes an extensive degree ( $\approx 90\%$ ) of biotransformation on first passage through the liver to metabolites of low glucocorticosteroid activity. The glucocorticosteroid activity of the major metabolites, 6 $\beta$ -hydroxy-budesonide and 16 $\alpha$ -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 of formoterol via TURBUHALER 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 should be stored at room temperature between 15°C and 30°C with the cover tightened.

### **SPECIAL HANDLING INSTRUCTIONS**

SYMBICORT TURBUHALER cannot be refilled and should be discarded when finished.

### **DOSAGE FORMS, COMPOSITION AND PACKAGING**

SYMBICORT TURBUHALER is a dry powder inhalation device and each dose 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 contains 100 mcg of budesonide and 6 mcg of formoterol fumarate dihydrate per dose. Each delivered dose contains 80 mcg of budesonide and 4.5 mcg of formoterol fumarate dihydrate.
- SYMBICORT **200** TURBUHALER contains 200 mcg of budesonide and 6 mcg of formoterol fumarate dihydrate per dose. Each delivered dose contains 160 mcg of budesonide and 4.5 mcg of formoterol fumarate dihydrate.

- SYMBICORT **FORTE** TURBUHALER contains 400 mcg of budesonide and 12 mcg of formoterol fumarate dihydrate per dose. Each delivered dose contains 320 mcg of budesonide and 9 mcg of formoterol fumarate dihydrate.

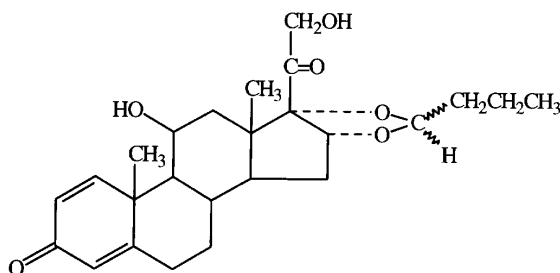
SYMBICORT **100** TURBUHALER is available in a 120 dose pack size, and SYMBICORT **200** TURBUHALER is available in 60 or 120 dose pack sizes. SYMBICORT **FORTE** TURBUHALER is available in a 60 dose pack size.

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

#### Drug Substance

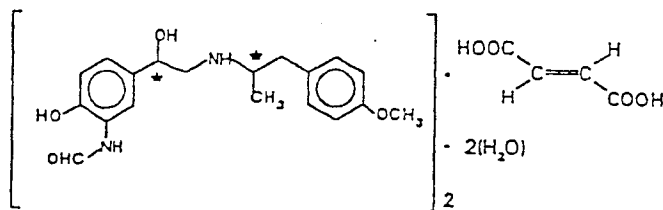
<b>Proper Name</b>	Budesonide
<b>Chemical Name</b>	Budesonide is a mixture of two isomers: 1. Pregna-1,4-diene-3,20-dione,16,17-butyldienebis(oxy)-11,21-dihydroxy-,[11 $\beta$ ,16 $\alpha$ (R)] and 2. Pregna-1,4-diene-3,20-dione,16,17-butyldienebis(oxy)-11,21-dihydroxy-,[11 $\beta$ ,16 $\alpha$ (S)].
<b>Molecular Formula and Molecular Mass</b>	C <sub>25</sub> H <sub>34</sub> O <sub>6</sub> 430.5
<b>Structural Formula</b>	



**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

<b>Proper Name</b>	formoterol fumarate dihydrate
<b>Chemical Name</b>	(R*,R*)-(±)-N-[2-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]formamide, (E)-2-butendioate(2:1), dihydrate
<b>Molecular Formula and Molecular Mass</b>	C <sub>42</sub> H <sub>56</sub> N <sub>4</sub> O <sub>14</sub> 840.9

**Structural Formula:****Physiochemical Properties**

Formoterol fumarate dihydrate is a white to off-white or slightly 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 TURBUHALER Anti-Inflammatory Reliever Therapy**

##### Trial Design and Study Demographics

The safety and efficacy of SYMBICORT **200** TURBUHALER (200/6 mcg) as needed was evaluated in patients with mild asthma in a clinical development program that included two 52-week randomized, double-blind, parallel-group studies (SYGMA 1 and 2). SYGMA 1 compared SYMBICORT **200** TURBUHALER as needed with terbutaline 0.4 mg as needed and with daily budesonide 200 mcg bid plus terbutaline 0.4 mg as needed. SYGMA 2 compared SYMBICORT **200** TURBUHALER as needed with daily budesonide 200 mcg bid plus terbutaline 0.4 mg as needed. Use of all trial medication was recorded electronically with an inhaler monitor.

The primary endpoint for SYGMA 1 was the average percentage of well-controlled asthma weeks (WCAW) over the 52-week treatment period. The primary endpoint for SYGMA 2 was the annual severe asthma exacerbation rate over the 52-week treatment period, which was also a secondary endpoint in SYGMA 1.

Other secondary endpoints were rates and time to the first moderate-to-severe exacerbation (SYGMA 1 only), time to the first severe exacerbation, Asthma Control Questionnaire (ACQ-5) scores, medication usage (use of as-needed medication, ICS-controller use and total inhaled steroid load, and number of days with systemic corticosteroid treatment), lung-function variables, quality of life (according to the Asthma Quality of Life Questionnaire [AQLQ] score) and eDiary variables (SYGMA 1 only).

In both studies, patients were required to be either uncontrolled on only short-acting inhaled bronchodilator as needed or controlled on a low dose of inhaled corticosteroids or leukotriene receptor agonist plus short-acting inhaled bronchodilator as needed. During a 2 – 4 week run-in period, patients were removed from previous asthma treatment and were treated with terbutaline 0.4 mg as needed only. For randomization, patients were required to use the as-needed terbutaline on at least 3 separate days during the last week of the run-in period to ensure they had mild asthma that should be treated with low dose inhaled corticosteroids.

A total of 8064 asthma patients with mild asthma ( $\geq 12$  years of age) were included in the SYGMA studies, of which 3384 patients were randomized to SYMBICORT **200** TURBUHALER as needed. In both studies, treatment arms were well balanced. The mean age of patients was 40 and 41 years, ~12.5% and 10% of patients were adolescents ( $\geq 12$  to  $< 18$  years of age), ~7% and 9% of patients were  $> 65$  years of age and there were more female patients (~61% and 62%), in SYGMA 1 and 2, respectively.

Baseline lung function showed similar mean pre-bronchodilator FEV<sub>1</sub> (~84%), post-bronchodilator FEV<sub>1</sub> (~96%), reversibility (~15%) across studies and ~20% of patients had a severe exacerbation in the 12 months prior to study. ACQ-5 scores reflected uncontrolled asthma at baseline, with mean score of ~1.5, and the mean number of as-needed inhalations at baseline was approximately 1.4 inhalations per day in all treatment arms in both studies. Overall, approximately 45% of patients were previously uncontrolled on bronchodilator and 55% of patients were previously controlled on inhaled corticosteroids or leukotriene receptor antagonists in both studies.

### Study Results

Median adherence with the intended use of maintenance treatment was ~85% in all treatment arms in SYGMA 1 (with twice daily electronic reminders) and ~68% in both treatment arms in SYGMA 2 (without any daily reminders).

#### *Primary endpoint*

The SYGMA 1 study demonstrated that SYMBICORT **200** TURBUHALER as needed was superior to terbutaline as needed in terms of WCAW (Table 4). The secondary analysis of the primary endpoint WCAW showed that non-inferiority for asthma symptom control was not met for SYMBICORT **200** TURBUHALER as needed compared with daily budesonide bid plus terbutaline as needed, in terms of WCAW (lower limit of the 2-sided 95% CI  $\geq 0.8$  for non-inferiority) (Table 4).

**Table 4 Well-controlled asthma weeks (WCAW) during the randomized 52-week study period, repeated measures logistic regression (SYGMA 1)**

			Comparison between SYMBICORT TURBUHALER as needed and control group		
Group	N	Mean percentage of WCAW <sup>a</sup> per patient	OR	95% CI	p-value
SYMBICORT TURBUHALER 200/6 mcg as needed	1269	34.4			
Terbutaline 0.4 mg as needed	1272	31.1	1.14	(1.00, 1.30)	0.046
Budesonide 200 mcg bid + terbutaline 0.4 mg as needed	1279	44.4	0.64	(0.57, 0.73) <sup>b</sup>	NA

OR = Odds Ratio; CI = Confidence interval; N = Number of patients in analysis

<sup>a</sup> WCAW is a composite endpoint capturing asthma symptoms, night-time awakenings, lung function, use of as-needed medication, and prescription of ICS and/or systemic glucocorticosteroid treatment for asthma. WCAW has 3 possible values: well-controlled, not-well-controlled and missing. The comparison of two different treatment approaches ('as needed' vs regular maintenance) should be interpreted with caution since 'as-needed' inhalations are counted in the assessment of WCAW.

<sup>b</sup> The non-inferiority margin comparing SYMBICORT TURBUHALER 200/6 mcg to Budesonide 200 mcg bid + terbutaline 0.4 mg as needed was the lower limit of the 2-sided 95% CI  $\geq 0.8$ .

In the SYGMA 2 study, SYMBICORT **200** TURBUHALER as needed was comparable (RR 0.97; 95% CI 0.78 to 1.20; upper limit of the 2-sided 95% CI <1.20 for non-inferiority) in the rate of severe exacerbations to a daily maintenance dose of budesonide bid plus terbutaline as-needed (Table 5).

**Table 5 Severe asthma exacerbations over the randomized treatment period, negative binominal model (full analysis set) (SYGMA 2)**

			Exacerbations / year		Comparison between SYMBICORT TURBUHALER as needed and control group		
Treatment group	N	Number of severe exacerbations <sup>a</sup>	Rate	95% CI	Rate Ratio	95% CI	p-value
SYMBICORT TURBUHALER 200/6 mcg as needed	2084	217	0.11	(0.10, 0.13)			
Budesonide 200 mcg bid + terbutaline 0.4 mg as needed	2083	221	0.12	(0.10, 0.14)	0.97	(0.78, 1.20) <sup>b</sup>	NA

CI = Confidence interval; N = Number of patients in analysis N/A = Not applicable

<sup>a</sup> Defined as deterioration of asthma requiring any of: use of systemic steroids for at least 3 days; inpatient hospitalization; or emergency room visit due to asthma that required systemic steroids.

<sup>b</sup> For the comparison of SYMBICORT TURBUHALER as needed vs. budesonide bid, an upper limit of the 2-sided 95% CI <1.20 indicates SYMBICORT TURBUHALER as needed is non-inferior to budesonide bid.

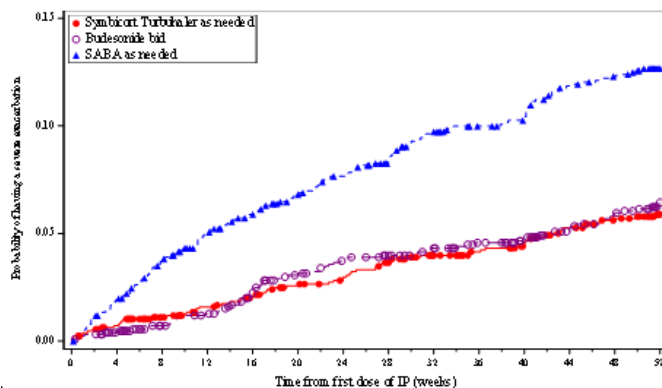
### Secondary endpoints

The SYGMA 1 study showed that SYMBICORT **200** TURBUHALER as needed provided a clinically meaningful reduction in the rate of annual severe exacerbation by 64% compared with terbutaline as-needed (annualized exacerbation rate, 0.07 (95% CI 0.06, 0.09) and 0.20 (95% CI 0.16, 0.24), respectively; [RR] 0.36, 95% CI 0.27, 0.49). Reduction in the annual rate of moderate-to-severe exacerbations (60%) was consistent with that observed for severe exacerbations (annualized exacerbation rate, 0.14 (95% CI 0.12, 0.17) and 0.36 (95% CI 0.31, 0.42), respectively; [RR] 0.40, 95% CI 0.32, 0.49). The rate of annual severe exacerbation was similar for SYMBICORT **200** TURBUHALER as needed compared to daily maintenance budesonide bid (annualized exacerbation rate, 0.07 (95% CI 0.06, 0.09) and 0.09 (95% CI 0.07, 0.11), respectively; [RR] 0.83, 95% CI 0.59, 1.16).

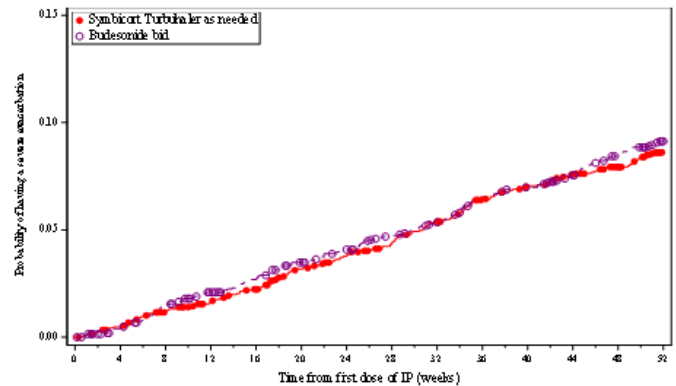
Analysis of time to first severe exacerbation in the SYGMA 1 study showed that SYMBICORT **200** TURBUHALER as-needed reduced the instantaneous risk of experiencing a severe exacerbation over the one year treatment period by 56% ([HR] 0.44, 95% CI: 0.33-0.58) compared to terbutaline as-needed (see Figure 1a).

There were no differences in the probability of experiencing a severe exacerbation over the treatment period between SYMBICORT **200** TURBUHALER as-needed and daily maintenance budesonide 200 mcg bid plus terbutaline as-needed (see Figure 1a and Figure 1b).

**Figure 1a** Time to first severe asthma exacerbation in SYGMA 1



**Figure 1b** Time to first severe asthma exacerbation in SYGMA 2



The SYMBICORT **200** TURBUHALER as needed treatment arms achieved comparable reduction in severe and moderate-to-severe exacerbations while reducing the median ICS load



by 75% to 83% compared to the budesonide bid arms (SYGMA 1: 48.3 mcg/day vs 276.2 mcg/day; SYGMA 2: 52.9 and 214.1 mcg/day).

In SYGMA 1, the mean total number of as-needed inhalations per day over the randomized treatment period was 0.47 for SYMBICORT **200** TURBUHALER as needed, 0.58 for terbutaline as needed, and 0.39 for budesonide bid. In SYGMA 2, the mean total number of as-needed inhalations per day over the randomized treatment period was 0.52 for the SYMBICORT **200** TURBUHALER as needed group and 0.49 for the budesonide bid group. In both studies, patients did not use any as-needed medication on most days (range: 69%-77%), and when patients used as-needed medication, the most frequent use was 1 to 2 inhalations per day.

In SYGMA 1, increases in lung function compared to baseline (mean pre-bronchodilator FEV<sub>1</sub>) were larger for patients on SYMBICORT **200** TURBUHALER as needed compared to patients on terbutaline as needed. In both SYGMA 1 and 2, smaller increases were observed for SYMBICORT **200** TURBUHALER as needed compared to daily maintenance budesonide bid with terbutaline as needed; for both comparisons, mean differences in treatments' effect were small (approximately 30 to 55 mL).

In the SYGMA 1 study, improvements in asthma control (as defined by ACQ-5) and in quality of life (as defined in AQLQ) in patients using SYMBICORT **200** TURBUHALER as needed were greater than improvements in patients using terbutaline as needed (ACQ-5: -0.15, 95% CI -0.20 to -0.11; AQLQ: 0.127; 95% CI 0.074 to 0.181). Improvements in asthma control were lower for SYMBICORT **200** TURBUHALER as needed compared to daily maintenance budesonide bid plus terbutaline as needed in both SYGMA 1 and 2 (ACQ-5: SYGMA 1: 0.15, 95% CI 0.10 to 0.20; SYGMA 2: 0.11, 95% CI 0.07 to 0.15; AQLQ: SYGMA 1: -0.102; 95% CI -0.155 to -0.049; SYGMA 2: -0.096; 95% CI -0.137 to -0.054).

For all comparisons, mean differences in treatment effect on ACQ-5 and AQLQ were not clinically meaningful (as assessed by a minimum clinically important difference of at least 0.5).

No safety concerns were identified for as-needed use of SYMBICORT **200** TURBUHALER. Safety findings were generally consistent across patient subgroups, and there were no safety concerns related to treatment class effects or the amount of medication usage.

### **SYMBICORT TURBUHALER Anti-inflammatory Reliever plus Maintenance Therapy (SYMBICORT SMART<sup>®</sup>)**

SYMBICORT TURBUHALER anti-inflammatory reliever plus maintenance therapy is supported by 5 double-blind, randomized, parallel-group multicentre clinical studies that compared the safety and efficacy of SYMBICORT TURBUHALER anti-inflammatory

reliever plus maintenance 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 TURBUHALER anti-inflammatory reliever plus maintenance 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 TURBUHALER anti-inflammatory reliever plus maintenance therapy provided statistically significant and clinically meaningful reductions in severe exacerbations by prolonging time to first event and reducing the event rate (Table 6), as compared with all comparator treatments, including SYMBICORT TURBUHALER at a higher maintenance dose (Study 735). Symptom control, lung function and reliever use were improved compared with SYMBICORT TURBUHALER 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 6).

In Study 735, SYMBICORT TURBUHALER anti-inflammatory reliever plus maintenance 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 TURBUHALER with terbutaline as reliever (see Table 6).

In Study 734, SYMBICORT TURBUHALER anti-inflammatory reliever plus maintenance therapy prolonged the time to the first exacerbation compared to SYMBICORT TURBUHALER 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 6).

In Studies 673, 668 and 667, SYMBICORT TURBUHALER anti-inflammatory reliever plus maintenance therapy prolonged the time to the first exacerbation compared to SYMBICORT TURBUHALER 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 TURBUHALER anti-inflammatory reliever plus maintenance therapy.

In the 5 long-term studies, patients receiving SYMBICORT TURBUHALER anti-inflammatory reliever plus maintenance 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<sub>2</sub>-agonist-related).

**Table 6 Summary of pivotal clinical studies in support of SYMBICORT TURBUHALER anti-inflammatory reliever plus maintenance therapy (SYMBICORT SMART) - Baseline characteristics, dose, and effect on severe exacerbations in double-blind, long-term studies**

	Study 735 <sup>a</sup> (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
<b>N randomized</b>	1107	1105	1113	1140	1141	925	909	926	947	943	355	342
<b>Study duration</b>	6 months		12 months			12 months			12 months		6 months	
<b>Age, years</b>	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	
<b>Gender, M/F</b>	1411/1924		1345/2049			1231/1529			798/1092		270/427	
<b>Race</b>	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	
<b>Baseline characteristics indicative of asthma severity</b>												
FEV <sub>1</sub> (%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 (%) <sup>b</sup>	45	46	59	58	59	28	28	27	44	43	22	18
<b>Daily use of GCS/LABA during treatment (budesonide/formoterol for SYMBICORT TURBUHALER. NB budesonide and formoterol as delivered dose)</b>												
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

	Study 735 <sup>a</sup> (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
<b>N randomized</b>	1107	1105	1113	1140	1141	925	909	926	947	943	355	342
Mean total dose (mcg)	483/13.6	640/18	483/13.6	320/14.5	320/9	240/13.5 <sup>c</sup>	160/9 <sup>c</sup>	640/0 <sup>c</sup>	466/13	640/0	242/16.7	320/0
<b>Incidence of severe exacerbations (excluding exacerbations due to PEF falls).</b>												
Symb + Symb was statistically significantly superior to all comparators for time to first severe exacerbation and total number of severe exacerbations.												
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 1 <sup>st</sup> severe asthma exacerbation	Hazard ratio for the time to 1 <sup>st</sup> severe exacerbation decreased with Symb + Symb versus Symb + terb by 26% (p=0.026)		Hazard ratio for the time to 1 <sup>st</sup> 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 1 <sup>st</sup> 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 1 <sup>st</sup> severe exacerbation decreased with Symb + Symb versus Bud + terb by 39% (p<0.001)		Hazard ratio for the time to 1 <sup>st</sup> 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

<sup>a</sup> The data from another inhaled corticosteroid/long-acting beta<sub>2</sub>-agonist treatment arm are not shown.

<sup>b</sup> As monoproduct or in combination with inhaled GCS.

<sup>c</sup> 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 7 Summary of results for key secondary efficacy variables in double-blind, long-term studies**

Study	Treatment arm	N <sup>a</sup>	Morning PEF (L/min) <sup>b</sup>	Total symptom score (0-6)		Total daily as-needed inhalations		Nights with awakenings due to asthma symptoms (%)		Comments
				Baseline	Treatment	Baseline	Treatment	Baseline	Treatment	
			<b>Change from baseline</b>							
735 <sup>c</sup>	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	

<sup>a</sup> Number refers to all patients analysed for efficacy; data were not available for every patient for every variable

<sup>b</sup> Primary efficacy parameter in study 667; time to 1<sup>st</sup> severe exacerbation was a secondary endpoint

<sup>c</sup> The data from another inhaled corticosteroid/long-acting beta<sub>2</sub>-agonist treatment arm are not shown.

## **SYMBICORT TURBUHALER Maintenance Therapy**

Clinical studies in asthmatic adults and adolescents showed that SYMBICORT TURBUHALER 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 ( $\leq 500$  mcg ICS daily) SYMBICORT TURBUHALER 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 ( $\geq 750$  mcg ICS daily), SYMBICORT TURBUHALER 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<sub>1</sub> ( $p<0.001$ ).

In this 24-week study, no new safety concerns were identified and similar safety profiles were observed between the SYMBICORT TURBUHALER 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 TURBUHALER and budesonide + formoterol treatment groups or within these groups over time. There were no statistically significant differences between the SYMBICORT TURBUHALER and budesonide + formoterol treatment groups regarding morning plasma cortisol or stimulated cortisol.

### **Clinical Studies in COPD**

The use of SYMBICORT **200** TURBUHALER (200/6 mcg) and SYMBICORT **FORTE** TURBUHALER (400/12 mcg) in the treatment of patients with moderate to severe COPD is supported by two 12-month, randomized, double-blind, placebo-controlled, parallel-group, multicentre clinical studies comparing efficacy and safety of SYMBICORT **200** TURBUHALER (given as 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<sub>1</sub> of  $\leq 50\%$  predicted normal, an FEV<sub>1</sub>/VC ratio of  $\leq 70\%$ , a history of at 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 TURBUHALER studies (0629 and 0670) were post-bronchodilator FEV<sub>1</sub> 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 randomized and received treatment. The average age of patients was 64 years, and 23% of those enrolled were female. The mean pre-bronchodilator FEV<sub>1</sub> 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 **200** TURBUHALER were statistically significantly superior to placebo for the following variables: post-bronchodilator FEV<sub>1</sub>, 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<sub>2</sub>-agonists.

SYMBICORT **200** TURBUHALER was also statistically significantly superior to budesonide for post-bronchodilator FEV<sub>1</sub>, morning and evening PEF, and use of short-acting beta<sub>2</sub>-agonists.

In comparison to formoterol, SYMBICORT **200** TURBUHALER 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 8). In Study 0629, the mean number of moderate to severe



exacerbations/patient-year was 1.42 for SYMBICORT **200** TURBUHALER, 1.84 for formoterol and 1.87 for placebo. Compared with formoterol, the treatment of SYMBICORT **200** TURBUHALER 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 **200** TURBUHALER, 1.85 for formoterol and 1.80 for placebo. The treatment of SYMBICORT **200** TURBUHALER reduced the exacerbation rate by 0.47 exacerbation/patient-year compared with formoterol. In comparison with formoterol, SYMBICORT **200** TURBUHALER statistically significantly improved post-bronchodilator FEV<sub>1</sub> (p=0.002) in Study 0670 but not in Study 0629 (p=0.487). SYMBICORT **200** TURBUHALER 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 8 Summary of key results for COPD studies 0629 and 0670**

		<b>SYMBICORT TURBUHALER 200/6 mcg vs placebo</b>	<b>SYMBICORT TURBUHALER 200/6 mcg vs formoterol</b>	<b>Formoterol vs placebo</b>
<b>Improvements in post-dose FEV<sub>1</sub></b>				
<b>Study 0629</b>	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
<b>Study 0670</b>	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
<b>Reductions in Moderate to Severe Exacerbations</b>				
<b>Study 0629</b>	Rate ratio <sup>a</sup> (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
<b>Study 0670</b>	Rate ratio <sup>a</sup> (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
<b>Improvements in Health-related Quality of Life: Change in total SGRQ score<sup>b</sup></b>				
<b>Study 0629</b>	Mean difference from baseline	-3.88	-0.34	-3.54
	P-value	0.009	0.816	0.018

		<b>SYMBICORT TURBUHALER 200/6 mcg vs placebo</b>	<b>SYMBICORT TURBUHALER 200/6 mcg vs formoterol</b>	<b>Formoterol vs placebo</b>
<b>Study 0670</b>	Mean difference from baseline	-7.46	-3.33	-4.13
	P-value	<0.001	0.014	0.002

<sup>a</sup> From Poisson regression model

<sup>b</sup> St. George's Respiratory Questionnaire

In both studies, adverse reactions associated with SYMBICORT **200** TURBUHALER 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 9 Summary of results of repeat dose toxicity studies**

Species	Route Duration	Treatment	Dose (mcg/kg)	Results and Observations
Rat	inhalation 13 weeks	budesonide	72	<ul style="list-style-type: none"> <li>- no mortalities or adverse clinical signs</li> <li>- decrease in body weight gain</li> <li>- increased hemoglobin (females) and red blood cells (males)</li> <li>- decreased white blood cells, lymphocytes and eosinophils</li> <li>- increased urea and alkaline phosphatase (males)</li> <li>- reduced thymus weights and increased kidney and heart weights</li> <li>- thymic atrophy</li> <li>- reduced incidence of extra medullary haemopoiesis in spleen (males)</li> </ul>
		formoterol	2.25	<ul style="list-style-type: none"> <li>- no mortalities or adverse clinical signs</li> <li>- slight increase in body weight gain</li> <li>- decreased white blood cells (females)</li> <li>- increased glucose (females) and alkaline phosphatase and phosphate (males)</li> <li>- increased weight of lung (males) and kidneys (females)</li> </ul>
		budesonide/f ormoterol	2.35/0.14 11.5/0.63 54/2.8	<ul style="list-style-type: none"> <li>- no mortalities or adverse clinical signs</li> <li>- dose-related decrease in body weight gain (significant in high dose group)</li> <li>- food consumption slightly reduced (high dose group)</li> <li>- increased hemoglobin (high dose group)</li> <li>- dose-related decrease in white blood cells, lymphocytes and eosinophils (most pronounced in high dose females)</li> <li>- increased urea, potassium, alkaline phosphatase and phosphate (males)</li> <li>- increased urine pH (high dose females)</li> <li>- increased weight of kidney (females), lung (males) and heart (females)</li> <li>- dose-related decrease in thymus weights</li> <li>- thymic atrophy (high dose group)</li> <li>- reduced incidence of extramedullary haemopoiesis in spleen (males)</li> </ul>

Species	Route Duration	Treatment	Dose (mcg/kg)	Results and Observations
Dog	Inhalation 13 weeks	budesonide	48.5	<ul style="list-style-type: none"> <li>- no mortalities or adverse clinical signs</li> <li>- reduced body weight gain</li> <li>- slightly reduced lymphocyte counts</li> <li>- slight increase in total plasma protein, cholesterol and ALP levels</li> <li>- slightly decreased glucose levels</li> <li>- suppression of ACTH-mediated cortisol release</li> <li>- decreased adrenal and thymus weights and slight decrease in lung weight (males)</li> <li>- increased weight of spleen (males and females) and liver (females)</li> <li>- slightly decreased lung weights (males only)</li> <li>- marked or severe atrophy of the thymus</li> <li>- marked or severe atrophy of the Zona fasciculata of the adrenal cortex</li> <li>- minimal or slight lymphoid depletion in spleen (females)</li> </ul>
		formoterol	2.65	<ul style="list-style-type: none"> <li>- no mortalities or adverse clinical signs</li> <li>- mild to moderate transient tachycardia one hour after dosing</li> <li>- slightly raised neutrophil counts</li> <li>- slightly decreased plasma glucose levels (females)</li> <li>- slightly increased plasma cholesterol levels (females)</li> <li>- slightly decreased weights of adrenals, thymus and lungs (males)</li> <li>- increased weight of spleen (males and females) and liver (females)</li> </ul>

Species	Route Duration	Treatment	Dose (mcg/kg)	Results and Observations
		budesonide/f ormoterol	2.05/0.105 9.8/0.5 49.5/2.7	<ul style="list-style-type: none"> <li>- no mortalities or adverse clinical signs</li> <li>- reduced body weight gain (mid-dose males and both sexes at high dose)</li> <li>- mild to moderate transient tachycardia one hour after dosing (high dose group)</li> <li>- slightly reduced lymphocyte counts</li> <li>- slightly increased levels of total plasma protein, cholesterol and ALP</li> <li>- slightly decreased plasma glucose levels</li> <li>- dose-related suppression of ACTH mediated cortisol release (mid and high dose groups)</li> <li>- dose-related decrease in adrenal and thymus weights</li> <li>- increased weight of spleen (low and mid dose) and liver (females)</li> <li>- slightly decreased lung weights (males)</li> <li>- 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)</li> <li>- 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)</li> <li>- minimal or slight lymphoid depletion in spleen (males at mid and high dose)</li> </ul>

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<sup>-1</sup>.day<sup>-1</sup> 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<sup>-1</sup>.day<sup>-1</sup> budesonide + 2.7 mcg.kg<sup>-1</sup>.day<sup>-1</sup> 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

 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<sub>2</sub>-agonist (LABA). It helps to rapidly open 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.

SYMBICORT TURBUHALER can be used for rapid relief of asthma symptoms. Asthma symptoms can lead to worsening asthma or an asthma "attack". Daily 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 NON-MEDICINAL 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

**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 TURBUHALER 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.

#### Patients with Asthma:

## IMPORTANT: PLEASE READ

When LABA medicines are used alone without an ICS, they increase the risk of hospitalization and death from asthma problems. SYMBICORT TURBUHALER contains both an ICS and LABA. Studies showed that when an ICS and LABA are used together, there is not a significant increased risk in hospitalizations and death from asthma problems.

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.

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;
- Diuretics or “water pills” used to lower blood pressure;
- Antidepressants, monoamine oxidase inhibitors used to treat depression.

## PROPER USE OF THIS MEDICATION

**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.**

### **DOSING**

#### **Patients with Asthma:**

Treatment with only SYMBICORT TURBUHALER is not enough to treat an asthma attack.

**For the treatment of asthma,** your doctor may instruct you to use SYMBICORT TURBUHALER in one of three ways:

- A) SYMBICORT TURBUHALER as reliever
- B) SYMBICORT TURBUHALER as reliever plus daily maintenance
- C) SYMBICORT TURBUHALER as daily maintenance

Each of these treatment plans is described below.

#### **A) SYMBICORT TURBUHALER as Reliever: Anti-inflammatory Reliever Therapy**

Only SYMBICORT **200** TURBUHALER is used for anti-inflammatory reliever therapy.

Using SYMBICORT **200** TURBUHALER for anti-inflammatory reliever therapy means:

- i. you take SYMBICORT **200** TURBUHALER anti-inflammatory reliever as needed for rapid relief of asthma symptoms.

**This means that you use one inhaler (SYMBICORT **200** TURBUHALER) for rapid symptom relief. You will not need a separate inhaler for rapid relief of symptoms.**

#### **Adults and adolescents (12 years and older)**

- 1 inhalation of SYMBICORT **200** TURBUHALER if you experience symptoms. Wait a few minutes. If you don't feel better, take another inhalation. Not more than 6 inhalations should be taken on any single occasion. The maximum recommended daily dose is 8 inhalations.

**Always carry SYMBICORT **200** TURBUHALER with you for rapid relief of symptoms.**

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

#### **B) SYMBICORT TURBUHALER as Reliever plus Daily Maintenance:**

## IMPORTANT: PLEASE READ

### Anti-inflammatory Reliever plus Maintenance Therapy (SYMBICORT SMART®)

Using SYMBICORT TURBUHALER for anti-inflammatory reliever plus maintenance therapy means:

- i. you take a regular daily maintenance dose of SYMBICORT TURBUHALER, PLUS
- ii. you use SYMBICORT TURBUHALER if you need extra doses for rapid relief of asthma symptoms.

**This means that you use one inhaler (SYMBICORT TURBUHALER) for both a regular daily dose and for rapid symptom relief. You will not need a separate inhaler for rapid relief of symptoms.**

#### Adults and adolescents (12 years and older)

- 1 or 2 inhalations of SYMBICORT **100** TURBUHALER or SYMBICORT **200** TURBUHALER twice daily or 2 inhalations once daily. You should take 1 additional inhalation of SYMBICORT **100** TURBUHALER or SYMBICORT **200** TURBUHALER 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 for rapid relief of symptoms. 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.**

Your doctor will adjust your maintenance medicine to the lowest dose that controls your asthma.

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

### C) SYMBICORT TURBUHALER as Maintenance

Using SYMBICORT TURBUHALER for daily maintenance therapy means:

- i. you take a daily maintenance dose of SYMBICORT TURBUHALER (fixed dose), AND
- ii. you use a separate inhaler, containing a short-acting bronchodilator (airway-widening medicine) for rapid relief of asthma symptoms.

This means that you use two separate inhalers.

#### Adults and adolescents (12 years and older)

- 1 or 2 inhalations of SYMBICORT **100** TURBUHALER or SYMBICORT **200** TURBUHALER once or twice daily. The maximum recommended daily maintenance dose is 4 inhalations.
- or
- 1 inhalation of SYMBICORT **FORTE** TURBUHALER once or twice daily. The maximum recommended daily maintenance dose is 4 inhalations.

**Always carry your short-acting bronchodilator (reliever medication) with you for rapid 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.**

Your doctor will adjust your maintenance medicine to the lowest dose that controls your asthma.

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

### Patients with COPD

#### Adults (18 years and older)

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

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

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

#### **MISSED DOSE:**

If you miss a maintenance dose, take it as soon as you remember and then go back to your regular schedule. Never take a double

## IMPORTANT: PLEASE READ

dose to make up for missed maintenance 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

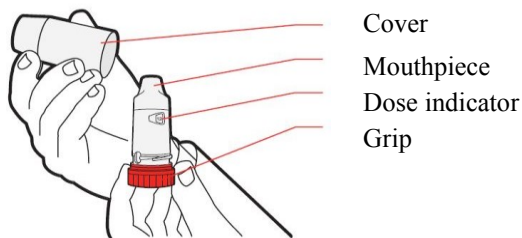
Before you start using SYMBICORT TURBUHALER for the first time it is important that you read the instructions below and follow them carefully. Your doctor, nurse or pharmacist should instruct you in the correct use of your inhaler.

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

 [Symbicort.ca/video](https://www.symbicort.ca/video)

If you are unsure about how to use your inhaler, ask your doctor, nurse or pharmacist.

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.

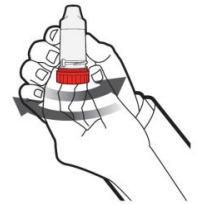
Figure 1



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 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.

Figure 2



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

Figure 2

## IMPORTANT: PLEASE READ

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).



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.



- 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.

Uncommon side effects are:

- Nausea;



**IMPORTANT: PLEASE READ**

- 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 SYMBICORT TURBUHALER as a reliever, or your fast-acting reliever medication without getting better asthma control within 2 weeks;
- 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% 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.**

<b>SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM</b>				
	Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and seek emergency medical attention
		Only if severe	In all cases	
Common	<b>Pneumonia</b> ( <i>an infection of the lungs</i> ): Fever, chills, increase in sputum production, change in sputum colour, increased cough or an increase in breathing difficulties.		✓	
Rare	<b>Bronchospasm:</b> Increased wheezing or tightness in the chest or difficulty in breathing immediately after inhalation of SYMBICORT TURBUHALER.			✓
	<b>Hypersensitivity reactions:</b> Skin rash, skin eruption or other effect on the skin or eyes, itching or fever.			✓



**IMPORTANT: PLEASE READ**

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

	<b>Allergic reactions:</b> 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	<b>Cushing's Syndrome</b> ( <i>hypercorticism</i> ): 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.		✓	
	<b>Increased blood sugar:</b> Frequent urination, thirst and hunger.			✓
Unknown	<b>Eosinophilic granulomatosis with polyangiitis</b> (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.		✓	

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

	<b>Glaucoma:</b> Increased pressure in your eyes, and/or eye pain.		✓	
	<b>Cataract:</b> Clouding of the lens in the eye, blurry vision, and/or eye pain.		✓	
	<b>Bone Fractures or Osteoporosis:</b> 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.		✓	

*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).

**REPORTING SIDE EFFECTS**

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345

*NOTE: Contact your health professional if you need information about how to manage your side effects. 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](http://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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