CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
21-929

LABELING
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 beta₂-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 beta₂-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 beta₂-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_{8} and its molecular weight is 430.5. Its structural formula is:

![Structural formula of budesonide]

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 x 10^{5}.

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-methyl]ethyl]amino]ethyl]phenyl]formamide, (E)-2-butenedioate(2:1), dihydrate. The empirical formula of formoterol is C_{42}H_{56}N_{4}O_{14} and its molecular weight is 840.9. Its structural formula is:

![Structural formula of formoterol]
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 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 β2-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
evrasivation 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 SYMBCORT in geriatric patients have not been specifically studied.

Pediatric

Plasma concentrations of budesonide were measured following administration of 4 inhalations of SYMBCORT 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 SYMBCORT 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 SYMBCORT have not been conducted. Population PK analysis of the SYMBCORT 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-hydroxybudesonide 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 SYMPLICORT were compared to budesonide 320 mcg alone. Dose-ordered improvements in FEV\textsubscript{1} were demonstrated when compared with budesonide. ECGs and blood samples for glucose and potassium were obtained post dose. For SYMPLICORT, 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, SYMPLICORT 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 $\geq$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 SYMPLICORT compared with patients treated with formoterol dry inhalation powder 4.5 mcg, 2 inhalations twice daily. No patient had a QT or QTc value $\geq$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 SYMBCORT 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 SYMBCORT group compared to placebo.

Overall, no clinically important effects on HPA axis, as measured by 24-hour urinary cortisol, were observed for SYMBCORT-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 FEV₁ 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 SYMBCORT compared with inhaled budesonide administered at the same delivered dose via a dry powder inhaler (see CLINICAL PHARMACOLOGY, Pharmacokinetics, SYMBCORT). Therefore, the systemic effects (HPA axis and growth) of budesonide delivered from SYMBCORT 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\textsubscript{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 FEV₁ at baseline was 68.1% and was similar across treatment groups. The co-primary efficacy endpoints were 12-hour-average post-dose FEV₁ at week 2, and pre-dose FEV₁ 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 FEV₁ 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)

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Patients withdrawn due to predefined asthma event*</td>
<td>13 (10.5)</td>
<td>13 (11.3)</td>
<td>22 (20.2)</td>
<td>44 (35.8)</td>
<td>62 (49.6)</td>
</tr>
<tr>
<td>Patients with a predefined asthma event*†</td>
<td>37 (29.8)</td>
<td>24 (20.9)</td>
<td>48 (44.0)</td>
<td>68 (55.3)</td>
<td>84 (67.2)</td>
</tr>
<tr>
<td>Decrease in FEV₁</td>
<td>4 (3.2)</td>
<td>8 (7.0)</td>
<td>7 (6.4)</td>
<td>15 (12.2)</td>
<td>14 (11.2)</td>
</tr>
<tr>
<td>Rescue medication use</td>
<td>2 (1.6)</td>
<td>0</td>
<td>3 (2.8)</td>
<td>3 (2.4)</td>
<td>7 (5.6)</td>
</tr>
<tr>
<td>Decrease in AM PEF</td>
<td>2 (1.6)</td>
<td>5 (4.3)</td>
<td>5 (4.6)</td>
<td>17 (13.8)</td>
<td>15 (12.0)</td>
</tr>
<tr>
<td>Nighttime awakening‡</td>
<td>24 (19.4)</td>
<td>11 (9.6)</td>
<td>29 (26.6)</td>
<td>32 (26.0)</td>
<td>49 (39.2)</td>
</tr>
<tr>
<td>Clinical exacerbation</td>
<td>7 (5.6)</td>
<td>6 (5.2)</td>
<td>5 (4.6)</td>
<td>17 (13.8)</td>
<td>16 (12.8)</td>
</tr>
</tbody>
</table>

*These criteria were assessed on a daily basis irrespective of the timing of the clinic visit, with the exception of FEV₁ 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 FEV₁ 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 FEV₁ results at the last available study visit (end of treatment, EOT) are also provided. Patients receiving SYMBCORT 160/4.5 mcg
had significantly greater mean improvements from baseline in predose FEV₁ 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 FEV₁ Over 12 Weeks (Study 1)

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)

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

*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 FEV₁ 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)

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

*These criteria were assessed on a daily basis irrespective of the timing of the clinic visit, with the exception of FEV<sub>1</sub> 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<sub>1</sub> over 12 weeks is displayed in Figure 2.
Figure 2 - Mean percent change from baseline in predose FEV₁ 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 FEV₁) was seen within 15 minutes. Maximum improvement in FEV₁ 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 FEV₁ 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, FEV₁ 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 FEV₁ following 12 weeks of therapy or at the last available visit.

FEV₁ data from Study 1 evaluating SYMBICORT 160/4.5 mcg is displayed in Figures 3 and 4.
Figure 3 - Mean Percent Change From Baseline in FEV₁ on Day of Randomization (Study 1)

- 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

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Figure 4 - Mean Percent Change From Baseline in FEV₁ 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 beta₂-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 beta₂-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 beta₂-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 beta₂-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 beta₂-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 beta₂-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 Beta₂-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 beta₂-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 Beta₂-Agonist in Conjunction With SYMBOICORT. Patients who are receiving SYMBOICORT twice daily should not use additional formoterol or other long-acting inhaled beta₂-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 SYMBOICORT already contains an inhaled, long-acting beta₂-agonist.

Do Not Exceed Recommended Dosage. SYMBOICORT 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 SYMBOICORT 160/4.5, patients treated with twice the highest recommended dose of SYMBOICORT demonstrated a similar safety profile to that of patients treated with the highest recommended dose.

Paradoxical Bronchospasm. As with other inhaled asthma medications SYMBOICORT, may produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with SYMBOICORT, treatment with SYMBOICORT 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 SYMBOICORT.
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 beta₂-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 SYMBCORT. 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 SYMBCORT.

Because of the possibility of systemic absorption of
inhaled corticosteroids, patients treated with
SYMBCORT 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
SYMBCORT should be reduced slowly, consistent with
accepted procedures for management of asthma
symptoms and for tapering of systemic steroids.

Budesonide, a component of SYMBCORT, may cause
a reduction in growth velocity when administered to
pediatric patients. Patients should be maintained on the
lowest dose of SYMBCORT 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
SYMBCORT 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 SYMBCORT.
Lower respiratory tract infections, including pneumonia, have been reported following the inhaled administration of corticosteroids, including budesonide, a component of SYMBCORT. 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 SYMBCORT compared to placebo.

In clinical studies with SYMBCORT, 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 SYMBCORT therapy, but at times the dose of SYMBCORT 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 SYMBCORT 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 SYMBCORT inhaler device appropriately and how SYMBCORT 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 SYMBCORT, other
inhaled drugs and asthma medications should be
used only as directed by a physician.

6. Patients who are receiving SYMBCORT should not
use formoterol or another long-acting inhaled beta₂-
agonist for prevention of exercise-induced
bronchospasm or maintenance treatment of asthma.

7. Patients should not stop therapy with SYMBCORT
without physician/provider guidance since
symptoms may recur after discontinuation.

8. Patients should be cautioned regarding common
adverse effects associated with beta₂-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 SYMBCORT, 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
SYMBCORT.

12. Results of clinical trials indicate that in most
patients, clinically significant improvement occurred
within 15 minutes of beginning treatment with
SYMBCORT. 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
SYMBCORT 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 SYMBCORT:

- Patients should not attempt to take the inhaler
  apart.

- SYMBCORT 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 SYMBCORT 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 SYMBCORT and other drugs, such as short-acting beta₂-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 SYMBCORT.

Short-Acting Beta₂-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 SYMBCORT twice daily was approximately 0.8 inhalations/day, and ranged from 0 to 14 inhalations/day. Approximately 2% (N= 8) of the SYMBCORT 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 SYMBCORT has not been completely evaluated. In clinical trials with SYMBCORT, 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 SYMPLICORT 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 SYMPLICORT. There were no important differences noted in the adverse event profiles between these groups.

Monoamine Oxidase Inhibitors and Tricyclic Antidepressants: SYMPLICORT 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 SYMPLICORT, on the vascular system may be potentiated by these agents. In clinical trials with SYMPLICORT, 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 SYMPLICORT, 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) (i.e., beta2-agonists, leukotriene receptor antagonists, cromones). The percentage of patients developing a seroprotective antibody titer of ≥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.

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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/m² 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/m² 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/m² 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/m² 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/m² 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
1367 inhalation dose on a mcg/m² basis). However, it caused
1368 a decrease in prenatal viability and viability in the pups
1369 at birth and during lactation, along with a decrease in
1370 maternal body-weight gain, at subcutaneous doses of 20
1371 mcg/kg and above (less than the maximum
1372 recommended human daily inhalation dose on a mcg/m²
1373 basis). No such effects were noted at 5 mcg/kg (less
1374 than the maximum recommended human daily
1375 inhalation dose on a mcg/m² basis).

1376 Formoterol
1377 Long-term studies were conducted in mice using oral
1378 administration and rats using inhalation administration
1379 to evaluate the carcinogenic potential of formoterol
1380 fumarate.

1382 In a 24-month carcinogenicity study in CD-1 mice,
1383 formoterol at oral doses of 0.1 mg/kg and above
1384 (approximately 20 times the maximum recommended
1385 human daily inhalation dose on a mcg/m² basis) caused
1386 a dose-related increase in the incidence of uterine
1387 leiomyomas.

1390 In a 24-month carcinogenicity study in Sprague-Dawley
1391 rats, an increased incidence of mesovarian leiomyoma
1392 and uterine leiomyosarcoma were observed at the
1393 inhaled dose of 130 mcg/kg (approximately 60 times the
1394 maximum recommended human daily inhalation dose on
1395 a mcg/m² basis). No tumors were seen at 22 mcg/kg
1396 (approximately 10 times the maximum recommended
1397 human daily inhalation dose on a mcg/m² basis).

1399 Other beta-agonist drugs, have similarly demonstrated
1400 increases in leiomyomas of the genital tract in female
1401 rodents. The relevance of these findings to human use is
1402 unknown.

1404 Formoterol was not mutagenic or clastogenic in Ames
1405 Salmonella/microsome plate test, mouse lymphoma test,
1406 chromosome aberration test in human lymphocytes, and
1407 rat micronucleus test.

1409 A reduction in fertility and/or reproductive performance
1410 was identified in male rats treated with formoterol at an
1411 oral dose of 15 mg/kg (approximately 7000 times the
maximum recommended human daily inhalation dose on a mcg/m² 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/m² 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/m² 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/m² 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/m² 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/m² 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/m² 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/m² basis) and 500 mcg/kg/day in rats (approximately 6 times the maximum recommended human daily inhalation dose on a mcg/m² 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/m² 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/m² 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/m² 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/m² 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/m² 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/m² 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/m² 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/m² 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/m² 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 beta2-agonists, special caution should be observed when using SYMBICORT in geriatric patients who have concomitant cardiovascular disease that could be adversely affected by beta2-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 beta2-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**

<table>
<thead>
<tr>
<th>Treatment*</th>
<th>SYMBICORT</th>
<th>Budesonide HFA MDI</th>
<th>Formoterol DPI</th>
<th>Placebo MDI and DPI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse Event</strong></td>
<td><strong>80/4.5 mcg N=277 (%)</strong></td>
<td><strong>160/4.5 mcg N=124 (%)</strong></td>
<td><strong>80 mcg N=121 (%)</strong></td>
<td><strong>160 mcg N=109 (%)</strong></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>10.5</td>
<td>9.7</td>
<td>14.0</td>
<td>11.0</td>
</tr>
<tr>
<td>Headache</td>
<td>6.5</td>
<td>11.3</td>
<td>11.6</td>
<td>12.8</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>7.6</td>
<td>10.5</td>
<td>8.3</td>
<td>9.2</td>
</tr>
<tr>
<td>Pharyngolaryngeal pain</td>
<td>6.1</td>
<td>8.9</td>
<td>5.0</td>
<td>7.3</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>5.8</td>
<td>4.8</td>
<td>5.8</td>
<td>2.8</td>
</tr>
<tr>
<td>Influenza</td>
<td>3.2</td>
<td>2.4</td>
<td>6.6</td>
<td>0.9</td>
</tr>
<tr>
<td>Back pain</td>
<td>3.2</td>
<td>1.6</td>
<td>2.5</td>
<td>5.5</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>2.5</td>
<td>3.2</td>
<td>2.5</td>
<td>3.7</td>
</tr>
<tr>
<td>Stomach discomfort</td>
<td>1.1</td>
<td>6.5</td>
<td>2.5</td>
<td>4.6</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1.4</td>
<td>3.2</td>
<td>0.8</td>
<td>2.8</td>
</tr>
<tr>
<td>Oral candidiasis</td>
<td>1.4</td>
<td>3.2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Average Duration of Exposure (days)</strong></td>
<td><strong>77.7</strong></td>
<td><strong>73.8</strong></td>
<td><strong>77.0</strong></td>
<td><strong>71.4</strong></td>
</tr>
</tbody>
</table>

*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 SYMBCORT 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 SYMBCORT 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 SYMBCORT 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 SYMBCORT, 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 overdose 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/m² 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/m² 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/m²
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/m² 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/m² basis) and less
than 100 mg/kg in rats (approximately 1300 times the
maximum recommended human daily inhalation dose on
a mcg/m² basis).
Formoterol: An overdose of formoterol would likely lead to an exaggeration of effects that are typical for beta2-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 beta₂-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 beta₂-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
SYMPLICORT 80/4.5 or 160/4.5, 2 inhalations twice daily depending upon asthma severity.

If a previously effective dosage regimen of SYMPLICORT fails to provide adequate control of asthma, the therapeutic regimen should be reevaluated and additional therapeutic options, e.g., replacing the current strength of SYMPLICORT 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 SYMPLICORT 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 SYMPLICORT 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.

SYMPLICORT is not approved for the treatment or prevention of exercise-induced bronchospasm. Patients who are receiving SYMPLICORT twice daily should not use formoterol or other long-acting beta2-agonists for prevention of exercise-induced bronchospasm, or for any other reason. If symptoms arise in the period between doses, an inhaled, short-acting beta2-agonist should be taken for immediate relief.

In clinical studies, significant improvement in FEV1 occurred within 15 minutes of beginning treatment with SYMPLICORT 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 SYMPLICORT 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.

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1977  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”).

1987

1988  Store at controlled room temperature 20°C to 25°C
(68°F to 77°F) [see USP]. Store the inhaler with the
mouthpiece down.

1992  For best results, the canister should be at room
temperature before use. Shake well for 5 seconds before
using.

1996  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.

1999  Exposure to temperatures over 120°F may cause
bursting. Never throw container into fire or incinerator.

2001

2002  SYMBICORT® is a registered trademark of the
2003  AstraZeneca group of companies
2004  ©AstraZeneca 2006. All rights reserved.

2006  Manufactured for: AstraZeneca LP, Wilmington, DE
2007  19850
2008  By: AstraZeneca Dunkerque Production, Dunkerque,

2009  France
2010
2011  Product of France
2012  XXXXXX-00
2013
2014  Rev. 7/20/06
2015

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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:
  o 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.
  o Formoterol (the same medicine found in FORADIL® AEROLIZER®), a long-acting beta2-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 beta₂-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 beta₂-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 beta₂-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 beta₂-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 beta2-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 beta₂-agonist medicine with you. Use your short-acting beta₂-agonist medicine if you have breathing problems between doses of SYMBICORT.

• **Call your healthcare provider or get medical care right away if:**
  o your breathing problems worsen with SYMBICORT
  o you need to use your short-acting beta₂-agonist medicine more often than usual
  o your short-acting beta₂-agonist medicine does not work as well for you at relieving symptoms
  o you need to use 4 or more inhalations of your short-acting beta₂-agonist medicine for 2 or more days in a row
  o you use 1 whole canister of your short-acting beta₂-agonist medicine in 8 weeks’ time
  o your peak flow meter results decrease. Your healthcare provider will tell you the numbers that are right for you.
  o 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 120°F 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.
286 **Figure 1**

287

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

292 **PREPARING YOUR INHALER FOR USE**

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

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

309 3. SHAKE THE INHALER WELL for 5 seconds
310 right before each use. Remove the mouthpiece
311 cover. Check the mouthpiece for foreign objects
312 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

Figure 3
USING YOUR SYMBOCORT 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 SYMICORT 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 SYMIBICORT INHALER**

It is very important that you keep track of the number of inhalations (puffs) you have taken from your SYMIBICORT inhaler. Discard SYMIBICORT 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.

SYMIBICORT 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 SYMIBICORT 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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This Medication Guide has been approved by the U.S. Food and Drug Administration.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Badrul Chowdhury
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