XXXXXX-XX

SYMBICORT 80/4.5

(budesonide 80 mcg and formoterol fumarate dihydrate 4.5 mcg) Inhalation Aerosol*

SYMBICORT 160/4.5

(budesonide 160 mcg and formoterol fumarate dihydrate 4.5 mcg) Inhalation Aerosol*

*3.7 mcg formoterol as the free base, equivalent to 4.5 mcg formoterol fumarate dihydrate

For Oral Inhalation Only

Rx only

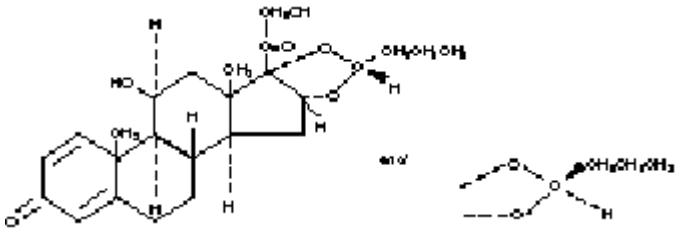
WARNING

Long-acting beta$_2$-adrenergic agonists may increase the risk of asthma-related death. Therefore, when treating patients with asthma, SYMBICORT should only be used for patients not adequately controlled on other asthma-controller medications (e.g., low-to-medium dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with two maintenance therapies. Data from a large placebo-controlled US study that compared the safety of another long-acting beta$_2$-adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol may apply to formoterol (a long-acting beta$_2$-adrenergic agonist), one of the active ingredients in SYMBICORT (see WARNINGS).

DESCRIPTION

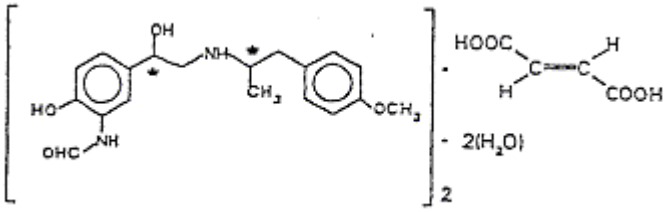
SYMBICORT 80/4.5 and SYMBICORT 160/4.5 each contain micronized budesonide and micronized formoterol fumarate dihydrate for oral inhalation only.

One active component of SYMBICORT is budesonide, a corticosteroid designated chemically as (RS)-11β, 16α, 17,21-Tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with butyraldehyde. Budesonide is provided as a mixture of two epimers (22R and 22S). The empirical formula of budesonide is $C_{25}H_{34}O_6$ and its molecular weight is 430.5. Its structural formula is:



Budesonide is a white to off-white, tasteless, odorless powder that is practically insoluble in water and in heptane, sparingly soluble in ethanol, and freely soluble in chloroform. Its partition coefficient between octanol and water at pH 7.4 is 1.6×10^3.

The other active component of SYMBICORT is formoterol fumarate dihydrate, a selective $beta_2$-agonist designated chemically as (R*,R*)-(±)-N-[2-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]formamide, (E)-2-butendioate(2:1), dihydrate. The empirical formula of formoterol is $C_{42}H_{56}N_4O_{14}$ and its molecular weight is 840.9. Its structural formula is:



Formoterol fumarate dihydrate is a powder which is slightly soluble in water. Its octanol-water partition coefficient at pH 7.4 is 2.6. The pKa of formoterol fumarate dihydrate at 25°C is 7.9 for the phenolic group and 9.2 for the amino group.

Each 10.2 g SYMBICORT 80/4.5 and SYMBICORT 160/4.5 canister is formulated as a hydrofluoroalkane (HFA 227; 1,1,1,2,3,3,3-heptafluoropropane)-propelled pressurized metered dose inhaler containing 120 actuations. After priming, each actuation meters either 91/5.1 mcg or 181/5.1 mcg from the valve and delivers either 80/4.5 mcg or 160/4.5 mcg (budesonide micronized/formoterol fumarate dihydrate micronized) from the actuator. The actual amount of drug delivered to the lung may depend on patient factors, such as the coordination between actuation of the device and inspiration through the delivery system. SYMBICORT also contains povidone K25 USP as a suspending agent and polyethylene glycol 1000 NF as a lubricant.

SYMBICORT should be primed before using for the first time by releasing 2 test sprays into the air away from the face, shaking well for 5 seconds before each spray. In cases where the inhaler has not been used for more than 7 days or when it has been dropped, prime the inhaler again by shaking well for 5 seconds before each spray and releasing 2 test sprays into the air away from the face.

CLINICAL PHARMACOLOGY

Mechanism of Action

SYMBICORT

SYMBICORT contains both budesonide and formoterol; therefore, the mechanisms of action described below for the individual components apply to SYMBICORT. These drugs represent two classes of medications (a synthetic corticosteroid and a long-acting selective beta$_2$-adrenoceptor agonist) that have different effects on clinical, physiological, and inflammatory indices of asthma.

Budesonide

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

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

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

Studies in asthmatic patients have shown a favorable ratio between topical anti-inflammatory activity and systemic corticosteroid effects over a wide range of doses of budesonide. This is explained by a combination of a relatively high local anti-inflammatory effect, extensive first pass hepatic degradation of orally absorbed drug (85-95%), and the low potency of formed metabolites.

Formoterol:

Formoterol fumarate is a long-acting selective $beta_2$-adrenergic agonist ($beta_2$-agonist) with a rapid onset of action. Inhaled formoterol fumarate acts locally in the lung as a bronchodilator. *In vitro* studies have shown that formoterol has more than 200-fold greater agonist activity at $beta_2$-receptors than at $beta_1$-receptors. The *in vitro* binding selectivity to $beta_2$- over $beta_1$-adrenoceptors is higher for formoterol than for albuterol (5 times), whereas salmeterol has a higher (3 times) beta $_2$-selectivity ratio than formoterol.

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

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

In vitro tests show that formoterol is an inhibitor of the release of mast cell mediators, such as histamine and leukotrienes, from the human lung. Formoterol also inhibits histamine-induced plasma albumin extravasation in anesthetized guinea pigs and inhibits allergen-induced eosinophil influx in dogs with airway hyper-responsiveness. The relevance of these in vitro and animal findings to humans is unknown.

Animal Pharmacology

Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines are administered concurrently. The clinical significance of these findings is unknown.

Pharmacokinetics

Symbicort

In a single-dose study, higher than recommended doses of SYMBICORT (12 inhalations of SYMBICORT 160/4.5 mcg) were administered to patients with moderate asthma. Peak plasma concentrations for budesonide of 4.5 nmol/L occurred at 20 minutes following dosing and peak concentrations for formoterol of 136 pmol occurred at 10 minutes following dosing. Approximately 8% of the delivered dose of formoterol was recovered in the urine as unchanged drug. This study also demonstrated that the total systemic exposure to budesonide from SYMBICORT was approximately 30% lower than from inhaled budesonide via a dry powder inhaler (DPI) at the same delivered dose. Following administration of SYMBICORT, the half-life of the budesonide component was 4.7 hours and for the formoterol component was 7.9 hours.

In a repeat dose study, the highest recommended dose of SYMBICORT (160/4.5 mcg, 2 inhalations twice daily) was administered to patients with moderate asthma and healthy subjects for one week. Peak plasma concentrations of budesonide (1.2 nmol/L) and formoterol (28 pmol/L) occurred at 21 and 10 minutes, respectively, in asthma patients. Peak plasma concentrations for budesonide and formoterol were about 30 to 40% higher in healthy subjects to that in asthma patients. However, the total systemic exposure was comparable to that in asthma patients.

Following administration of SYMBICORT (160/4.5 mcg, two or four inhalations twice daily) for five days in healthy subjects, plasma concentrations of budesonide and formoterol generally increased in proportion to dose. Additionally in this study, the accumulation index

for the two inhalation groups was 1.32 for budesonide and 1.77 for formoterol.

Special Populations

Geriatric

The pharmacokinetics of SYMBICORT in geriatric patients have not been specifically studied.

Pediatric

Plasma concentrations of budesonide were measured following administration of 4 inhalations of SYMBICORT 160/4.5 mcg in a single dose study in pediatric patients with asthma, 6-11 years of age. Urine was collected for determination of formoterol excretion. Peak budesonide concentrations of 1.4 nmol/L occurred at 20 minutes post-dose. Approximately 3.5% of the delivered formoterol dose was recovered in the urine as unchanged formoterol. This study also demonstrated that the total systemic exposure to budesonide from SYMBICORT was approximately 30% lower than from inhaled budesonide via a dry powder inhaler which was also evaluated at the same delivered dose.

Gender/Race

Specific studies to examine the effects of gender and race on the pharmacokinetics of SYMBICORT have not been conducted. Population PK analysis of the SYMBICORT data indicates that gender does not affect the pharmacokinetics of budesonide and formoterol. No conclusions can be drawn on the effect of race due to the low number of non-Caucasians evaluated for PK.

Renal or Hepatic Insufficiency

There are no data regarding the specific use of SYMBICORT in patients with hepatic or renal impairment. Reduced liver function may affect the elimination of corticosteroids. Budesonide pharmacokinetics was affected by compromised liver function as evidenced by a doubled systemic availability after oral ingestion. The intravenous budesonide pharmacokinetics was, however, similar in cirrhotic patients and in healthy subjects. Specific data with formoterol is not available, but since formoterol is primarily eliminated via hepatic metabolism, an increased exposure can be expected in patients with severe liver impairment.

Drug-Drug Interactions

A single dose crossover study was conducted to compare the pharmacokinetics of eight inhalations of the following: budesonide, formoterol, and budesonide plus formoterol administered concurrently. The results of the study indicated that there was no evidence of a pharmacokinetic interaction between the two components of SYMBICORT.

Ketoconazole, a potent inhibitor of cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4), the main metabolic enzyme for corticosteroids, increased plasma levels of orally ingested budesonide. At recommended doses, cimetidine had a slight but clinically insignificant effect on the pharmacokinetics of oral budesonide. Specific drug-drug interaction studies with formoterol have not been performed.

Budesonide

Absorption

Orally inhaled budesonide is rapidly absorbed in the lungs and peak concentration is typically reached within 20 minutes. After oral administration of budesonide, peak plasma concentration was achieved in about 1 to 2 hours and the absolute systemic availability was 6-13%, due to extensive first pass metabolism. In contrast, most of the budesonide delivered to the lungs was systemically absorbed. In healthy subjects, 34% of the metered dose was deposited in the lung (as assessed by plasma concentration method and using a budesonide containing dry-powder inhaler) with an absolute systemic availability of 39% of the metered dose. Peak steady-state plasma concentrations of budesonide administered by DPI in adults with asthma averaged 0.6 and 1.6 nmol/L at doses of 180 mcg and 360 mcg twice daily, respectively.

In asthmatic patients, budesonide showed a linear increase in AUC and C_{max} with increasing dose after both a single dose and repeated dosing of inhaled budesonide.

Distribution

The volume of distribution of budesonide was approximately 3 L/kg. It was 85-90% bound to plasma proteins. Protein binding was constant over the concentration range (1-100 nmol/L) achieved with, and exceeding, recommended inhaled doses. Budesonide showed little or no binding to corticosteroid binding globulin. Budesonide rapidly equilibrated with red blood cells in a concentration independent manner with a blood/plasma ratio of about 0.8.

Metabolism

In vitro studies with human liver homogenates have shown that budesonide was rapidly and extensively metabolized. Two major metabolites formed via cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4) catalyzed biotransformation have been isolated and identified as 16α-hydroxyprednisolone and 6β-hydroxybudesonide. The corticosteroid activity of each of these two metabolites was less than 1% of that of the parent compound. No qualitative differences between the in vitro and in vivo metabolic patterns were detected. Negligible metabolic inactivation was observed in human lung and serum preparations.

Excretion/Elimination

Budesonide was excreted in urine and feces in the form of metabolites. Approximately 60% of an intravenous radiolabeled dose was recovered in the urine. No unchanged budesonide was detected in the urine. The 22R form of budesonide was preferentially cleared by the liver with systemic clearance of 1.4 L/min vs. 1.0 L/min for the 22S form. The terminal half-life, 2 to 3 hours, was the same for both epimers and was independent of dose.

Formoterol

Absorption

Inhaled formoterol is rapidly absorbed; peak plasma concentrations are typically reached at the first plasma sampling time, within 5-10 minutes after dosing. As with many drug products for oral inhalation, it is likely that the majority of the inhaled formoterol delivered is swallowed and then absorbed from the gastrointestinal tract.

Distribution

Over the concentration range of 10-500 nmol/L, plasma protein binding for the RR and SS enantiomers of formoterol was 46 and 58%, respectively. The concentrations of formoterol used to assess the plasma protein binding were higher than those achieved in plasma following inhalation of a single 54 mcg dose.

Metabolism and Excretion

The metabolism and excretion of formoterol were studied in 4 healthy subjects following simultaneous administration of radiolabeled formoterol via the oral and IV routes. In that study, 62% of the radiolabeled formoterol was excreted in the urine while 24% was eliminated in the feces. The primary metabolism of formoterol is by direct glucuronidation and by O-demethylation followed by conjugation to inactive metabolites. Secondary metabolic pathways include deformylation and sulfate conjugation. CYP2D6 and CYP2C have been identified as being primarily responsible for O-demethylation.

Pharmacodynamics

Symbicort

In a single-dose cross-over study involving 201 patients with persistent asthma, single-dose treatments of 4.5, 9, and 18 mcg of formoterol in combination with 320 mcg of budesonide delivered via SYMBICORT were compared to budesonide 320 mcg alone. Dose-ordered improvements in FEV_1 were demonstrated when compared with budesonide. ECGs and blood samples for glucose and potassium were obtained post dose. For SYMBICORT, small mean increases in serum glucose and decreases in serum potassium (+0.44 mmol/L and -0.18 mmol/L at the highest dose, respectively) were observed with increasing doses of formoterol, compared to budesonide. In ECGs, SYMBICORT produced small dose-related mean increases in heart rate (approximately 3 bpm at the highest dose), and QTc intervals (3-6 msec) compared to budesonide alone. No subject had a QT or QTc value ≥500 msec.

In the United States, five 12-week, active- and placebo-controlled studies evaluated 2152 patients aged 12 and older with asthma. Systemic pharmacodynamic effects of formoterol (heart/pulse rate, blood pressure, QTc interval, potassium, and glucose) were similar in patients treated with SYMBICORT compared with patients treated with formoterol dry inhalation powder 4.5 mcg, 2 inhalations twice daily. No patient had a QT or QTc value ≥500 msec during treatment.

In 3 placebo-controlled studies in adolescents and adults with asthma aged 12 and older, a total of 1232 patients (553 patients in the SYMBICORT group) had evaluable continuous 24-hour electrocardiographic monitoring. Overall, there were no important differences in the occurrence of ventricular or supraventricular ectopy and no evidence of increased risk for clinically significant dysrhythmia in the SYMBICORT group compared to placebo.

Overall, no clinically important effects on HPA axis, as measured by 24-hour urinary cortisol, were observed for SYMBICORT-treated adult or adolescent patients at doses up to 640/18 mcg/day compared to budesonide.

Budesonide

To confirm that systemic absorption is not a significant factor in the clinical efficacy of inhaled budesonide, a clinical study in patients with asthma was performed comparing 400 mcg budesonide administered via a pressurized metered dose inhaler with a tube spacer to 1400 mcg of oral budesonide and placebo. The study demonstrated the efficacy of inhaled budesonide but not orally ingested budesonide despite comparable systemic levels. Thus, the therapeutic effect of conventional doses of orally inhaled budesonide are largely explained by its direct action on the respiratory tract.

Inhaled budesonide has been shown to decrease airway reactivity to various challenge models, including histamine, methacholine, sodium metabisulfite, and adenosine monophosphate in patients with hyperreactive airways. The clinical relevance of these models is not certain.

Pretreatment with inhaled budesonide, 1600 mcg daily (800 mcg twice daily) for 2 weeks reduced the acute (early-phase reaction) and delayed (late-phase reaction) decrease in FEV_1 following inhaled allergen challenge.

The systemic effects of inhaled corticosteroids are related to the systemic exposure to such drugs. Pharmacokinetic studies have demonstrated that in both adults and children with asthma the systemic exposure to budesonide is lower with SYMBICORT compared with inhaled budesonide administered at the same delivered dose via a dry powder inhaler (see **CLINICAL PHARMACOLOGY, Pharmacokinetics, SYMBICORT**). Therefore, the systemic effects (HPA axis and growth) of budesonide delivered from SYMBICORT would be expected to be no greater than what is reported for inhaled budesonide when administered at comparable doses via the dry powder inhaler (see **PRECAUTIONS, Pediatric Use)**.

The effects of inhaled budesonide administered via a dry powder inhaler on the hypothalamic-pituitary-adrenal (HPA) axis were studied in 905 adults and 404 pediatric patients with asthma. For most patients, the ability to increase cortisol production in response to stress, as assessed by cosyntropin (ACTH) stimulation test, remained intact with budesonide treatment at recommended doses. For adult patients treated with 100, 200, 400, or 800 mcg twice daily for 12 weeks, 4%, 2%, 6%, and 13% respectively, had an abnormal stimulated cortisol response (peak cortisol <14.5 mcg/dL assessed by liquid chromatography following short-cosyntropin test) as compared to 8% of patients treated with placebo. Similar results were obtained in pediatric patients. In another study in adults, doses of 400, 800 and 1600 mcg of inhaled budesonide twice daily for 6 weeks were examined; 1600 mcg twice daily (twice the maximum recommended dose) resulted in a 27% reduction in stimulated cortisol (6-hour ACTH infusion) while 10 mg prednisone resulted in a 35% reduction. In this study, no patient on budesonide at doses of 400 and 800 mcg twice daily met the criterion for an abnormal stimulated cortisol response (peak cortisol <14.5 mcg/dL assessed by liquid chromatography) following ACTH infusion. An open-label, long-term follow-up of 1133 patients for up to 52 weeks confirmed the minimal effect on the HPA axis (both basal and stimulated plasma cortisol) of budesonide when administered at recommended doses. In patients who had previously been oral steroid-dependent, use of budesonide in recommended doses was associated with higher stimulated cortisol response compared to baseline following 1 year of therapy.

Formoterol

While the pharmacodynamic effect is via stimulation of beta-adrenergic receptors; excessive activation of these receptors commonly leads to skeletal muscle tremor and cramps, insomnia, tachycardia, decreases in plasma potassium, and increases in plasma glucose. Inhaled formoterol, like other beta-adrenergic agonist drugs, can produce dose-related cardiovascular effects and effects on blood glucose and/or serum potassium (see **PRECAUTIONS, General**). For Symbicort, these effects are detailed in the **CLINICAL**

PHARMACOLOGY, Pharmacodynamics, SYMBICORT section.

Use of long-acting beta$_2$-adrenergic agonist drugs can result in tolerance to bronchoprotective and bronchodilatory effects.

Rebound bronchial hyper-responsiveness after cessation of chronic long-acting beta-agonists therapy has not been observed.

Clinical Studies

SYMBICORT has been studied in patients with asthma 12 years of age and older. In two clinical studies comparing SYMBICORT with the individual components, improvements in most efficacy endpoints were greater with SYMBICORT than with the use of either budesonide or formoterol alone. In addition, one clinical study showed similar results between SYMBICORT and the concurrent use of budesonide and formoterol at corresponding doses from separate inhalers.

The safety and efficacy of SYMBICORT were demonstrated in two randomized, double-blind, placebo-controlled US clinical studies involving 1076 patients 12 years of age and older. Fixed SYMBICORT dosages of 160/9 mcg, and 320/9 mcg twice daily (each dose administered as 2 inhalations of the 80/4.5- and 160/4.5-mcg strengths, respectively) were compared with the monocomponents (budesonide and formoterol) and placebo to provide information about appropriate dosing to cover a range of asthma severity.

Study 1: Clinical Study with SYMBICORT 160/4.5: This 12-week study evaluated 596 patients 12 years of age and older by comparing: SYMBICORT 160/4.5 mcg, the free combination of budesonide 160 mcg plus formoterol 4.5 mcg in separate inhalers, budesonide 160 mcg, formoterol 4.5 mcg, and placebo; each administered as 2 inhalations twice daily. The study included a 2-week run-in period with budesonide 80 mcg, 2 inhalations twice daily. Most patients had moderate to severe asthma and were using moderate to high doses of inhaled corticosteroids prior to study entry. Randomization was stratified by previous inhaled corticosteroid treatment (71.6% on moderate- and 28.4% on high-dose inhaled corticosteroid). Mean percent predicted FEV_1 at baseline was 68.1% and was similar across treatment groups. The co-primary efficacy endpoints were 12-hour-average post-dose FEV_1 at week 2, and pre-dose FEV_1 averaged over the course of the study. The study also required that patients who satisfied a pre-defined asthma worsening criterion to be withdrawn. The pre-defined asthma worsening criteria were: a clinically important decrease in FEV_1 or peak expiratory flow (PEF), increase in rescue albuterol use, nighttime awakening due to asthma, emergency intervention or hospitalization due to asthma, or requirement for asthma medication not allowed by the protocol. For the criterion of nighttime awakening due to asthma, patients were allowed to remain in the study at the discretion of the investigator if none of the other asthma worsening criteria were met. The percentage of patients withdrawing due to or meeting predefined criteria for worsening asthma is shown in Table 1.

Table 1 – The number and percentage of patients withdrawing due to or meeting predefined criteria for worsening asthma (Study 1)

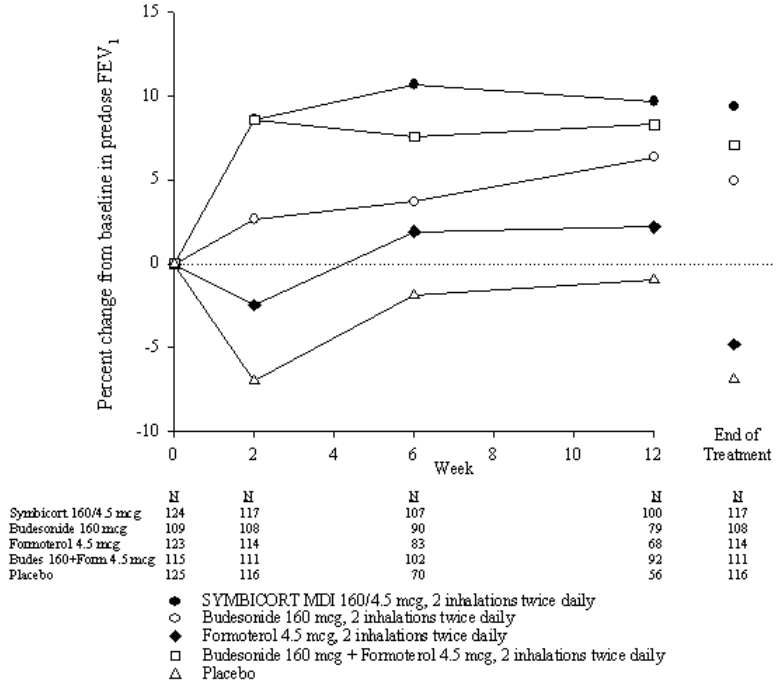
	SYMBICORT 160/4.5 (N=124)	Budesonide 160 mcg plus Formoterol 4.5 mcg (N=115)	Budesonide 160 mcg (N=109)	Formoterol 4.5 mcg (N=123)	Placebo (N=125)
Patients withdrawn due to predefined asthma event*	13 (10.5)	13 (11.3)	22 (20.2)	44 (35.8)	62 (49.6)
Patients with a predefined asthma event*†	37 (29.8)	24 (20.9)	48 (44.0)	68 (55.3)	84 (67.2)
Decrease in FEV_1	4 (3.2)	8 (7.0)	7 (6.4)	15 (12.2)	14 (11.2)
Rescue medication use	2 (1.6)	0	3 (2.8)	3 (2.4)	7 (5.6)
Decrease in AM PEF	2 (1.6)	5 (4.3)	5 (4.6)	17 (13.8)	15 (12.0)
Nighttime awakening‡	24 (19.4)	11 (9.6)	29 (26.6)	32 (26.0)	49 (39.2)
Clinical exacerbation	7 (5.6)	6 (5.2)	5 (4.6)	17 (13.8)	16 (12.8)

*These criteria were assessed on a daily basis irrespective of the timing of the clinic visit, with the exception of FEV_1 which was assessed at each clinic visit.
†Individual criteria are shown for patients meeting any predefined asthma event, regardless of withdrawal status.
‡For the criterion of nighttime awakening due to asthma, patients were allowed to remain in the study at the discretion of the investigator if none of the other criteria were met.

Mean percent change from baseline in FEV_1 measured immediately prior to dosing (predose) over 12 weeks is displayed in Figure 1. Because this study used predefined withdrawal criteria for worsening asthma, which caused a differential withdrawal rate in the treatment groups, predose FEV_1 results at the last available study visit (end of treatment, EOT) are also provided. Patients receiving SYMBICORT 160/4.5 mcg

had significantly greater mean improvements from baseline in predose FEV_1 at the end of treatment (0.19 L, 9.4%) compared with budesonide 160 mcg (0.10 L, 4.9%), formoterol 4.5 mcg (-0.12 L, -4.8%), and placebo (-0.17 L, -6.9%).

Figure 1 - Mean Percent Change From Baseline in predose FEV_1 Over 12 Weeks (Study 1)



	N	N	N	N	N
Symbicort 160/4.5 mcg	124	117	107	100	117
Budesonide 160 mcg	109	108	90	79	108
Formoterol 4.5 mcg	123	114	83	68	114
Budes 160+Form 4.5 mcg	115	111	102	92	111
Placebo	125	116	70	56	116

● SYMBICORT MDI 160/4.5 mcg, 2 inhalations twice daily
○ Budesonide 160 mcg, 2 inhalations twice daily
◆ Formoterol 4.5 mcg, 2 inhalations twice daily
□ Budesonide 160 mcg + Formoterol 4.5 mcg, 2 inhalations twice daily
△ Placebo

The effect of SYMBICORT 160/4.5 mcg 2 inhalations twice daily on selected secondary efficacy variables, including morning and evening PEF, albuterol rescue use, and asthma symptoms over 24 hours on a 0-3 scale is shown in Table 2.

Table 2 - Mean values for selected secondary efficacy variables (Study 1)

Efficacy Variable	SYMBICORT 160/4.5 (N*=124)	Budesonide 160 mcg + Formoterol 4.5 mcg (N*=115)	Budesonide 160 mcg (N*=109)	Formoterol 4.5 mcg (N*=123)	Placebo (N*=125)
AM PEF (L/min)					
Baseline	341	338	342	339	355
Change from Baseline	35	28	9	–9	–18
PM PEF (L/min)					
Baseline	351	348	357	354	369
Change from Baseline	34	26	7	–7	–18
Albuterol rescue use					
Baseline	2.1	2.3	2.7	2.5	2.4
Change from Baseline	–1.0	–1.5	–0.8	–0.3	0.8
Average symptom score/day (0-3 scale)					
Baseline	0.99	1.03	1.04	1.04	1.08
Change from Baseline	–0.28	–0.32	–0.14	–0.05	0.10

*Number of patients (N) varies slightly due to the number of patients for whom data were available for each variable. Results shown are based on last available data for each variable.

The subjective impact of asthma on patients' health-related quality of life was evaluated through the use of the standardized Asthma Quality of Life Questionnaire (AQLQ(S)) (based on a 7-point scale where 1 = maximum impairment and 7 = no impairment). Patients receiving SYMBICORT 160/4.5 had clinically meaningful improvement in overall asthma-specific quality of life, as defined by a mean difference between treatment groups of >0.5 points in change from baseline

in overall AQLQ score (difference in AQLQ score of 0.70 [95% CI 0.47, 0.93] compared to placebo).

Study 2: Clinical Study with SYMBICORT 80/4.5

This 12-week study was similar in design to Study 1, and included 480 patients 12 years of age and older. This study compared: SYMBICORT 80/4.5 mcg, budesonide 80 mcg, formoterol 4.5 mcg, and placebo; each administered as 2 inhalations twice-daily. The study included a 2-week placebo run-in period. Most patients had mild to moderate asthma and were using low to moderate doses of inhaled corticosteroids prior to study entry. Mean percent predicted FEV_1 at baseline was 71.3% and was similar across treatment groups. Efficacy variables and endpoints were identical to those in Study 1.

The percentage of patients withdrawing due to or meeting predefined criteria for worsening asthma is shown in Table 3. The method of assessment and criteria used were identical to that in Study 1.

Table 3 - The number and percentage of patients withdrawing due to or meeting predefined criteria for worsening asthma (Study 2)

	SYMBICORT 80/4.5 (N=123)	Budesonide 80 mcg (N=121)	Formoterol 4.5 mcg (N=114)	Placebo (N=122)
Patients withdrawn due to predefined asthma event*	9 (7.3)	8 (6.6)	21 (18.4)	40 (32.8)
Patients with a predefined asthma event*†	23 (18.7)	26 (21.5)	48 (42.1)	69 (56.6)
Decrease in FEV_1	3 (2.4)	3 (2.5)	11 (9.6)	9 (7.4)
Rescue medication use	1 (0.8)	3 (2.5)	1 (0.9)	3 (2.5)
Decrease in AM PEF	3 (2.4)	1 (0.8)	8 (7.0)	14 (11.5)
Nighttime awakening‡	17 (13.8)	20 (16.5)	31 (27.2)	52 (42.6)
Clinical exacerbation	1 (0.8)	3 (2.5)	5 (4.4)	20 (16.4)

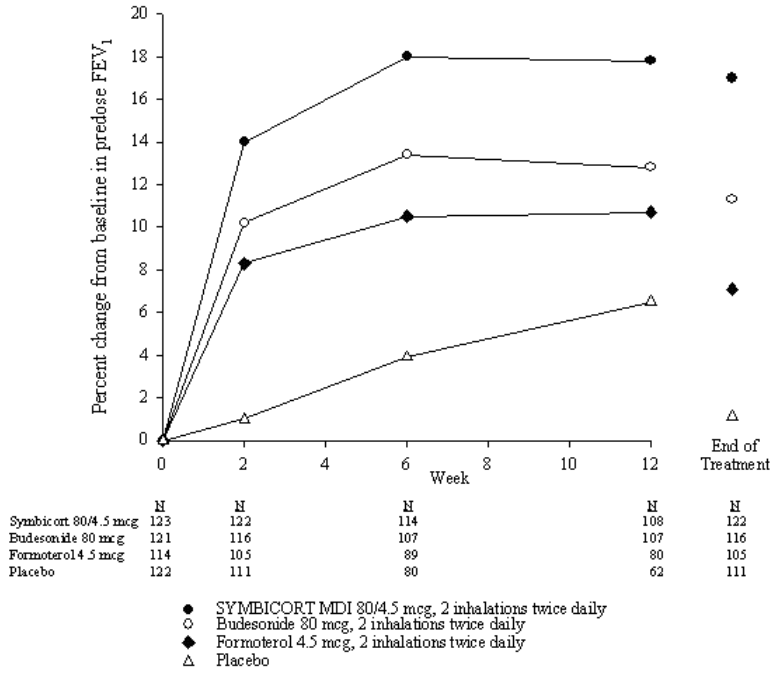
*These criteria were assessed on a daily basis irrespective of the timing of the clinic visit, with the exception of FEV_1 which was assessed at each clinic visit.

†Individual criteria are shown for patients meeting any predefined asthma event, regardless of withdrawal status.

‡For the criterion of nighttime awakening due to asthma, patients were allowed to remain in the study at the discretion of the investigator if none of the other criteria were met.

Mean percent change from baseline in predose FEV_1 over 12 weeks is displayed in Figure 2.

Figure 2 - Mean percent change from baseline in predose FEV_1 over 12 weeks (Study 2)



Efficacy results for other secondary endpoints, including quality of life, were similar to those observed in Study 1.

Onset and Duration of Action and Progression of Improvement in Asthma Control

The onset of action and progression of improvement in asthma control were evaluated in the 2 pivotal clinical studies. The median time to onset of clinically significant bronchodilation (>15% improvement in FEV_1) was seen within 15 minutes. Maximum improvement in FEV_1 occurred within 3 hours, and clinically significant improvement was maintained over 12 hours. Figures 3 and 4 show the percent change from baseline in postdose FEV_1 over 12 hours on the day of randomization and on the last day of treatment for Study 1.

Reduction in asthma symptoms and in albuterol rescue use, as well as improvement in morning and evening

PEF, occurred within 1 day of the first dose of SYMBICORT; improvement in these variables were maintained over the 12 weeks of therapy.

Following the initial dose of SYMBICORT, FEV_1 improved markedly during the first 2 weeks of treatment, continued to show improvement at the Week 6 assessment, and was maintained through Week 12 for both studies.

No diminution in the 12-hour bronchodilator effect was observed with either SYMBICORT 80/4.5 mcg or SYMBICORT 160/4.5 mcg as assessed by FEV_1 following 12 weeks of therapy or at the last available visit.

FEV_1 data from Study 1 evaluating SYMBICORT 160/4.5 mcg is displayed in Figures 3 and 4.

719
720 **Figure 3 - Mean Percent Change From Baseline in**
721 **FEV_1 on Day of Randomization**
722 **(Study 1)**

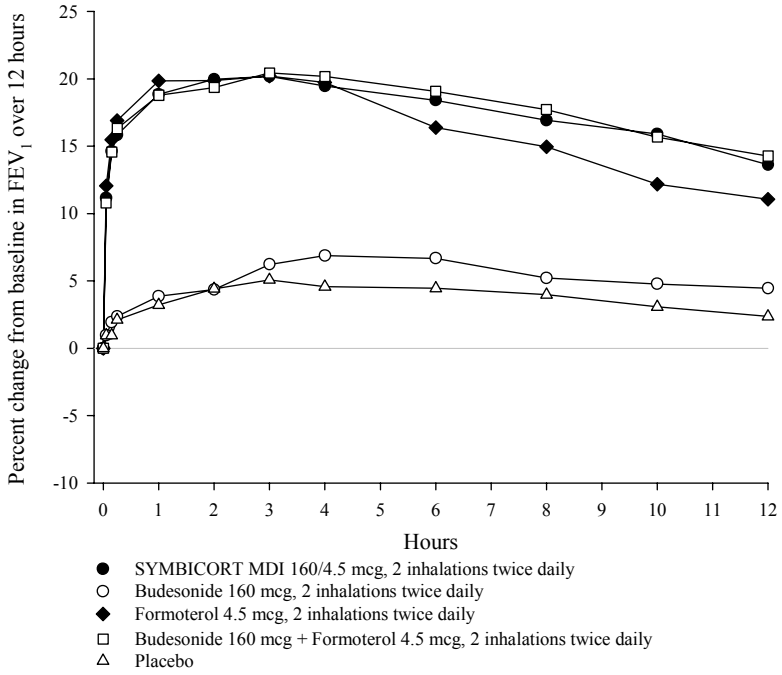


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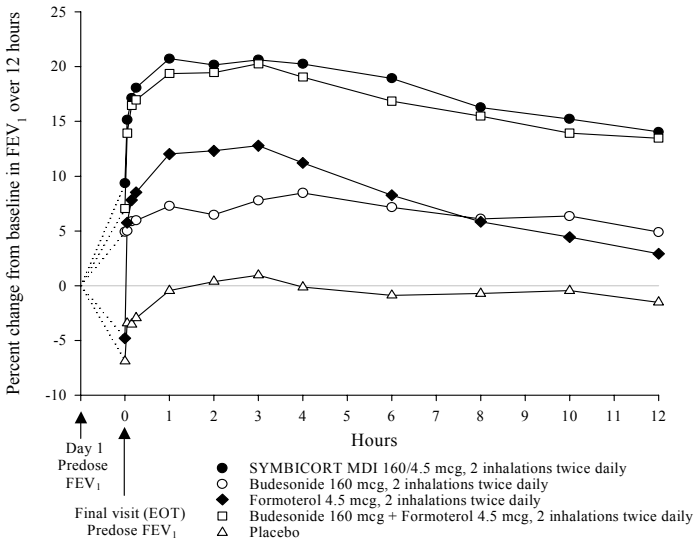
Figure 4 - Mean Percent Change From Baseline in FEV_1 At End of Treatment (Study 1)



INDICATIONS AND USAGE

SYMBICORT is indicated for the long-term maintenance treatment of asthma in patients 12 years of age and older.

Long-acting $beta_2$-adrenergic agonists may increase the risk of asthma-related death (see WARNINGS). Therefore, when treating patients with asthma, SYMBICORT should only be used for patients not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with two maintenance therapies. SYMBICORT is not indicated in patients whose asthma can be successfully managed by inhaled corticosteroids along with occasional use of inhaled, short-acting $beta_2$-agonists.

SYMBICORT is NOT indicated for the relief of acute bronchospasm.

CONTRAINDICATIONS

SYMBICORT is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.

Hypersensitivity to any of the ingredients in SYMBICORT contraindicates its use.

WARNINGS

Long-acting beta$_2$-adrenergic agonists may increase the risk of asthma-related death. Therefore, when treating patients with asthma, SYMBICORT should only be used for patients not adequately controlled on other asthma-controller medications (e.g., low-to-medium dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with two maintenance therapies.

- A 28-week, placebo controlled US study comparing the safety of salmeterol with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in patients receiving salmeterol (13/13,176 in patients treated with salmeterol vs 3/13,179 in patients treated with placebo; RR 4.37, 95% CI 1.25, 15.34). The increased risk of asthma-related death may represent a class effect of the long-acting beta$_2$-adrenergic agonists, including formoterol. No study adequate to determine whether the rate of asthma-related death is increased with SYMBICORT has been conducted.

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

SYMBICORT Should Not Be Initiated In Patients During Rapidly Deteriorating Or Potentially Life-Threatening Episodes Of Asthma.

Do Not Use SYMBICORT to Treat Acute Symptoms. SYMBICORT should not be used to treat acute symptoms of asthma. An inhaled, short-acting $beta_2$-agonist (e.g., albuterol), should be used to relieve acute asthma symptoms. Therefore, when prescribing SYMBICORT, the physician must also provide the patient with an inhaled, short-acting $beta_2$-agonist for treatment of symptoms that occur acutely, despite regular twice-daily (morning and evening) use of SYMBICORT.

When beginning treatment with SYMBICORT, patients who have been taking oral or inhaled, short-acting $beta_2$-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs. For patients on SYMBICORT, short-acting, inhaled $beta_2$-agonists should only be used for symptomatic relief of acute asthma symptoms (see **PRECAUTIONS, Information for Patients**).

Watch for Increasing Use of Inhaled, Short-Acting $Beta_2$-Agonists, Which Is a Marker of Deteriorating Asthma. Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient's inhaled, short-acting $beta_2$-agonist becomes less effective, the patient needs more inhalations than usual, or the patient develops a significant decrease in lung function, these may be markers of destabilization of asthma. In this setting, the patient requires immediate reevaluation and reassessment of the treatment regimen, giving special consideration to the possible need for replacing the current strength of SYMBICORT with a higher strength, adding additional inhaled corticosteroid, or initiating systemic corticosteroids. Patients should not use more than two actuations twice daily (morning and evening) of SYMBICORT.

SYMBICORT Should Not be Used For Transferring Patients from Systemic Corticosteroid Therapy. Particular care is needed for patients who are transferred from systemically active corticosteroids to inhaled corticosteroids. Deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months may be required for recovery of HPA function. Patients who have been previously maintained on 20 mg or more per day of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although inhaled corticosteroid therapy may provide control of asthma symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of glucocorticoid systemically and does NOT provide the mineralocorticoid activity that is necessary for coping with these emergencies.

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

Do Not Use an Inhaled, Long-Acting Beta$_2$-Agonist in Conjunction With SYMBICORT. Patients who are receiving SYMBICORT twice daily should not use additional formoterol or other long-acting inhaled beta$_2$-agonists (e.g., salmeterol) for prevention of exercise-induced bronchospasm (EIB) or the maintenance treatment of asthma. Additional benefit would not be gained from using supplemental formoterol or salmeterol for prevention of EIB since SYMBICORT already contains an inhaled, long-acting beta$_2$-agonist.

Do Not Exceed Recommended Dosage. SYMBICORT should not be used more often or at higher doses than recommended. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs in patients with asthma. The exact cause of death is unknown, but cardiac arrest following an unexpected development of a severe acute asthmatic crisis and subsequent hypoxia is suspected. In addition, data from clinical studies with formoterol dry powder inhaler suggest that the use of doses higher than recommended (24 mcg twice daily) is associated with an increased risk of serious asthma exacerbations. In a 52-week active-controlled safety study evaluating SYMBICORT 160/4.5, patients treated with twice the highest recommended dose of SYMBICORT demonstrated a similar safety profile to that of patients treated with the highest recommended dose.

Paradoxical Bronchospasm. As with other inhaled asthma medications SYMBICORT, may produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with SYMBICORT, treatment with SYMBICORT should be discontinued immediately and alternate therapy should be instituted.

Immediate Hypersensitivity Reactions. Immediate hypersensitivity reactions, such as urticaria, angioedema, rash, and bronchospasm may occur after administration of SYMBICORT.

Cardiovascular Disorders. SYMBICORT, like all products containing sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension. Formoterol, a component of SYMBICORT, may produce a clinically significant cardiovascular effect in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of SYMBICORT at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiogram (ECG) changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown.

Discontinuation of Systemic Corticosteroids. Transfer of patients from systemic corticosteroid therapy to inhaled corticosteroids may unmask conditions previously suppressed by the systemic corticosteroid therapy, e.g., rhinitis, conjunctivitis, eczema, and arthritis.

Immunosuppression. Persons who are using 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 using corticosteroids. In such children or adults who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. It is unknown how the dose, route, and duration of corticosteroid administration affect the risk of developing a disseminated infection. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If a patient on immunosuppressant doses of corticosteroids is exposed to chicken pox, therapy with varicella zoster immune globulin (VZIG) or pooled intramuscular immunoglobulin (IG), as appropriate may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered. The immune responsiveness to varicella vaccine was evaluated in pediatric patients with asthma ages 12 months to 8 years with budesonide inhalation suspension (see **PRECAUTIONS, Drug Interactions**).

PRECAUTIONS

General

Sympathomimetic Effects. 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, a component of SYMBICORT, and may require discontinuation of SYMBICORT. SYMBICORT, like all medications containing sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive disorders, untreated hypokalemia, or thyrotoxicosis; and in patients who are unusually responsive to sympathomimetic amines.

As has been described with other beta-adrenergic agonist bronchodilators, clinically important changes in electrocardiograms, systolic and/or diastolic blood pressure, and pulse rate were seen infrequently in individual patients during controlled clinical studies with SYMBICORT at recommended doses.

Metabolic and Other Effects. Long-term use of orally inhaled corticosteroids, such as budesonide, a component of SYMBICORT, may affect normal bone metabolism resulting in a loss of bone mineral density. In patients with major risk factors for decreased bone mineral content, such as tobacco use, advanced age, sedentary lifestyle, poor nutrition, family history or osteoporosis, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants and corticosteroids), orally inhaled corticosteroids may pose an additional risk.

Doses of the related $beta_2$-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis. High doses of beta-adrenergic agonist medications may produce significant hypokalemia in some patients, through intracellular shunting, which may have the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation.

Clinically important changes in blood glucose and/or serum potassium were seen rarely during clinical studies with SYMBICORT at recommended doses.

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

Budesonide, a component of SYMBICORT, will often permit control of asthma symptoms with less suppression of HPA function than therapeutically equivalent oral doses of prednisone. Since budesonide is absorbed into the circulation and can be systemically

active, patients should not exceed the recommended dosage of SYMBICORT. Individual patients should be titrated to the lowest effective dose in order to minimize HPA dysfunction. Since individual sensitivity to effects on cortisol production exists, physicians should consider this information when prescribing SYMBICORT.

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

It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear in a small number of patients, particularly at higher doses. If such changes occur, the total daily dose of SYMBICORT should be reduced slowly, consistent with accepted procedures for management of asthma symptoms and for tapering of systemic steroids.

Budesonide, a component of SYMBICORT, may cause a reduction in growth velocity when administered to pediatric patients. Patients should be maintained on the lowest dose of SYMBICORT that effectively controls their asthma (see **PRECAUTIONS, Pediatric Use**).

The long-term effects resulting from chronic use of budesonide on developmental or immunological processes in the mouth, pharynx, trachea, and lung are unknown. The local and systemic effects of SYMBICORT in humans have been studied for up to one year (see **ADVERSE REACTIONS, Long Term Safety**).

Rare instances of glaucoma, increased intraocular pressure, and cataracts have been reported following the inhaled administration of corticosteroids, including budesonide, a component of SYMBICORT.

Lower respiratory tract infections, including pneumonia, have been reported following the inhaled administration of corticosteroids, including budesonide, a component of SYMBICORT. In the 3 placebo-controlled US clinical studies, the incidence of lower respiratory tract infections, including pneumonia, was low, with no consistent evidence of increased risk for SYMBICORT compared to placebo.

In clinical studies with SYMBICORT, localized infections with *Candida albicans* have occurred in the mouth and pharynx. If oropharyngeal candidiasis develops, it should be treated with appropriate local or systemic (ie, oral) antifungal therapy while still continuing with SYMBICORT therapy, but at times the dose of SYMBICORT may need to be temporarily decreased or interrupted under close medical supervision.

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

Information for Patients

Patients should be instructed to read the accompanying Medication Guide with each new prescription and refill.

Patients being treated with SYMBICORT should receive the following information and instructions. This information is intended to aid the patient in the safe and effective use of the medication. It is not a disclosure of all possible adverse or intended effects.

It is important that patients understand how to use the SYMBICORT inhaler device appropriately and how SYMBICORT should be used in relation to other asthma medications they are taking.

1. **Patients should be informed that long-acting beta$_2$-adrenergic agonists may increase the risk of asthma-related death.** Patients should also be informed that data are not adequate to determine whether the concurrent use of inhaled corticosteroids, such as budesonide, the other component of SYMBICORT, or other asthma-controller therapy modifies this risk.
2. Patients should be instructed that the correct dose of SYMBICORT is 2 puffs inhaled twice daily of the appropriate dosage strength, 80/4.5 or 160/4.5. They should take 2 puffs of SYMBICORT in the morning and 2 puffs in the evening every day. The maximum daily recommended dose is 640/18 mcg budesonide/formoterol (given as two inhalations of SYMBICORT 160/4.5 twice daily). Do not use more than twice daily or use a higher number of inhalations (more than 2 inhalations twice daily) of the prescribed strength of SYMBICORT as this will result in a daily dose of formoterol in excess of the dose determined to be safe. **Patients should also be instructed not to take SYMBICORT more often or use more puffs than you have prescribed.** If they miss a dose, they should be instructed to take their next dose at the same time they normally do.
3. **SYMBICORT is not meant to relieve acute asthma symptoms and extra doses should not be used for that purpose.** Acute symptoms should be treated with an inhaled, short-acting beta$_2$-agonist such as albuterol (the physician should provide the patient with such medication and instruct the patient on how it should be used).
4. The physician should be notified immediately if any of the following situations occur, which may be a sign of seriously worsening asthma:
   - Decreasing effectiveness of inhaled, short-acting beta$_2$-agonists
   - Need for more inhalations than usual of inhaled, short-acting beta$_2$-agonists
   - Significant decrease in lung function as outlined by the physician
   - Marked change in symptoms

5. When patients are prescribed SYMBICORT, other inhaled drugs and asthma medications should be used only as directed by a physician.
6. Patients who are receiving SYMBICORT should not use formoterol or another long-acting inhaled $beta_2$-agonist for prevention of exercise-induced bronchospasm or maintenance treatment of asthma.
7. Patients should not stop therapy with SYMBICORT without physician/provider guidance since symptoms may recur after discontinuation.
8. Patients should be cautioned regarding common adverse effects associated with $beta_2$-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.
9. Patients should be warned to avoid exposure to chicken pox or measles and if they are exposed, to consult their physicians without delay.
10. Long-term use of inhaled corticosteroids, including budesonide, a component of SYMBICORT, may increase the risk of some eye problems (cataracts or glaucoma). Regular eye examinations should be considered.
11. If the patient is pregnant or nursing, they should contact their physician about the use of SYMBICORT.
12. Results of clinical trials indicate that in most patients, clinically significant improvement occurred within 15 minutes of beginning treatment with SYMBICORT. The maximum benefit may not be achieved for 2 weeks or longer after starting treatment. Individual patients may experience a variable time to onset and degree of symptom relief.
13. The bronchodilation from a dose (2 inhalations) of SYMBICORT has been shown to last up to 12 hours or longer. The recommended dosage should not be exceeded.
14. The following measures should be observed when using SYMBICORT:
    - Patients should not attempt to take the inhaler apart.
    - SYMBICORT should be primed before using the first time and also when the inhaler has not been used for more than 7 days by releasing 2 test sprays into the air away from the face, shaking well for 5 seconds before each spray.

- Patients should replace the mouthpiece cover after each use.
- To remove any excess medication, patients should rinse their mouth with water after each dose (do not swallow) to decrease the risk of the development of oral candidiasis.
- Patients should clean the inhaler every 7 days by wiping the mouthpiece with a dry cloth.
- Use SYMBICORT only with the actuator supplied with the product. Discard the inhaler after 120 sprays have been used by the patient.
- Store in a dry place at controlled room temperature 20°C to 25°C (68°F to 77°F) [see USP] and out of the reach of children.

Drug Interactions

In clinical studies, concurrent administration of SYMBICORT and other drugs, such as short-acting beta$_2$-agonists, intranasal corticosteroids, and antihistamines/decongestants has not resulted in an increased frequency of adverse events. No formal drug interaction studies have been performed with SYMBICORT.

Short-Acting Beta$_2$-Agonists: In three 12-week, placebo-controlled US clinical studies, the mean daily need for albuterol rescue use in 401 adult and adolescent patients using SYMBICORT twice daily was approximately 0.8 inhalations/day, and ranged from 0 to 14 inhalations/day. Approximately 2% (N= 8) of the SYMBICORT patients in these studies averaged 6 or more inhalations per day. No cardiac adverse events were reported in these patients.

Methylxanthines and leukotriene modifying agents: The concurrent use of intravenously or orally administered methylxanthines (e.g., aminophylline, theophylline) by patients receiving SYMBICORT has not been completely evaluated. In clinical trials with SYMBICORT, limited number of patients received concurrent methylxanthines or leukotriene modifying agents, and therefore no clinically meaningful conclusions on adverse events can be made.

Intranasal and systemic corticosteroids: Among adult and adolescent patients participating in active- and placebo-controlled US clinical trials, twice daily SYMBICORT was used concurrently with intranasal budesonide in 105 patients and with any intranasal corticosteroids in 585 patients. Two hundred seventeen patients used courses of systemic corticosteroids while taking SYMBICORT. There were no important differences noted in the adverse event profiles between these groups.

Monoamine Oxidase Inhibitors and Tricyclic Antidepressants: SYMBICORT should be administered with caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of formoterol, a component of SYMBICORT, on the vascular system may be potentiated by these agents. In clinical trials with SYMBICORT, a limited number of patients received tricyclic antidepressants and therefore no clinically meaningful conclusions on adverse events can be made.

Beta-Adrenergic Receptor Blocking Agents: Beta-blockers (including eye drops) may not only block the pulmonary effect of beta-agonists, such as formoterol, a component of SYMBICORT, but may produce severe bronchospasm in patients with asthma. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with asthma. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

Diuretics: The ECG changes and/or hypokalemia that may result from the administration of nonpotassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of SYMBICORT with nonpotassium-sparing diuretics.

Ketoconazole and Other Inhibitors of Cytochrome p450: The main route of metabolism of corticosteroids, including budesonide, a component of SYMBICORT, is via cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4). After oral administration of ketoconazole, a potent inhibitor of CYP3A4, the mean plasma concentration of orally administered budesonide increased. Concomitant administration of other known inhibitors of CYP3A4 (e.g., itraconazole, clarithromycin, erythromycin, etc.) may inhibit the metabolism of, and increase the systemic exposure to, budesonide. Caution should be exercised when considering the coadministration of SYMBICORT with long-term ketoconazole and other known potent CYP3A4 inhibitors.

Varicella Vaccine: An open-label non-randomized clinical study examined the immune responsiveness to varicella vaccine in 243 asthma patients 12 months to 8 years of age who were treated with budesonide inhalation suspension 0.25 mg to 1 mg daily (n=151) or non-corticosteroid asthma therapy (n=92) (ie, $beta_2$-agonists, leukotriene receptor antagonists, cromones). The percentage of patients developing a seroprotective antibody titer of $\geq$5.0 (gpELISA value) in response to the vaccination was similar in patients treated with budesonide inhalation suspension (85%) compared to patients treated with non-corticosteroid asthma therapy (90%). No patient treated with budesonide inhalation suspension developed chickenpox as a result of vaccination.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Budesonide

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

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

In a 91-week study in mice, budesonide caused no treatment-related carcinogenicity at oral doses up to 200 mcg/kg (approximately equal to the maximum recommended human daily inhalation dose on a mcg/m^2 basis).

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

In rats, budesonide had no effect on fertility at subcutaneous doses up to 80 mcg/kg (approximately equal to the maximum recommended human daily

inhalation dose on a mcg/m^2 basis). However, it caused a decrease in prenatal viability and viability in the pups at birth and during lactation, along with a decrease in maternal body-weight gain, at subcutaneous doses of 20 mcg/kg and above (less than the maximum recommended human daily inhalation dose on a mcg/m^2 basis). No such effects were noted at 5 mcg/kg (less than the maximum recommended human daily inhalation dose on a mcg/m^2 basis).

Formoterol

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

In a 24-month carcinogenicity study in CD-1 mice, formoterol at oral doses of 0.1 mg/kg and above (approximately 20 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis) caused a dose-related increase in the incidence of uterine leiomyomas.

In a 24-month carcinogenicity study in Sprague-Dawley rats, an increased incidence of mesovarian leiomyoma and uterine leiomyosarcoma were observed at the inhaled dose of 130 mcg/kg (approximately 60 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). No tumors were seen at 22 mcg/kg (approximately 10 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis).

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

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

A reduction in fertility and/or reproductive performance was identified in male rats treated with formoterol at an oral dose of 15 mg/kg (approximately 7000 times the

maximum recommended human daily inhalation dose on a mcg/m^2 basis). In a separate study with male rats treated with an oral dose of 15 mg/kg (approximately 7000 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis), there were findings of testicular tubular atrophy and spermatic debris in the testes and oligospermia in the epididymides. No such effect was seen at 3 mg/kg (approximately 1400 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). No effect on fertility was detected in female rats at doses up to 15 mg/kg (approximately 7000 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis).

Pregnancy

Symbicort

Teratogenic Effects: Pregnancy Category C

SYMBICORT has been shown to be teratogenic and embryocidal in rats when given at inhalation doses of 12/0.66 mcg/kg (budesonide/formoterol) and above (less than the maximum recommended human daily inhaled dose on a mcg/m^2 basis). Umbilical hernia, a malformation, was observed for fetuses at doses of 12/0.66 mcg/kg and above (less than the maximum recommended human daily inhaled dose on a mcg/m^2 basis). No teratogenic or embryocidal effects were detected at 2.5/0.14 mcg/kg (less than the maximum recommended human daily inhaled dose on a mcg/m^2 basis). There are no adequate and well-controlled studies in pregnant women. SYMBICORT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Budesonide

Teratogenic Effects:

As with other corticosteroids, budesonide has been shown to be teratogenic and embryocidal in rabbits and rats. Budesonide produced fetal loss, decreased pup weight, and skeletal abnormalities at subcutaneous doses of 25 mcg/kg/day in rabbits (less than the maximum recommended human daily inhalation dose on a mcg/m^2 basis) and 500 mcg/kg/day in rats (approximately 6 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). In another study in rats, no teratogenic or embryocidal effects were seen at inhalation doses up to 250 mcg/kg/day (approximately 3 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis).

Experience with oral corticosteroids since their introduction in pharmacologic as opposed to physiologic doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans.

Studies of pregnant women, however, have not shown that inhaled budesonide increases the risk of abnormalities when administered during pregnancy. The results from a large population-based prospective cohort epidemiological study reviewing data from three Swedish registries covering approximately 99% of the pregnancies from 1995-1997 (ie, Swedish Medical Birth Registry; Registry of Congenital Malformations; Child Cardiology Registry) indicate no increased risk for congenital malformations from the use of inhaled budesonide during early pregnancy. Congenital malformations were studied in 2014 infants born to mothers reporting the use of inhaled budesonide for asthma in early pregnancy (usually 10-12 weeks after the last menstrual period), the period when most major organ malformations occur. The rate of recorded congenital malformations was similar compared to the general population rate (3.8% vs. 3.5%, respectively). In addition, after exposure to inhaled budesonide, the number of infants born with orofacial clefts was similar to the expected number in the normal population (4 children vs. 3.3, respectively).

These same data were utilized in a second study bringing the total to 2534 infants whose mothers were exposed to inhaled budesonide. In this study, the rate of congenital malformations among infants whose mothers were exposed to inhaled budesonide during early pregnancy was not different from the rate for all newborn babies during the same period (3.6%).

Formoterol

Teratogenic Effects:

Formoterol fumarate has been shown to be teratogenic, embryocidal, increase pup loss at birth and during lactation, and decreased pup weights in rats when given at oral doses of 3 mg/kg/day and above (approximately 1400 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). Umbilical hernia, a malformation, was observed in rat fetuses at oral doses of 3 mg/kg/day and above (approximately 1400 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). Brachygnathia, a skeletal malformation, was observed for rat fetuses at an oral dose of 15 mg/kg/day (approximately 7000 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). Pregnancy was prolonged at an oral dose of 15 mg/kg/day (approximately 7000 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). In another study in rats, no teratogenic effects were seen at inhalation doses up to 1.2 mg/kg/day (approximately 500 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis).

Formoterol fumarate has been shown to be teratogenic in rabbits when given at an oral dose of 60 mg/kg (approximately 54,000 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). Subcapsular cysts on the liver were observed for rabbit fetuses at an oral dose of 60 mg/kg (approximately 54,000 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). No teratogenic effects were observed at oral doses up to 3.5 mg/kg (approximately 3200 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis).

There are no adequate and well-controlled studies with formoterol in pregnant women.

Nonteratogenic Effects

Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

Use in Labor and Delivery

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

Nursing Mothers

Since there are no data from controlled trials on the use of SYMBICORT by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue SYMBICORT, taking into account the importance of SYMBICORT to the mother.

It is not known whether budesonide, one of the main components of SYMBICORT, is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised if budesonide is administered to nursing women.

In reproductive studies in rats, formoterol was excreted in the milk. It is not known whether formoterol is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised if formoterol is administered to nursing women.

Pediatric Use

Safety and effectiveness of SYMBICORT in patients 12 years of age and older have been established in studies up to 12 months. In the two 12-week, double-blind, placebo-controlled US pivotal studies 25 patients 12 to 17 years of age were treated with SYMBICORT twice daily. Efficacy results in this age group were similar to those observed in patients 18 years and older. There were no obvious differences in the type or frequency of

adverse events reported in this age group compared with patients 18 years of age and older.

The effectiveness of SYMBICORT in patients 6 to < 12 years of age has not been established.

Overall 1447 patients 6 to <12 years of age participated in placebo- and active-controlled SYMBICORT studies. Of these 1447 patients, 539 received SYMBICORT twice daily. The overall safety profile of these patients was similar to that observed in patients ≥12 years of age who also received SYMBICORT twice daily in studies of similar design.

Controlled clinical studies have shown that orally inhaled corticosteroids including budesonide, a component of SYMBICORT, may cause a reduction in growth velocity in pediatric patients. This effect has been observed in the absence of laboratory evidence of HPA axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The long-term effect of this reduction in growth velocity associated with orally inhaled corticosteroids, including the impact on final height are unknown. The potential for "catch-up" growth following discontinuation of treatment with orally inhaled corticosteroids has not been adequately studied.

In a study of asthmatic children 5-12 years of age, those treated with budesonide DPI 200 mcg twice daily (n=311) had a 1.1-centimeter reduction in growth compared with those receiving placebo (n=418) at the end of one year; the difference between these two treatment groups did not increase further over three years of additional treatment. By the end of four years, children treated with budesonide DPI and children treated with placebo had similar growth velocities. Conclusions drawn from this study may be confounded by the unequal use of corticosteroids in the treatment groups and inclusion of data from patients attaining puberty during the course of the study.

The growth of pediatric patients receiving orally inhaled corticosteroids, including SYMBICORT, should be monitored. If a child or adolescent on any corticosteroid appears to have growth suppression, the possibility that he/she is particularly sensitive to this effect should be considered. The potential growth effects of prolonged treatment should be weighed against the clinical benefits obtained. To minimize the systemic effects of orally inhaled corticosteroids, including SYMBICORT, each patient should be titrated to the lowest strength that effectively controls his/her asthma (see **DOSAGE AND ADMINISTRATION**).

Geriatric Use

In three 12-week, double-blind, placebo-controlled US clinical studies, 17 patients treated with SYMBICORT twice daily were 65 years of age or older, of whom 2 were 75 years of age or older. Of the total number of patients in clinical studies treated with SYMBICORT twice daily, 149 were 65 years of age or older, of whom, 25 were 75 years of age or older. No overall differences in safety were observed between these patients and younger patients. As with other products containing $beta_2$-agonists, special caution should be observed when using SYMBICORT in geriatric patients who have concomitant cardiovascular disease that could be adversely affected by $beta_2$-agonists. Based on available data for SYMBICORT or its active components, no adjustment of dosage of SYMBICORT in geriatric patients is warranted.

ADVERSE REACTIONS

Long-acting $beta_2$-adrenergic agonists may increase the risk of asthma-related death (See **Boxed WARNING, WARNINGS, AND PRECAUTIONS** sections).

The incidence of common adverse events in the table below is based upon three 12-week, double-blind, placebo-controlled US clinical studies in which 401 adult and adolescent patients (148 males and 253 females) age 12 years and older were treated twice daily with 2 inhalations of SYMBICORT 80/4.5 or SYMBICORT 160/4.5, budesonide HFA metered dose inhaler (MDI) 80 or 160 mcg, formoterol dry powder inhaler (DPI) 4.5 mcg, or placebos (MDI and DPI).

Table 4 - Adverse Events (regardless of causality) Occurring at an Incidence of ≥3% and more Commonly than Placebo in any SYMBICORT Group

Treatment*	**SYMBICORT**		**Budesonide HFA MDI**		**Formoterol DPI**	**Placebo MDI and DPI**
Adverse Event	**80/4.5 mcg N=277 (%)**	**160/4.5 mcg N=124 (%)**	**80 mcg N=121 (%)**	**160 mcg N=109 (%)**	**4.5 mcg N=237 (%)**	**N=400 (%)**
Nasopharyngitis	10.5	9.7	14.0	11.0	10.1	9.0
Headache	6.5	11.3	11.6	12.8	8.9	6.5
Upper respiratory tract infection	7.6	10.5	8.3	9.2	7.6	7.8
Pharyngo-laryngeal pain	6.1	8.9	5.0	7.3	3.0	4.8
Sinusitis	5.8	4.8	5.8	2.8	6.3	4.8
Influenza	3.2	2.4	6.6	0.9	3.0	1.3
Back pain	3.2	1.6	2.5	5.5	2.1	0.8
Nasal congestion	2.5	3.2	2.5	3.7	1.3	1.0
Stomach discomfort	1.1	6.5	2.5	4.6	1.3	1.8
Vomiting	1.4	3.2	0.8	2.8	1.7	1.0
Oral candidiasis	1.4	3.2	0	0	0	0.8
Average Duration of Exposure (days)	77.7	73.8	77.0	71.4	62.4	55.9

*All treatments were administered as two inhalations twice daily.

The table above includes all events (whether or not considered drug-related by the investigators) that

occurred at an incidence of ≥3% in any one SYMBICORT group and that were more common than in the placebo group with twice daily dosing. In considering these data, the increased average duration of exposure for SYMBICORT patients should be taken into account, as incidences are not adjusted for unequal treatment duration.

The following additional adverse events occurred in patients ≥12 years of age in the active and placebo-controlled clinical studies among 2344 patients treated with SYMBICORT twice daily with an incidence of ≥1% to <3% regardless of relationship to treatment, and are listed in decreasing order of incidence: asthma, nausea, dysphonia, pyrexia, sinus headache, diarrhea, pharyngitis, tremor, lower respiratory tract infection, muscle spasms, urinary tract infection, rhinitis, arthralgia, myalgia, dyspepsia, gastroenteritis viral, abdominal pain upper, dizziness, sinus congestion, rhinitis allergic, pain in extremity, palpitations, bronchitis acute, tension headache, migraine, post procedural pain. Additionally, the incidence of cough, bronchitis, and viral upper respiratory tract infection was ≥3% (but each <4%) in this population but did not meet criteria for inclusion in the above table, as these data are not derived from placebo-controlled trials for subjects ≥12 years old.

The following adverse events occurred in this same population (patients ≥12 years of age) with an incidence <1%, and are listed because they have previously been reported during treatment with any formulation of inhaled SYMBICORT, budesonide and/or formoterol, regardless of the indication: immediate and delayed hypersensitivity reactions, e.g., rash, pruritus, urticaria, angioedema; cardiac events, e.g., tachycardia, coronary ischemia, atrial and ventricular tachyarrhythmias; variations in blood pressure, e.g., hypotension, hypertension, hypertensive crisis; hypokalemia; hyperglycemia; taste disturbance; psychiatric symptoms, e.g., irritability, anxiety, restlessness, nervousness, agitation, depression; skin bruising.

Long-Term Safety: Long-term safety studies in adolescent and adult patients 12 years of age and older,

treated for up to one year at doses up to 1280/36 mcg/day (640/18 mcg twice daily), revealed neither clinically important changes in the incidence nor new types of adverse events emerging after longer periods of treatment. Similarly, no significant or unexpected patterns of abnormalities were observed for up to one year in safety measures including chemistry, hematology, ECG, Holter monitor, and HPA axis assessments.

Adverse Event Reports From Other Sources: Other relevant rare adverse events reported in the published literature, clinical trials or from worldwide marketing experience with any formulation of inhaled SYMBICORT, budesonide and/or formoterol, regardless of the indication include: immediate hypersensitivity reactions, such as anaphylactic reaction and bronchospasm; symptoms of hypocorticism and hypercorticism; glaucoma, cataracts, psychiatric symptoms, including aggressive reactions, behavioral disturbances, psychosis.

OVERDOSAGE

SYMBICORT: SYMBICORT contains both budesonide and formoterol; therefore, the risks associated with overdosage for the individual components described below apply to SYMBICORT. In pharmacokinetic studies, a total of 1920/54 mcg (12 actuations of SYMBICORT 160/4.5) was administered as a single dose to both healthy subjects and patients with asthma and was well tolerated. In a long-term active-controlled safety study, SYMBICORT 160/4.5 was well tolerated for up to 12 months at doses up to twice the highest recommended daily dose.

Clinical signs in dogs that received a single inhalation dose of SYMBICORT (a combination of budesonide and formoterol) in a dry powder included tremor, mucosal redness, nasal catarrh, redness of intact skin, abdominal respiration, vomiting, and salivation; in the rat, the only clinical sign observed was increased respiratory rate in the first hour after dosing. No deaths occurred in rats given a combination of budesonide and formoterol at acute inhalation dose of 97 and 3 mg/kg,

respectively (approximately 1200 and 1350 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). No deaths occurred in dogs given a combination of budesonide and formoterol at the acute inhalation dose of 732 and 22 mcg/kg, respectively (approximately 30 times the maximum recommended human daily inhalation dose of budesonide and formoterol on a mcg/m^2 basis).

Budesonide: The potential for acute toxic effects following overdose of budesonide is low. If used at excessive doses for prolonged periods, systemic corticosteroid effects such as hypercorticism may occur (see **PRECAUTIONS**). Budesonide at five times the highest recommended dose (3200 mcg daily) administered to humans for 6 weeks caused a significant reduction (27%) in the plasma cortisol response to a 6-hour infusion of ACTH compared with placebo (+1%). The corresponding effect of 10 mg prednisone daily was a 35% reduction in the plasma cortisol response to ACTH.

In mice the minimal inhalation lethal dose was 100 mg/kg (approximately 600 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). In rats there were no deaths following the administration of an inhalation dose of 68 mg/kg (approximately 900 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). The minimal oral lethal dose in mice was 200 mg/kg (approximately 1300 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis) and less than 100 mg/kg in rats (approximately 1300 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis).

Formoterol: An overdose of formoterol would likely lead to an exaggeration of effects that are typical for beta$_2$-agonists; therefore, the following adverse experiences may occur: angina, hypertension or hypotension, palpitations, tachycardia, arrhythmia, prolonged QTc-interval, headache, tremor, nervousness, muscle cramps, dry mouth, insomnia, fatigue, malaise, seizures, metabolic acidosis, hypokalemia, hyperglycemia, nausea and vomiting. As with all sympathomimetic medications, cardiac arrest and even death may be associated with abuse of formoterol. Formoterol was well tolerated at a delivered dose of 90 mcg/day over 3 hours in adult patients with acute bronchoconstriction and when given three times daily for a total dose of 54 mcg/day for 3 days to stable asthmatics.

Treatment of formoterol overdosage consists of discontinuation of the medication together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdosage of formoterol. Cardiac monitoring is recommended in cases of overdosage.

No deaths were seen in mice given formoterol at an inhalation dose of 276 mg/kg (more than 62,200 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). In rats the minimum lethal inhalation dose was 40 mg/kg (approximately 18,000 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). No deaths were seen in mice that received an oral dose of 2000 mg/kg (more than 450,000 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). Maximum non-lethal oral doses were 252 mg/kg in young rats and 1500 mg/kg in adult rats (approximately 114,000 times and 675,000 times the maximum recommended human inhalation dose on a mcg/m^2 basis).

DOSAGE AND ADMINISTRATION

SYMBICORT should be administered by the orally inhaled route in patients with asthma 12 years of age and older. SYMBICORT should not be used for transferring patients from systemic corticosteroid therapy.

Long-acting beta$_2$-adrenergic agonists may increase the risk of asthma-related death (see **WARNINGS**). Therefore, when treating patients with asthma, SYMBICORT should only be used for patients not adequately controlled on other asthma-controller medications (e.g., low-to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with two maintenance therapies. SYMBICORT is not indicated for patients whose asthma can be successfully managed by inhaled corticosteroids or other controller medications along with occasional use of inhaled short-acting beta$_2$-agonists.

SYMBICORT is available in 2 strengths, SYMBICORT 80/4.5 and SYMBICORT 160/4.5, containing 80 and 160 mcg of budesonide, respectively, and 4.5 mcg of formoterol fumarate dihydrate per inhalation. Each dose is administered as 2 inhalations twice daily (in the morning and the evening) by the orally inhaled route only. Rinsing the mouth after every dose is advised.

For patients who are currently receiving medium to high doses of inhaled corticosteroid therapy, and whose disease severity clearly warrants treatment with two maintenance therapies, the recommended starting dose is SYMBICORT 160/4.5, 2 inhalations twice daily.

For patients who are currently receiving low to medium doses of inhaled corticosteroid therapy, and whose disease severity clearly warrants treatment with two maintenance therapies, the recommended starting dose is SYMBICORT 80/4.5, 2 inhalations twice daily.

For patients who are not currently receiving inhaled corticosteroid therapy, but whose disease severity clearly warrants initiation of treatment with two maintenance therapies, the recommended starting dose is

SYMBICORT 80/4.5 or 160/4.5, 2 inhalations twice daily depending upon asthma severity.

If a previously effective dosage regimen of SYMBICORT fails to provide adequate control of asthma, the therapeutic regimen should be reevaluated and additional therapeutic options, e.g., replacing the current strength of SYMBICORT with a higher strength, adding additional inhaled corticosteroid, or initiating oral corticosteroids, should be considered.

The maximum daily recommended dose is 640/18 mcg budesonide/formoterol (given as two inhalations of SYMBICORT 160/4.5 twice daily) for patients 12 years of age and older. Do not use more than twice daily or use a higher number of inhalations (more than 2 inhalations twice daily) of the prescribed strength of SYMBICORT as this will result in a daily dose of formoterol in excess of the dose determined to be safe. For all patients, consideration should be given to titrating to the lowest effective strength after adequate asthma stability has been achieved.

SYMBICORT is not approved for the treatment or prevention of exercise-induced bronchospasm. Patients who are receiving SYMBICORT twice daily should not use formoterol or other long-acting $beta_2$-agonists for prevention of exercise-induced bronchospasm, or for any other reason. If symptoms arise in the period between doses, an inhaled, short-acting $beta_2$-agonist should be taken for immediate relief.

In clinical studies, significant improvement in FEV_1 occurred within 15 minutes of beginning treatment with SYMBICORT in most patients and improvement in asthma control (asthma symptoms, albuterol rescue use, PEF) occurred within one day. The maximum benefit may not be achieved for 2 weeks or longer after beginning treatment. Individual patients may experience a variable time to onset and degree of symptom relief.

For patients who do not respond adequately to the starting dose after 1-2 weeks of therapy with SYMBICORT 80/4.5, replacing the strength with

SYMBICORT 160/4.5 may provide additional asthma control.

SYMBICORT should be primed before using for the first time by releasing 2 test sprays into the air away from the face, shaking well for 5 seconds before each spray. In cases where the inhaler has not been used for more than 7 days or when it has been dropped, prime the inhaler again by shaking well before each spray and releasing 2 test sprays into the air away from the face.

Geriatric Use

In studies where geriatric patients (65 years of age or older, see **PRECAUTIONS, Geriatric Use**) have been treated with SYMBICORT, efficacy and safety did not differ from that in younger patients. Based on available data for SYMBICORT and its active components, no dosage adjustment is recommended.

HOW SUPPLIED

SYMBICORT is available in two strengths:

SYMBICORT 80/4.5 (NDC 0186-0372-20) and **SYMBICORT 160/4.5 (NDC 0186-0370-20)**. Each strength is supplied as a pressurized aluminum canister with a shield component, with a red plastic actuator body with white mouthpiece and attached gray dust cap. Each canister contains 120 inhalations and has a net fill weight of 10.2 grams. Each canister is packaged in a foil overwrap pouch with desiccant sachet and placed into a carton. Each carton contains one canister and a Medication Guide.

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

The correct amount of medication in each inhalation cannot be ensured after the labeled number of inhalations from the canister have been used, even though the inhaler may not feel completely empty and may continue to operate. The inhaler should be discarded when the labeled number of inhalations have been used or within 3 months after removal from the foil pouch. Never immerse the canister into water to determine the amount remaining in the canister ("float test").

Store at controlled room temperature 20°C to 25°C (68°F to 77°F) [see USP]. Store the inhaler with the mouthpiece down.

For best results, the canister should be at room temperature before use. Shake well for 5 seconds before using.

Keep out of the reach of children. Avoid spraying in eyes. Contents under pressure. Do not puncture or incinerate. Do not store near heat or open flame. Exposure to temperatures over 120ºF may cause bursting. Never throw container into fire or incinerator.

SYMBICORT® is a registered trademark of the AstraZeneca group of companies

Manufactured for: AstraZeneca LP, Wilmington, DE 19850
By: AstraZeneca Dunkerque Production, Dunkerque, France

Product of France
XXXXXX-00

Rev. 7/20/06

MEDICATION GUIDE

SYMBICORT 80/4.5

(budesonide 80 mcg and formoterol fumarate dihydrate 4.5 mcg) Inhalation Aerosol

SYMBICORT 160/4.5

(budesonide 160 mcg and formoterol fumarate dihydrate 4.5 mcg) Inhalation Aerosol

Read the Medication Guide that comes with SYMBICORT before you start using it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is the most important information I should know about SYMBICORT?

- SYMBICORT contains 2 medicines:
  - Budesonide (the same medicine found in PULMICORT TURBUHALER®) an inhaled corticosteroid medicine. Inhaled corticosteroids help to decrease inflammation in the lungs. Inflammation in the lungs can lead to asthma symptoms.
  - Formoterol (the same medicine found in FORADIL® AEROLIZER®), a long-acting $beta_2$-agonist medicine or LABA. LABA medicines are used in patients with asthma. LABA medicines help the muscles around the airways in your lungs stay relaxed to prevent asthma symptoms, such as wheezing and shortness of breath. These symptoms can happen when the muscles around the airways tighten. This makes it hard to breathe. In severe cases, wheezing can stop your breathing and may lead to death if not treated right away.

- **In patients with asthma, LABA medicines such as formoterol (one of the medicines in SYMBICORT) may increase the chance of death**

from asthma problems. In a large asthma study, more patients who used another LABA medicine, died from asthma problems compared with patients who did not use that LABA medicine. Talk with your healthcare provider about this risk and the benefits of treating your asthma with SYMBICORT.

- **SYMBICORT does not relieve sudden symptoms. Always have an inhaled short-acting beta$_2$-agonist medicine with you to treat sudden symptoms. If you do not have this type of medicine, contact your healthcare provider to have one prescribed for you.**

- **Do not stop using SYMBICORT unless told to do so by your healthcare provider because your symptoms might get worse.**

- **SYMBICORT should be used only if your healthcare provider decides that another asthma-controller medicine alone does not control your asthma or that you need 2 asthma-controller medicines.**

- **Call your healthcare provider if breathing problems worsen over time while using SYMBICORT. You may need different treatment.**

- **Get emergency medical care if:**
  - **Breathing problems worsen quickly, and**
  - **You use your short-acting beta$_2$-agonist medicine, but it does not relieve your breathing problems.**

What is SYMBICORT?

SYMBICORT combines an inhaled corticosteroid medicine, budesonide (the same medicine found in PULMICORT TURBUHALER), and a long-acting beta$_2$-agonist medicine (LABA), formoterol (the same medicine found in FORADIL AEROLIZER).

SYMBICORT is used long-term, twice a day, everyday to control symptoms of asthma, and prevent symptoms such as wheezing in patients 12 years of age and older.

SYMBICORT contains formoterol (the same medicine found in FORADIL AEROLIZER). Because LABA medicines such as formoterol may increase the chance of death from asthma problems, SYMBICORT is not for patients with asthma who:

- are well controlled with another asthma-controller medicine such as a low to medium dose of an inhaled corticosteroid medicine
- only need short-acting $beta_2$-agonist medicines once in awhile

What should I tell my healthcare provider before using SYMBICORT?

Tell your healthcare provider about all of your health conditions, including if you:

- **have heart problems**
- **have high blood pressure**
- **have seizures**
- **have thyroid problems**
- **have diabetes**
- **have liver problems**
- **have osteoporosis**
- **have an immune system problem**
- **are pregnant or planning to become pregnant.** It is not known if SYMBICORT may harm your unborn baby.
- **are breastfeeding.** It is not known if SYMBICORT passes into your milk and if it can harm your baby.
- **are allergic to SYMBICORT or any other medicines**
- **are exposed to chickenpox or measles**

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

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

How do I use SYMBICORT?

See the step-by-step instructions for using SYMBICORT at the end of this Medication Guide. Do not use SYMBICORT unless your healthcare provider has taught you and you understand everything. Ask your healthcare provider or pharmacist if you have any questions.

- Use SYMBICORT exactly as prescribed. **Do not use SYMBICORT more often than prescribed.** SYMBICORT comes in 2 strengths. Your healthcare provider has prescribed the strength that is best for you.

- SYMBICORT should be taken as 2 puffs in the morning and 2 puffs in the evening every day. If you miss a dose of SYMBICORT, you should take your next dose at the same time you normally do. Do not take SYMBICORT more often or use more puffs than you have been prescribed.

- Rinse your mouth with water after each dose (2 puffs) of SYMBICORT.

- **While you are using SYMBICORT twice a day, do not use other medicines that contain a long-acting beta$_2$-agonist (LABA) for any reason, such as SEREVENT DISKUS (salmeterol xinafoate inhalation powder), ADVAIR DISKUS or ADVAIR HFA (fluticasone propionate and salmeterol), or FORADIL AEROLIZER (formoterol fumarate inhalation powder).**

- Do not change or stop any of your medicines used to control or treat your breathing problems. Your healthcare provider will adjust your medicines as needed.

- Make sure you always have a short-acting beta$_2$-agonist medicine with you. Use your short-acting beta$_2$-agonist medicine if you have breathing problems between doses of SYMBICORT.

- **Call your healthcare provider or get medical care right away if:**
  - your breathing problems worsen with SYMBICORT
  - you need to use your short-acting beta$_2$-agonist medicine more often than usual
  - your short-acting beta$_2$-agonist medicine does not work as well for you at relieving symptoms
  - you need to use 4 or more inhalations of your short-acting beta$_2$-agonist medicine for 2 or more days in a row
  - you use 1 whole canister of your short-acting beta$_2$-agonist medicine in 8 weeks' time
  - your peak flow meter results decrease. Your healthcare provider will tell you the numbers that are right for you.
  - your asthma symptoms do not improve after using SYMBICORT regularly for 1 week.

What are the possible side effects with SYMBICORT?

SYMBICORT contains formoterol. In patients with asthma, LABA medicines such as formoterol may increase the chance of death from asthma problems. See "What is the most important information I should know about SYMBICORT?"

Other possible side effects with SYMBICORT include:

- **serious allergic reactions including rash, hives, swelling of the face, mouth, and tongue, and breathing problems.** Call your healthcare provider or get emergency medical care if you get any symptoms of a serious allergic reaction.

- **chest pain**

- **increased blood pressure**
- **a fast and irregular heartbeat**
- **headache**
- **tremor**
- **nervousness**
- **immune system effects and a higher chance for infections**
- **eye problems including glaucoma and cataracts.** Regular eye exams should be considered while using SYMBICORT.
- **lower bone mineral density.** This may be a problem for people who already have a higher chance for low bone mineral density (osteoporosis).
- **slowed growth in children.** A child's growth should be checked often.
- **throat irritation.**

Tell your healthcare provider about any side effect that bothers you or that does not go away.

These are not all the side effects with SYMBICORT. Ask your healthcare provider or pharmacist for more information.

How do I store SYMBICORT?

- Store SYMBICORT at room temperature 68°F to 77°F (20°C to 25°C). Store with the mouthpiece down.
- The contents of your SYMBICORT canister are under pressure. Do not puncture or throw the canister into a fire or incinerator. Do not use or store it near heat or open flame. Storage above 120ºF may cause the canister to burst.

- **Keep SYMBICORT and all medicines out of the reach of children.**

General Information about SYMBICORT

Medicines are sometimes prescribed for purposes not mentioned in a Medication Guide. Do not use SYMBICORT for a condition for which it was not prescribed. Do not give your SYMBICORT to other people, even if they have the same condition. It may harm them.

This Medication Guide summarizes the most important information about SYMBICORT. If you would like more information, talk with your healthcare provider or pharmacist. You can ask your healthcare provider or pharmacist for information about SYMBICORT that was written for healthcare professionals. You can also contact the company that makes SYMBICORT (toll free) at 1-800-236-9933 or visit our website at www.symbicort-us.com.

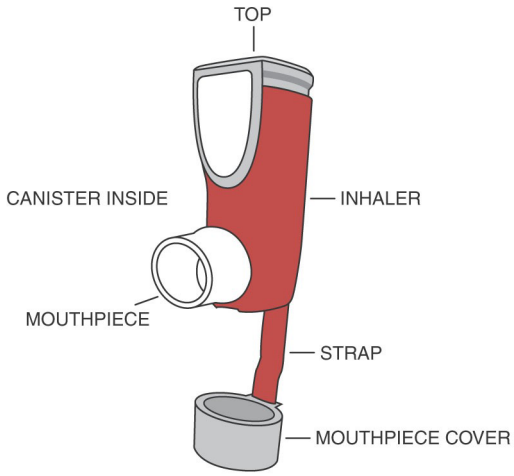


Figure 1

HOW TO USE SYMBICORT

Follow the instructions below for using SYMBICORT. You will breathe-in (inhale) the medicine. If you have any questions, ask your doctor or pharmacist.

PREPARING YOUR INHALER FOR USE

1. Take your SYMBICORT inhaler out of the moisture-protective foil pouch before you use it for the first time and throw the foil away. Write the date that you open the foil pouch on the dose tracker card that comes with your inhaler. You should discard the inhaler when the labeled number of inhalations have been used or within 3 months of opening the foil pouch.

2. Use the SYMBICORT canister only with the red SYMBICORT inhaler supplied with the product. Parts of the SYMBICORT inhaler should not be used with parts from any other inhalation drug product.

3. SHAKE THE INHALER WELL for 5 seconds right before each use. Remove the mouthpiece cover. Check the mouthpiece for foreign objects prior to use.

4. SYMBICORT should be primed before using it for the first time and also when the inhaler has not been used for more than 7 days. Prime the inhaler by shaking the inhaler well for 5 seconds and then releasing a test spray. Then shake the inhaler again and release a second test spray. Your inhaler is now primed and ready for use.

Do not spray the medicine in your eyes during priming or use.

WAYS TO HOLD THE INHALER FOR USE

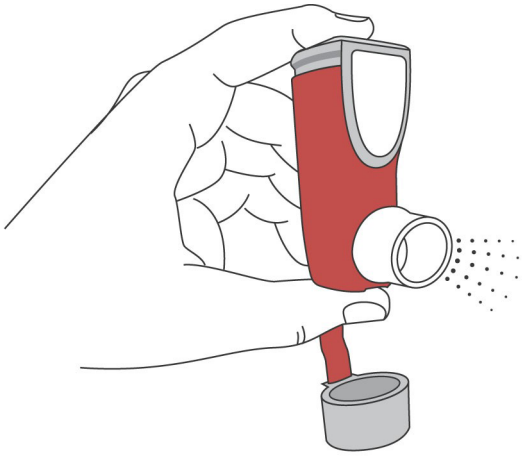


Figure 2

OR

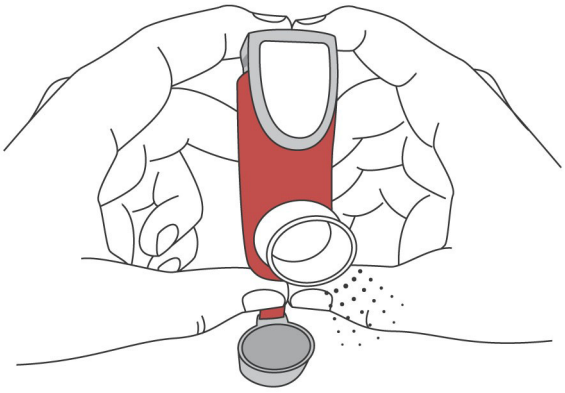


Figure 3

USING YOUR SYMBICORT INHALER

5. SHAKE THE INHALER WELL for 5 seconds. Remove the mouthpiece cover. Check the mouthpiece for foreign objects.

6. Breathe out fully (exhale). Raise the inhaler up to your mouth. Place the white mouthpiece fully into your mouth and close your lips around it. Make sure that the inhaler is upright and that the opening of the mouthpiece is pointing towards the back of your throat (see Figure 4).

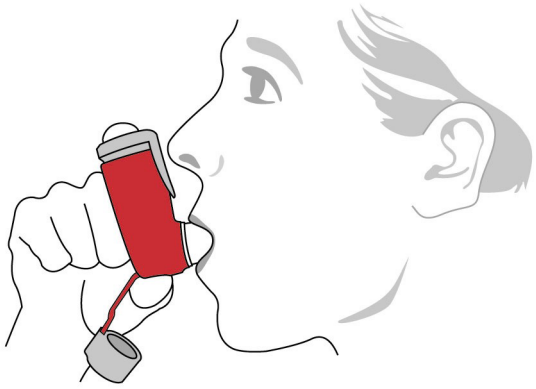


Figure 4

7. While breathing in deeply and slowly through your mouth, press down firmly and fully on the grey top of the inhaler to release the medicine (see Figures 2 and 3).

8. Continue to breathe in and hold your breath for about 10 seconds, or for as long as is comfortable. Before breathing out, release your finger from the grey top and remove the inhaler from your mouth while keeping the inhaler upright.

9. Shake the inhaler again for 5 seconds and repeat steps 6 through 8.

AFTER USING YOUR SYMBICORT INHALER

10. Replace the mouthpiece cover after use.

11. After you finish taking this medicine (2 puffs), rinse your mouth with water. Spit out the water. Do not swallow it.

12. Use the enclosed dose tracker card to track the number of puffs you have taken by marking off or punching through each of your morning and evening doses.

OTHER IMPORTANT INFORMATION ABOUT YOUR SYMBICORT INHALER

It is very important that you keep track of the number of inhalations (puffs) you have taken from your SYMBICORT inhaler. Discard SYMBICORT after you have used the number of inhalations on the product label and box. Your inhaler may not feel empty, but you will not get the right amount of medicine if you keep using it.

SYMBICORT should also be discarded within 3 months after it is taken out of its foil pouch.

- For best results, use and store at room temperature. Avoid exposing product to extreme heat and cold. Store with the mouthpiece down.

HOW TO CLEAN YOUR SYMBICORT INHALER

Clean the white mouthpiece of the inhaler every 7 days. To clean the mouthpiece:

- Remove the grey mouthpiece cover
- Wipe the inside and outside of the white mouthpiece opening with a clean, dry cloth
- Replace the mouthpiece cover
- **Do not put the inhaler into water**
- Do not try to take the inhaler apart

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Product of France

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This Medication Guide has been approved by the U.S. Food and Drug Administration.