



U.S. Food and Drug Administration

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7. Reference list For Division Memorandum

DIVISION MEMORANDUM

Date: Feb 12, 2010

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To: Members, Pulmonary-Allergy Drugs Advisory Committee (PADAC) Drug Safety and Risk Management Advisory Committee (DSARM,) and Pediatric Advisory Committee (PAC)

Subject: Design of safety studies for long-acting beta₂-agonists (LABAs) used for the treatment of asthma

1. Introduction

Thank you for your participation in the upcoming Advisory Committee meeting to be held on March 10 and 11, 2010. As members of FDA Advisory Committees (AC), we consider your expert scientific advice and recommendations to the FDA very important to our regulatory decision making processes. The objective of the upcoming meeting is to discuss clinical trial designs for studies in the adult/adolescent (12 years of age and older), and pediatric (4 to 11 years of age) asthma population to evaluate serious asthma outcomes (such as asthma-related deaths, hospitalizations, or intubations) with long-acting beta₂ agonists used for the treatment of asthma. The products under consideration for the safety studies are Advair Diskus®, Advair® HFA Inhalation Aerosol, Symbicort® Inhalation Aerosol, Serevent® Diskus®, and Foradil® Aerolizer®. All of these products are approved and marketed in the U.S. for the maintenance treatment of asthma. Two other long-acting beta₂ agonist products, Brovana Inhalation Solution, and Perforomist Inhalation Solution, are also approved and marketed in the U.S. but they are only approved for use in patients with chronic obstructive pulmonary disease (COPD) and, therefore, are not under consideration for these safety studies in the asthmatic population.

The background materials for the meeting include: (i) the documents prepared by the Agency for this upcoming meeting (this Division memorandum, a Statistical Briefing document, and a briefing document from the Office of Surveillance and Epidemiology [OSE]), (ii) the documents prepared by the Agency for the December 2008 AC meeting (the Division memorandum, the statistical briefing document and the OSE briefing document), (iii) the summary minutes of the 2008 AC meeting, (v) product labels for all the relevant products (vi) copies of some references and (vii) a reference list of all the references cited in this document.

This memorandum will focus on providing information relevant to the design and conduct considerations for safety studies for long-acting beta₂ agonists and includes: (i) an overview of asthma prevalence, morbidity (specifically related to hospitalizations for asthma exacerbations and intubations) and mortality, since this information is pertinent to the considerations regarding critical elements for the study design such as the safety endpoint selection, sample size, and level of risk to exclude; (ii) a discussion of general issues related to the proposed safety studies, (iii) the synopsis of a proposed safety study for adults and adolescents, (iv) the synopsis of a proposed safety study for the pediatric population, and (v), the issues and questions for discussion at this meeting.

The regulatory history regarding the safety of long-acting beta₂-agonists for the treatment of asthma will be described very briefly. The reader is referred to the Division Director memorandum prepared for the December 2008 AC meeting that provides more extensive background and regulatory information regarding the safety issues surrounding long-acting beta₂-agonists for the treatment of asthma.

2. Background

Salmeterol (as Serevent® Inhalation Aerosol) was the first long-acting beta₂-agonist (LABA) approved in the U.S. Following the approval of salmeterol in 1994, GSK initiated a large safety study, the Salmeterol Multicenter Asthma Research Trial (SMART) in 1996. The SMART study was conducted at the Agency's request and was prompted by reports of serious asthma exacerbations and deaths in patients treated with salmeterol soon after its approval, and, by findings of the Salmeterol Nationwide Surveillance (SNS) study that had been conducted in the United Kingdom in the mid 1990s. The SNS study compared salmeterol twice daily with salbutamol (albuterol in the U.S.) administered four times daily in patients who were considered to need regular beta₂-agonist therapy. The SNS study showed a non-significant but 3-fold increase in death in patients taking scheduled salbutamol [1].

The SMART study is published in the literature along with a number of commentaries [2-5]. The study enrolled asthmatic patients 12 years and older not currently using a LABA and randomized them to salmeterol (Serevent® Inhalation Aerosol) or placebo twice daily added to usual asthma therapy. There was only one baseline study visit, and inhaled corticosteroid as baseline asthma therapy was not mandated. The proposed treatment duration was 28 weeks with a revised target sample size of 60,000 patients. The SMART study was prematurely halted in 2003 after a planned interim analysis suggested that salmeterol may be associated with an increased risk of severe asthma exacerbations including asthma-related death (relative risk 4.37 [CI 1.25, 15.34]) [2]. This finding led to labeling changes (initial changes in 2003 with subsequent updates) including a boxed warning for all LABA products with the inhaled corticosteroid (ICS) and LABA fixed dose combination products labeled with the same warning as the single ingredient products.

Since the approval of salmeterol, the safety of LABAs in asthma patients has been discussed at 3 advisory committee meetings (July 2005, November 2007, and December 2008). The goal of the December 2008 meeting was to revisit the safety of the LABAs and to assess the risk-benefit of this class of drugs for the treatment of asthma in the adult and pediatric populations. The December 2008 advisory committee meeting was prompted by a recommendation from the advisory committee meeting in November 2007. That meeting was a Pediatric Advisory Committee (PAC) that was held in keeping with the Best

Pharmaceuticals for Children Act (BPCA) that required advisory committee discussion of adverse events reports after one year of granting marketing exclusivity for pediatric studies. At the 2007 PAC meeting, the committee agreed with the Agency's recommendation to revisit the safety of salmeterol. The focus of the December 2008 meeting expanded to include safety and risk-benefit assessment of LABAs for the entire asthma population (adults and pediatrics). At the December meeting, the committee stressed the need for more safety data, especially in the pediatric population where the data were very limited [6]. To this end, the Agency is proposing that additional safety studies be conducted in adults and children with the LABA products that are approved for the treatment of asthma to further evaluate the safety concerns of this drug class in the asthmatic population.

Of the LABA products under consideration for the safety studies, three are ICS/LABA fixed dose combination products: Advair Diskus®, Advair® HFA Inhalation Aerosol, and Symbicort® Inhalation Aerosol, and two of the products, Serevent® Diskus® and Foradil® Aerolizer®, are single-ingredient LABAs. Advair® Diskus and Advair® HFA Inhalation Aerosol contain fluticasone propionate (the ICS) and salmeterol xinafoate (the LABA), and Symbicort Inhalation Aerosol contains budesonide (the ICS) and formoterol fumarate (the LABA). Formulation and dosage strengths, manufacturer, approved age ranges, and dosing recommendations for these products are summarized in Table 1.

Table 1. Products under consideration for the LABA Safety Studies

Product/Dosage Strength	Manufacturer	Approved Age Range	Dosing Recommendations
<ul style="list-style-type: none"> • Advair Diskus 100/50 (fluticasone propionate 100 mcg and salmeterol 50 mcg inhalation powder) • Advair Diskus 250/50 (fluticasone propionate 250 mcg and salmeterol 50 mcg inhalation powder) • Advair Diskus 500/50 (fluticasone propionate 500 mcg and salmeterol 50 mcg inhalation powder) 	GlaskoSmithKline (GSK)	4 years of age and older (Note: The Advair Diskus 100/50 product is the only strength approved in children 4 -11 years of age)	One inhalation twice daily
<ul style="list-style-type: none"> • Advair ® HFA 45/21 (fluticasone propionate 45 mcg and salmeterol 21 mcg) Inhalation Aerosol • Advair ® HFA 115/21 (fluticasone propionate 115 mcg and salmeterol 21 mcg) Inhalation Aerosol • Advair® HFA 230/21 (fluticasone 230 mcg and salmeterol 21 mcg) Inhalation Aerosol 	GSK	12 years of age and older	Two inhalations twice daily
<ul style="list-style-type: none"> • 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 dehydrate 4.5 mcg) Inhalation Aerosol 	AstraZeneca	12 years of age and older	Two inhalations twice daily
<ul style="list-style-type: none"> • Serevent Diskus (salmeterol xinafoate inhalation powder)/50 mcg 	GSK	4 years of age and older	One inhalation twice daily
<ul style="list-style-type: none"> • Foradil Aerolizer (formoterol fumarate inhalation powder) 12 mcg 	Novartis	5 years of age and older	One inhalation twice daily

3. Asthma Prevalence

Asthma is a serious chronic lung disease caused by continual airway inflammation with episodes of increased inflammation and narrowing of small airways manifested clinically with symptoms such as shortness of breath, cough, wheezing, and chest tightness which can vary from mild to life threatening. Worldwide, asthma is recognized as the most common chronic disease of childhood, and the World Health Organization estimates that 300 million people worldwide suffer from asthma [7]. The global prevalence of asthma ranges from 1% - 18% of the population in different countries. The burden of asthma is continuing to rise worldwide as evidenced by the increases in asthma symptom prevalence in Africa, Latin America, and parts of Asia, but overall prevalence differences between countries are decreasing [8].

In the United States, asthma remains a leading cause of chronic childhood illness. Data from the Center for Disease Control and Prevention's National Center for Health Statistics, National Health Interview Survey 1999-2007 indicate that approximately 22.9 million Americans (including 6.7 million children) had asthma in 2007. This corresponds to a rate of 77.1 per 1,000 population. The overall prevalence rate in persons under 18 years of age was significantly greater (90.9 per 1,000 population) than in persons over 18 years of age (72.5 per 1,000 population). The highest prevalence rate for asthma was in children 5 -17 years of age irrespective of race (99.9 per 1000 population) [9].

There continues to be racial disparity in the prevalence of asthma in the United States. In 2007, the asthma prevalence rate was 39% higher in blacks than whites (103.2 per 1,000 persons versus 74.5 per 1,000 persons, respectively). The 2007 data also showed that current asthma prevalence rates in Hispanics were significantly lower than non-Hispanic blacks and non-Hispanic whites in 2007. Within the Hispanic subgroups, studies have suggested that Puerto Ricans may have higher rates of asthma than other Hispanic subgroups and non-Hispanic whites [9].

4. Asthma-related Mortality

Deaths due to asthma are rare events, and two different patterns of fatal asthma have been described. The majority (80 – 85%) of deaths from asthma occur in patients with severe and poorly controlled disease, who gradually deteriorate over days or weeks, a pattern that is generally considered preventable. However, in a small proportion of patients, death from asthma is sudden and unexpected without obvious prior gradual deterioration of asthma control [10]. The National Asthma Education and Prevention Program (NAEPP) Expert panel report lists several risk factors for death from asthma, one of which is 2 or more hospitalizations for asthma in the past year [11]. While the literature suggests that a history of recent hospitalizations may be more common in fatal asthma, the majority of patients who are hospitalized for asthma will not die from asthma. In an article published by Krishnan et al. on the outcomes of patients hospitalized for asthma, they reported that only 33% of all the asthma deaths reported by the CDC in 2000 occurred in patients hospitalized for asthma exacerbation [12]. This finding suggests that the majority of asthma deaths occur before reaching the hospital.

Annually, an estimated 250,000 people die from asthma worldwide, and mortality rates do not appear to correlate well with prevalence [8]. In the United States, mortality due to

asthma has shown a declining trend since 1999. This decrease in asthma death is probably an indicator of how well the disease is diagnosed and controlled. A total of 3,884 asthma deaths (age-adjusted death rate 1.3 per 100,000) were reported for 2005. The age-adjusted death rate was three times higher among the black population than among the white population, and black women had the highest age-adjusted mortality rate (3.3 per 100,000) due to asthma. Asthma deaths are rare among children. A total of 138 children under 15 years of age (0.2 per 100,000) died from asthma in 2005 [9].

5. Asthma-related Hospitalizations

Most asthma exacerbations are managed in the outpatient setting, but more severe exacerbations may require hospitalizations. In the United States, hospitalizations due to asthma have decreased since 1999, and between 2003 and 2006, there was a 25% decrease in the hospitalization discharge rate for asthma in the United States [9]. This steady decline in hospitalizations for asthma is probably a reflection of improved diagnosis and management.

In the United States, 444,000 hospital discharges (14.9 per 10,000 population) in 2006 were attributed to asthma and the hospitalization rate for blacks was 240% higher than for whites [13]. The race disparity in asthma was evaluated by Gupta et.al. using data from the National Hospital Discharge Survey and the US vital statistics system. They reported that the black/white (B/W) rate ratio for asthma hospitalizations increased from 2.8 to 4 from 1980 through 2002, and the B/W rate difference increased from 16.3 to 18.5 discharges/10,000 population. Most of the increase between black and white rates was seen in children 5 to 18 years of age [14].

Data from the Center for Disease Control's National Center for Health Statistics indicate that hospitalization rates are higher in children than adults. The data show that for 2004, there were 497,000 hospitalizations for asthma (17 per 10,000 population), and of this number, 198,000 (27 per 10,000) hospitalizations were among children 0 to 17 years of age. Among children, the age group with the highest (60 per 10,000) hospitalizations was the 0 to 4 year old group [15].

6. Asthma-related Intubations/mechanical ventilation

Intubation and mechanical ventilation is an uncommon event in patients hospitalized for asthma. Krishnan et. al. reported that intubation/mechanical ventilation occurred in 4% of all asthma admissions and intubation/mechanical ventilation was associated with a significantly higher risk of death. Intubation rates varied depending on geographic location, type of hospital (teaching versus non-teaching) and urban versus rural hospitals. Intubation and mechanical ventilation was higher in the Western regions of the United States, and in teaching and urban hospitals [12].

7. Considerations for the Proposed Safety Studies

A. Objective

The primary objective of the proposed safety studies is to determine the safety of LABAs added to inhaled corticosteroids (ICS) compared to ICS alone for the treatment of asthma. Whether corticosteroid therapy ameliorates the risk of LABAs has been discussed in the literature [16]. The design of the SMART study is not adequate to address this issue since

patients enrolled in SMART were not required to be on mandatory ICS therapy, and data on the type and dose of ICS use at baseline were limited. Asthma is an inflammatory disease, and the mainstay of asthma control is to treat the underlying inflammation. Inhaled corticosteroids (ICS) are recognized as the controller medication of choice for patients with persistent asthma. The NAEPP and GINA guidelines recommend LABA use in combination with ICS in persistent asthma, but proscribe the use of LABAs as monotherapy for long-term asthma control. Uncertainty remains regarding the extent to which serious asthma outcomes may be worsened by the addition of LABAs to ICS. Therefore, assessment of whether the addition of LABAs confers greater risk of serious asthma outcomes compared to ICS alone is relevant to a better understanding of the risk-benefit of LABAs for the treatment of asthma.

Although safety is the primary objective of the studies, efficacy as a secondary objective is also under consideration. The idea of conducting a large safety study with no efficacy outcomes might be less attractive to patients and other interested parties. The inclusion of efficacy in the study, however, raises questions about what efficacy measures would be most appropriate for this type of study and increases complexity in terms of additional assessments and analyses that would need to be performed. The LABA products were approved on the basis of improvement in lung function (FEV_1), an acceptable endpoint given that the mechanism of action of these agents is bronchodilation. Lung function measures do not seem appropriate for the proposed safety studies because of the practicality of doing spirometry in a large multi-center study, and the fact that efficacy using FEV_1 has already been firmly established. Outcome measures using validated Patient Reported Outcome instruments to evaluate asthma-related quality of life, and endpoints to capture events that may be impacted by asthma control (e.g. missed school or work days, or additional corticosteroid use) may be a consideration for efficacy assessment. However, the logistical challenges of including efficacy assessments in a large safety study must be taken into account. A potential way to address these issues could be to conduct efficacy assessments in a subset of patients.

B. hypothesis/risk assumptions

The proposed hypothesis to be tested is that the addition of LABAs to ICS in patients with moderate to severe asthma does not increase the risk of serious asthma outcomes. With this hypothesis, a non-inferiority (NI) trial would be the appropriate study design. Scientifically, since the risk of a serious asthma-related outcome would not be expected to increase in a subject receiving treatment for asthma, the NI margin (i.e. the risk increase) should be relatively small to be of clinical significance. The NI margin selected would affect the sample size, and this factor cannot be overlooked. Selecting too small a margin may result in an unrealistically large sample size; however, a margin that is too large would lack clinical significance. The Agency's Division of Biostatistics has provided a range of sample sizes for NI margins of 0.2, 0.3 and 0.5 for consideration (*Dr. Ben Neustifter – Statistics Briefing Document*). The initial proposed minimal level of risk considered acceptable to rule out is 20%; however, ruling out a 25% or 30% increase in risk may also be reasonable.

C. Population

Age range

The studies will need to address the study hypothesis in all age groups. We are considering a separate study for adults/adolescents 12 years of age and older and pediatric patients 4 to 11 years of age. However, alternative strategies, such as one study with stratification that appropriately represents all age groups could be an option. For adult asthma development programs, the Agency has allowed inclusion of pediatric patients 12 to 17 years of age in the adult studies. At the December 2008 AC meeting, the committee was asked to discuss the safety and risk-benefit of LABAs for the pediatric population broken down by the age group of adolescents (12 to 17 years) and children (4 to 11 years). The adult drug development programs for the combination products Advair Diskus and Symbicort included adolescents 12 to 17 years of age, and SMART was conducted in patients 12 years of age and older. It therefore seems reasonable for the safety studies in adults to include adolescents 12 to 17 years of age, rather than having separate studies in subjects 12 -17 years of age. However, to obtain meaningful information in this age group, the studies would need to include a representative sample of 12 to 17 year old patients to allow for an adequate assessment of safety.

The drug products under evaluation are also approved for use in chronic obstructive pulmonary disease (COPD). Discrepancies in the diagnosis of asthma are known to exist with adults because of misclassification of asthma with chronic obstructive pulmonary disease in older adults [17]. To address this concern, the inclusion of an upper age limit in the adult/adolescent studies could be one of the study criterion. Alternatively, the age limit could be a functional exclusion achieved by virtue of study inclusion and exclusion criteria that would allow for elimination of older subjects with chronic lung diseases other than asthma.

Race

Post-hoc subpopulation analyses of the SMART data suggested that there was a higher overall rate of asthma-related deaths in African-American subjects (2). Given the race disparities in asthma prevalence and serious asthma outcomes, inclusion of a representative sample of African-Americans in a large safety study is an important issue. However, it is unlikely that even a representative sample of African American subjects could be large enough to show statistical significance in a large global study. In addition, multiplicity issues must be taken into account in the subpopulation analyses in order to make meaningful conclusions. Nevertheless, the concern of a heightened safety signal in the African-American population can not be ignored, and planned future safety studies with LABAs should attempt to address this concern.

D. The safety endpoint – Serious asthma outcomes

The primary outcome of interest for the adult/adolescent safety studies is asthma-related deaths. This was the safety signal that was seen in the SMART study although the primary endpoint of the study was respiratory-related deaths or life-threatening experiences [2]. Ideally, asthma-related deaths would be the primary endpoint of interest, however, death from asthma is such a rare event that a study with this endpoint would require such a large number of subjects that it would not be feasible (*see Dr. Ben Neustifter's statistical briefing document*). A composite endpoint of asthma-related hospitalizations, asthma-related intubations, and asthma-related deaths is being proposed for the adult/adolescent safety studies. This was the endpoint used in the Agency's meta-analysis (*see Dr. Mark*

Levenson's statistical briefing package for December 10-11 2008 Advisory Committee meeting). However, this composite endpoint has limitations for evaluating the event of main interest (i.e., asthma-related deaths). The composite would be driven primarily by hospitalizations which as previously discussed, do not directly correlate with asthma-related deaths. Furthermore, since all intubations will require hospitalizations, the analysis would have to ensure that these events occurring in the same patient are not double counted. In spite of these limitations, the composite endpoint appears to be the best option for a safety endpoint to allow for a feasible study in the adult/adolescent population.

The selection of a safety endpoint for the pediatric (4 to 11 years) study is even more problematic. The proposed composite endpoint for the adult/adolescent studies seems less appropriate for the pediatric study. As presented earlier in this document, asthma-related death, and intubations – events that are very rare overall, occur even less frequently in children. In the Agency's meta-analysis prepared for the 2008 Advisory Committee meeting, there were no deaths or intubations in patients 4 to 11 years exposed to a LABA, and only one death in 4 to 11 year olds in the no LABA group. Asthma-related hospitalizations appear to be the best option for the safety endpoint for the pediatric study. That said, the socioeconomic factors other than asthma control that may drive hospitalizations (i.e. access to care, education, socio-economic status, etc.) play an even greater role in children, and may impact the interpretation of the results.

E. Drug Products

The following sections are written with the assumption that there will be two studies, one in adult/adolescents (12 years of age and older), and the other in pediatrics (4 to 11 years of age).

Adult/adolescent studies

The drug products for the adult/adolescent safety studies contain either salmeterol or formoterol as the LABA.

The salmeterol-containing products under consideration are:

- Advair Diskus®
- Advair ®HFA Inhalation Aerosol
- Serevent® Diskus®

The formoterol-containing products under consideration are:

- Symbicort® Inhalation Aerosol
- Foradil® Aerolizer®

The salmeterol combination products Advair Diskus and Advair HFA Inhalation Aerosol differ in formulation and delivery device (dry powder versus inhalation aerosol; Diskus device versus press-and-breathe canister with actuator) but contain the same ICS/LABA combination in similar dosage strengths. Therefore, a separate safety study with both Advair products seems unnecessary. Since the Advair Diskus product is approved in patients down to 4 years of age, a study using Advair Diskus is proposed. For Advair Diskus, only the medium and high dose strength products (Advair Diskus 250/50 and Advair Diskus 500/50) are under consideration for the adult/adolescent study, since the anticipated study population would be subjects with moderate to severe persistent asthma who would be candidates for

medium to high dose ICS +/- LABA therapy. Since the dose and delivery of the single ingredient salmeterol product – Serevent® Diskus is the same as for Advair Diskus, a separate study with Serevent® Diskus® seems unnecessary. Also, a large safety study (SMART) has already been conducted (albeit with limitations) with another salmeterol product (Serevent Inhalation Aerosol). Additionally, all the salmeterol products are developed by the same manufacturer (GSK).

Unlike the salmeterol-containing products, the formoterol-containing products Symbicort Inhalation Aerosol and Foradil Aerolizer are developed by different manufacturers (AstraZeneca, and Novartis respectively) and the two products have very different formulations and delivery devices. The Symbicort Inhalation Aerosol is formulated as a HFA-propelled pressurized metered dose inhaler, whereas, Foradil Aerolizer consists of a capsule dosage form containing a dry powder formulation of formoterol fumarate for oral inhalation with the Aerolizer inhaler. Each clear, hard gelatin capsule of Foradil contains a dry powder blend of 12 mcg of formoterol fumarate and 25 mg of lactose. There is not a tight pharmacokinetic and pharmacodynamic link between Foradil Aerolizer and Symbicort Inhalation Aerosol for the formoterol component and there is no assurance that the dose and delivery from the two formoterol-containing products (Symbicort and Foradil Aerolizer) are the same. Therefore, separate studies for these two formoterol products will be needed.

For the Symbicort study, the selection of the monotherapy inhaled corticosteroid comparator will be a challenge because there is no single-ingredient budesonide product approved in the United States in the same formulation and delivery device as Symbicort. The single-ingredient budesonide product with a nominal dose that is closest to the nominal dose in the Symbicort products is Pulmicort Flexhaler™. However, Pulmicort Flexhaler™ is a dry powder formulation available in two dose strengths, 90 mcg and 180 mcg, whereas, Symbicort is an inhalation aerosol formulation containing 80 mcg and 160 mcg of budesonide in each product. Since Symbicort Inhalation Aerosol and Pulmicort Flexhaler™ have different delivery devices, it cannot be assumed that the amount of budesonide deposited in the lungs from the two different products is the same. Therefore, the preferred option would be for the company to develop and use an investigational budesonide product that delivers budesonide at the same dose, using the same device and formulation as the Symbicort product. This option is feasible, as they have already developed a single-ingredient budesonide product that was used for the U.S. development program for Symbicort Inhalation Aerosol.

Pediatric (4 to 11 years of age) Study

For the pediatric safety study, the only product under consideration is Advair Diskus 100/50 as this is the only ICS/LABA combination product approved in children less than 12 years of age. At the December 2008 AC meeting, the committee voted unanimously that the risk of the single ingredient LABAs salmeterol and formoterol outweighed the benefits of these products in children 4 to 11 years of age. In addition, the NAEPP guidelines note that the efficacy evidence for LABAs (in combination with ICS) in children 5 to 11 years of age was less robust (Evidence B) than for asthmatics ≥ 12 years of age (Evidence A).¹ For these reasons safety studies with single-ingredient LABA products are not being considered.

¹ Evidence category A = Randomized controlled trials (RCTs), rich body of data; Evidence category B = RCTs, limited body of data

F. Treatment Comparison/Study Design Options

Adult/adolescent studies

For the adult/adolescent safety studies there are potentially multiple treatment comparison options, i.e. study arms, and these will be briefly presented below. All of these options assume a parallel group study design. For these treatment options, the subjects enrolled will all be stable (requiring only as needed short acting beta₂-agonists) on medium to high dose ICS, or medium to high dose ICS +/- a LABA at baseline. It is important that subjects are stable at baseline since they would potentially be randomized to receive less asthma therapy (i.e. the subjects who are on ICS and LABAs at baseline, who are then randomized to the ICS only arm).

The study could be designed as a “real world” study allowing for titration of the ICS dose in both treatment arms depending on clinical criteria. Since the “real world” option allows for titration of the ICS in both treatment arms, the subjects at baseline would need to be on medium dose ICS [+/- LABAs] to allow for upward titration of the ICS. For the “real world” option, blinding the study would be challenging. While a “real world” option is attractive, it may result in data that are difficult to interpret. For instance, an excess of adverse events in one arm may be due to a relative lack of ICS or excess of ICS, rather than the addition of a LABA to ICS. Also, the sample size of the treatment arms may become skewed in such a way that the sample size comparisons are no longer as meaningful.

For a study design where the dose of ICS remains fixed in both treatment arms, the study would still need to include general measures for management of asthma worsening/exacerbations per the physicians’ discretion.

Treatment arm options for the adult/adolescent (12 years of age and older) studies

Advair Diskus safety study

Option 1: Two treatment arms and fixed dose of ICS

- Advair Diskus + Flovent Diskus placebo
- Flovent Diskus + Advair placebo

Dosing regimen: One inhalation twice daily

The single ingredient Flovent Diskus arm is the same strength as the fluticasone in the combination product. For example, if Advair Diskus 250/50 is selected to study, then the Flovent Diskus only arm is Flovent Diskus 250.

Option 2: Three treatment arms and fixed dose of ICS

- Advair Diskus 250/50 + Flovent Diskus Placebo
- Flovent Diskus 250 + Advair Diskus placebo
- Flovent Diskus 500 + Advair Diskus placebo

Dosing regimen: One inhalation twice daily

This option would be able to compare the safety of a high dose of ICS monotherapy versus medium dose ICS and LABA. However, a three-arm study would increase the sample size, complicate study conduct logistics, and could be too challenging to perform.

Option 3: Two treatment arms and variable dose of ICS – the “real world” option

- Advair Diskus 250/50 + Flovent Diskus placebo
- Flovent Diskus 250 + Advair Diskus placebo

Subjects would be randomized to Advair Diskus 250/50 or Flovent 250 but the study would allow for titration of the dose of ICS in both treatment arms based on pre-defined criteria.

Symbicort safety study

Option 1: Two treatment arms and fixed dose ICS

- Symbicort Inhalation Aerosol + single-ingredient budesonide placebo
- Single-ingredient budesonide + Symbicort Inhalation Aerosol placebo

The dosing regimen is two inhalations twice daily.

Option 2: Two treatment arms and variable dose of ICS – the “real world” option)

- Symbicort 80/4.5 + placebo budesonide
- Budesonide ICS medium dose + Symbicort placebo

Patients would be randomized to Symbicort 80/4.5 or a single-ingredient budesonide product but the study would allow for titration of the dose of ICS in both treatment arms based on pre-defined criteria. ICS would be titrated using the single ingredient budesonide product.

Foradil Aerolizer safety study

Option 1: Two treatment arms and fixed dose of ICS

- Foradil Aerolizer + Baseline ICS (high dose)
- Baseline ICS + Placebo

Option 2: Two treatment arms and variable dose of ICS – “the real world” option

- Foradil Aerolizer + Baseline ICS (medium dose)
- Baseline ICS (medium dose) + Placebo

The ICS in the Foradil Aerolizer study would be any medium dose ICS other than budesonide. To allow for titration of the ICS, the baseline dose should be lower than the maximum dose (in order to allow for titration of the ICS dose).

Treatment arm options for the pediatric (4 to 11 years of age) Study

We are proposing a “real world” study design that would allow for titration of ICS or the use of corticosteroid bursts in both treatment arms. The treatment arms for the pediatric study would be:

- Advair Diskus 100/50 + baseline therapy
- Flovent 100 + baseline therapy

Since Advair Diskus 100/50 is the only product under consideration for patients 4 to 11 years of age, it is conceivable that one large safety study with Advair Diskus that covers the entire age spectrum of pediatrics and adults could be conducted. Such a study would need to ensure that the 4 to 11 year age group is adequately represented and covered with the same level of rigor as a separate pediatric study would cover. In addition, inclusion of both adult and pediatric patients in the same study would complicate collection of safety [and efficacy] endpoint data, since these may be different in the two populations.

G. Study Duration

For the adult/adolescent studies, treatment duration of 12 months appears to be adequate to allow sufficient time for patients to experience one of the serious asthma outcomes of the composite. However, the potential for drop outs is increased with a longer study, and a large percentage of drop outs could make the study difficult to interpret. A shorter study (e.g. a 6-month treatment duration) may result in fewer drop outs, however, a shorter study would require a larger sample size, and may not be adequate to account for the seasonal variations that can be seen with asthma exacerbations. 12-month treatment duration may be more feasible with a “real world” study design.

For the pediatric study, 6-month treatment duration appears to be adequate to capture sufficient events since the primary safety endpoint proposed is asthma-related hospitalizations. Hospitalizations for asthma are highest among children (0 to 17 years of age) [13].

H. Sample Size Considerations

Depending on the level of risk to be excluded, the study duration, number of treatment arms, the primary endpoint, and the power, the sample size can vary from several thousand patients for a composite endpoint to prohibitively several million patients for a primary endpoint of asthma-related deaths. The reader is referred to the statistical briefing document (*Dr. Ben Neustifter*) for details regarding sample size considerations.

8. Proposed Study Synopses

Two proposed study synopses, one for the adult safety study and one for the pediatric safety study, are presented below. The proposed synopses assume a randomized double-blind study with a double-dummy design to maintain the blind. As previously discussed, the design of the study using a fixed dose of ICS, or a design that allows for titration of the ICS in each treatment arm to reflect a more “real world” approach are possible considerations. An example of a proposed study synopsis for one of the adult/adolescent safety studies with a fixed dose combination LABA product is presented below using the two treatment arms fixed dose ICS option (treatment option 1). An example of a proposed synopsis for the pediatric study with Advair 100/50 is also presented below.

The proposed patient population would be asthmatics with moderate to severe persistent asthma who would be candidates for medium or high dose ICS +/- LABA, who are currently stable on their baseline medications. One concern is that enrolling patients who are stable on a current regimen of ICS/LABA could lead to rapid loss of control in these patients if they are randomized to ICS monotherapy. This scenario would not be desirable. Excluding patients who are on ICS/LABA at baseline could address this issue, but recruitment of a large number of patients with moderate to severe asthma who are not on a LABA at baseline does not seem feasible.

8A. ADULT STUDY SYNOPSIS

Objective

Primary: To determine the safety of a LABA added to ICS compared to ICS alone as measured by a composite endpoint of asthma-related hospitalizations, asthma-related intubations, and asthma-related deaths.

Secondary: Efficacy measures to assess asthma impacts such as quality of life

Hypothesis to be tested

The addition of LABA to high dose ICS in patients with moderate to severe asthma does not increase the risk of serious asthma outcomes namely - asthma-related hospitalizations, asthma-related intubations, and asthma-related deaths.

Design

Multi-center, multi-national double-blind, randomized, parallel group active controlled trial

Treatment Arms (ICS/LABA fixed dose combination product)

Option 1: (Two treatment arms and fixed dose of ICS)

- ICS/LABA + ICS placebo
- ICS (fixed dose) + ICS/LABA placebo

Methodology

The study would have a screening visit for determination of study eligibility followed by a double-blind randomization period where patients are randomized to study treatment for 6 - 12 months. Patients are seen at 6-week to 3 month intervals for safety (collect data on number of events during each the time period) and efficacy assessments, with telephone follow-up between scheduled visits.

Patient Population

Adult and adolescents 12 years of age and older with moderate to severe asthma who are on medium/high dose ICS or ICS/LABA, or who meet the criteria for treatment with medium/high dose ICS.

Major Inclusion/Exclusion criteria

Inclusions:

- Male and female patients with a diagnosis of asthma for at least 2 years
- History of asthma exacerbation in the last year prior to enrollment
- Stable at screening on their baseline mid/high dose ICS or ICS/LABA treatment requiring only p.r.n. rescue medication

Exclusions:

- Standard exclusion criteria
- Exclude current smokers (current smokers include smokers who quit within the last 6 months prior to enrollment)
- Criteria to ensure patients with COPD are excluded

Number of patients

The sample size depends on various factors, and can vary from several thousand to over a million depending on the primary endpoint selected and level of risk to exclude.

Study treatment duration

6 - 12 months

Study Endpoints

Primary endpoint: Composite safety endpoint of asthma-related hospitalizations, intubations, and asthma-related death.

Secondary endpoint: Efficacy assessments that could address impact of asthma control

End of adult study synopsis

8B. PEDIATRIC STUDY SYNOPSIS

Objectives

Primary: To determine the safety of Advair Diskus 100/50 in pediatric patients 4 to 12 years of age with asthma, as measured by asthma-related hospitalizations

Secondary: Efficacy measures of impacts (e.g. missed school days, and quality of life)

Hypothesis to be tested

The use of Advair Diskus 100/50 in pediatric patients with moderate to severe asthma does not increase the risk of asthma-related hospitalizations.

Design

Multi-center, multi-national double-blind, randomized, parallel group active controlled trial

Treatment Arms

1. Advair 100/50 + Flovent placebo
2. Flovent Diskus 100 + Advair 100/50 placebo

Methodology

The study would have a screening visit for determination of study eligibility followed by a double-blind randomization period where patients are randomized to study treatment for 6 months. Patients are seen at regular intervals (~ every 6 weeks) for safety (collect data on number of events during each the time period) and efficacy assessments, with telephone follow up in between scheduled visits. Patients enrolled in the study would have moderate/severe persistent asthma (candidates for controller therapy in addition to ICS (e.g. ICS and leukotrienes, or ICS and LABA). Patients would continue on other baseline asthma medication (e.g. leukotrienes), and the study would have pre-defined criteria for increasing ICS or adding systemic corticosteroids (e.g. oral prednisone).

Patient Population

Pediatric patients 4 – 11 years of age

Major Inclusion/Exclusion criteria

Inclusions:

- Male and female patients aged 4 – 11 years with a diagnosis of asthma for at least 6 months
- Have moderate/severe persistent asthma on controller medication at baseline (ICS or Advair +/- leukotrienes)
- History of asthma exacerbation/ ER visit or hospitalization in the last year prior to enrollment
- Stable at screening on their baseline asthma medication requiring only p.r.n. rescue medication

Exclusions:

- Standard exclusion criteria

Number of Patients

The number of patients would vary depending on several factors including the level of risk to be excluded, and may range from approximately 10,000 to 100,000 patients (*see Dr. Ben Neustifter's statistics briefing document*)

Study treatment duration

6 months

Study Endpoints

Primary endpoint: Safety as measured by asthma-related hospitalizations

Secondary endpoint: Efficacy assessment(s) that (indirectly) capture (s) the impact of serious asthma outcomes on children (e.g. missed school days)

End of Pediatric Study Synopsis

9. Issues and Questions for discussion

A major consideration for this study is the choice of the safety endpoint and the level of risk to exclude. For the adult/adolescent study, the asthma outcome of interest is asthma-related deaths but the sample size for a study with death as the primary endpoint approaches levels that make the study prohibitive. The proposed composite endpoint poses challenges as well given that hospitalization – the event that will drive the composite endpoint is not a strong predictor of asthma-related death. Further, several factors such as socio-economic status, education, access care, as well as health care practices in a particular region (i.e. threshold for hospitalization) can influence hospitalizations rates particularly in children. These factors would need to be considered given that this safety study would be a multicenter international study.

A large safety study would require several years to complete. For the SMART study it took about 7 years to enroll approximately 30,000 (50% of the target sample size) patients. Depending on the sample size, it is conceivable that the proposed safety study could take longer, and the fact that there are multiple products to be studied in the same patient population could magnify this issue.

We have drafted questions for discussion grouped by the major issues for the proposed safety studies (i.e. study endpoints, study design, and length of exposure). The draft questions are presented below to help focus the discussion of the main points; however, all issues regarding the design and conduct of a large safety study to further assess the risk of LABAs in asthma are open for discussion, including the additional questions. These questions are tentative and may change prior to the meeting.

We thank you in advance for your participation and look forward to the discussion.

Draft Questions

Study Endpoints

1. A composite safety endpoint of asthma-related hospitalizations, asthma-related intubations, and asthma-related deaths is proposed for the adult/adolescent safety study.

Discuss:

- a) The adequacy of the primary endpoint to address the safety concerns of LABAs for the treatment of asthma in adults/adolescents
- b) What level of risk for LABAs would be considered acceptable to rule out; i.e., what would be an acceptable upper bound of the 95% confidence interval?
- c) Alternative endpoints that could be considered to evaluate the safety of LABAs for the treatment of asthma in adults/adolescents

2. A safety endpoint of asthma-related hospitalizations is proposed for the pediatric safety study.

Discuss:

- a) The adequacy of the primary endpoint to address the safety concerns of LABAs for the treatment of asthma in pediatrics
- b) What level of risk for LABAs would be considered acceptable to rule out; i.e., what would be an acceptable upper bound of the 95% confidence interval?
- c) Alternative endpoints that could be considered to evaluate the safety of LABAs for the treatment of asthma in pediatrics

Study Design

3. Given the hypothesis to be tested, discuss the advantages and disadvantages of a study design with a “real world” approach where patients enrolled are allowed titration of the inhaled corticosteroid (ICS) dose compared to a study design where the dose of ICS remains fixed. Which of these designs would be more appropriate to address the safety concerns of LABAs for the treatment of asthma?

- a) in adults/adolescents
- b) in pediatrics

4. For a study design where the ICS dose remains fixed, discuss whether the ICS dose should be the same in the treatment arms or whether the ICS monotherapy group should have a higher dose.

Length of Exposure

5. Discuss the adequacy of a 6 to 12 month treatment period to address the safety concerns of LABAs for the treatment of asthma

- a) in adults/adolescents
- b) in pediatrics
- c) Discuss the advantages and disadvantages of a shorter treatment period e.g. 3 months

Additional Questions

1. Discuss what would be a reasonable timeframe for completion of the safety study.
2. Given that data from the SMART study suggest a higher safety signal in African-Americans, and national statistics indicate a higher rate of serious asthma outcomes in the African-American population, a representative number of African-Americans are proposed for inclusion in the U.S. study sites. Discuss the challenges for obtaining meaningful information from sub-group analyses from the proposed study and possible options to address them.

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Sample Size Estimates for Long-Acting Beta-Agonists Safety Trials

Statistical Briefing Package for
Joint Meeting of the Pulmonary-Allergy Drugs Advisory Committee
and the Drug Safety and Risk Management Advisory Committee
on March 10–11, 2010

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Summary

The following memorandum contains sample size estimates to assist the Office of New Drugs in designing clinical trials regarding the safety of long-acting beta agonists (LABAs) as combined with inhaled corticosteroids (ICSs). These trials are meant to determine whether a treatment of LABA with ICS is non-inferior to a ICS-alone treatment with regards to the occurrence of severe asthma events. These approximate estimates for sample size are provided in Tables 1 and 2 at the end of this document.

The figures in these tables represent approximations based on asymptotic formulae and varying assumptions detailed in the memorandum. As such, they should be used with caution and the recognition that they do not guarantee a successful or adequately-powered trial. There are numerous assumptions in place that are necessary to determine a sample size estimate; changes in these assumptions can result in varying results for sample size calculations. Among these assumptions are: the model and test statistics used (here risk difference and relative risk); the background rate of severe asthma events; the choice of non-inferiority margin; treatment duration, which impacts the background event rate; maximum allowable Type I error (α); desired power, and the definition for the study endpoint, which has a strong impact upon the background event rate.

Objective

This memorandum is meant to provide sample size estimates for the proposed post-marketing safety trials for long-acting beta agonists (LABAs). These trials are being designed to determine whether the addition of LABAs to inhaled corticosteroid (ICS) treatments increases the risk of asthma hospitalizations, asthma intubations, and asthma-related deaths. This memorandum discusses the estimation of rates of such events, the assumptions behind sample size calculations, and a variety of sample size estimates for the proposed study design, as well as similar tables for proposed pediatric safety studies.

The sample size numbers provided in this memorandum are not meant to be exact quantities, but rather represent approximate estimates based on asymptotic formulae and varying assumptions regarding background rates and margins of clinical significance.

Background

A joint Meeting of the Pulmonary-Allergy Drugs Advisory Committee, Drug Safety and Risk Management Advisory Committee and Pediatric Advisory Committee in December 2008 discussed the safety effects of LABAs in moderate to severe asthma patients, both adult and pediatric. Presented during this meeting was a meta-analysis of LABA data (Levenson 2008) suggesting a higher risk related to use of LABAs compared to placebo or other asthma drugs. For trials that compared LABA with ICS to ICS alone, the effect was less clear. The Office of New Drugs (OND) and Office of Surveillance and Epidemiology (OSE), in response, are preparing recommendations for post-marketing safety clinical trials

to further examine this possible relationship. These recommendations will be presented to an Advisory Committee in March 2010. In January 2010, the OND contacted OB Division VII with a request to assist in the calculation of estimated sample sizes for the study to assist in its design and allow the AC to make a more complete decision.

Study Design

While many details of the study design are still under consideration by OND, some specific details of the studies that have impact upon sample size estimation are:

- There will be two separate studies: one on adults, one on a pediatric population.
- Each study is to be a non-inferiority trial comparing a combination of LABA and ICS to a treatment of ICS alone.
- While the endpoint of clinical interest is asthma-related death, a composite endpoint of asthma-related death, asthma hospitalizations, and asthma intubations can be considered to reduce the necessary sample size.

Using this information, as well as some parameter assumptions that will be detailed in the following section, it is possible to give approximate estimates of the sample sizes necessary to sufficiently power non-inferiority studies on the safety of LABAs combined with ICS drugs versus an ICS-only treatment.

Model

The Office of New Drugs has expressed the goal of the study to test the hypothesis that “the addition of LABA to high dose ICS in patients with moderate to severe asthma does not increase the risk of serious asthma outcomes.” This hypothesis indicates the desired study design as a non-inferiority trial. If we define p_L as the background rate of endpoint (whether asthma death or the composite endpoint defined above) for combined LABA and ICS treatment, and p_C as the background rate of endpoint for the ICS-alone treatment, there are two possibilities for how the hypotheses may be construed for this study. If the risk difference is chosen as the test statistic, the hypotheses to be tested for this study are:

$$H_0 : p_L - p_C \geq \delta \tag{1}$$

and

$$H_1 : p_L - p_C < \delta, \tag{2}$$

where δ represents the *non-inferiority margin*, or the risk increase of clinical significance. The exact value of δ to be used in these trials is a decision left to the clinical team and advisory committee; as will be discussed later, the sample size calculations will be carried

out with a variety of δ values to provide information on how its choice will affect the necessary recruitment for the study.

Alternately, the risk ratio can be chosen as the test statistic of interest, in which case the hypotheses for the trial are

$$H_0 : p_L/p_C \geq \delta' \quad (3)$$

and

$$H_1 : p_L/p_C < \delta'. \quad (4)$$

The choice of hypotheses will have an effect on the estimates for necessary sample size, as will be seen in the following sections. Note that both hypotheses are structured so that the null hypothesis, H_0 , is that the combined treatment *does* have a clinically significantly larger risk of severe asthma events than the ICS-alone treatment. Rather than assuming that safety is the norm and forcing the evidence to contradict this assumption to show a risk to the combined treatments, a non-inferiority safety trial assumes a larger risk and forces the evidence from the trial to show that LABA with ICS does not increase the risk above ICS.

Parameter Assumptions

In order to estimate the sample size necessary for a properly-powered clinical trial, some assumptions must be made about various parameters involved in the calculations. Specifically: a maximum allowable chance of Type I error, α ; the desired power, $1 - \beta$ of the test; the non-inferiority margin, δ , and the background rates of events, p_L and p_C . The assumptions made for this memorandum are addressed in this section.

Type I Error

For two-sided hypotheses, it is typical to take $\alpha = .05$, setting the maximum probability of making a Type I error (rejecting H_0 when it is true) to 5%. In the hypotheses detailed above, a Type I error would result in decided that LABA with ICS does not increase the risk of severe asthma events above ICS alone, when it truly is associated with greater risk. Since the hypotheses of interest are one-sided, we will take $\alpha = .025$, which is equivalent to taking the half of a two-sided $\alpha = .05$ test that matches the hypotheses proposed above.

Power

Power, parameterized as $1 - \beta$, is the chances of rejecting the null hypothesis when it is false. In this context, the power is the probability of correctly concluding from the evidence that the LABA and ICS treatment does not increase the risk above ICS-alone treatment past the clinical significance margin of δ . Common choices of desired power for sample size calculations are $1 - \beta = .80$ and $1 - \beta = .90$, and will be the two options chosen for the estimates given below.

Non-inferiority Margin

The choice of the non-inferiority margin, δ , requires clinical expertise as well as consideration of the realistic recruitment limits of the proposed clinical trial. Frequently, non-inferiority margins are taken to be some proportion of the true event rate p , discussed below. To provide a spread of reasonable values of δ for the consideration of the clinical team and the advisory committee, the sample size estimates provided in this memorandum are based on values of $\delta = 0.2 * p, 0.3 * p$, and $0.5 * p$, where p is the true background event rate of severe asthma events for both treatments, as discussed below. These rates were chosen to provide a spread of possible values and are based on comments by the clinical team.

Background event rate

For the correct estimation of approximate sample size for this clinical trial, the true background rate of events for both treatment arm must be assumed. We first assume that the true background rate of severe asthma events is equal between the LABA/ICS combination arm and the ICS-alone arm; that is, that $p_L = p_C = p$ for some p . It is necessary to get an accurate estimate of p in order to ensure that the sample size approximation is accurate enough to sufficiently power the planned trial. Note that the value of p is dependent upon the length of treatment; generally, as the length of time that a subject will be exposed to a treatment increases, the probability that the subject will experience an endpoint also increases. In the case of LABAs, it appears from the 2008 meta-analysis (Levenson 2008) that asthma death and other severe asthma events occur at a constant rate across time, meaning p is directly proportional to the length of treatment.

If the desired endpoint is asthma-related death only, then the estimate for p will be quite small. The 2008 meta-analysis (Levenson 2008) had 1 asthma death out of 15192 subjects across both arms in the trial of LABA with ICS versus ICS alone, giving an approximate rate of 0.0065% for the study. The median length of treatment in the studies involved was 91 days, or approximately one-quarter of a year. Assuming that asthma-related deaths occur at a constant rate throughout the trial—which cannot be confirmed by the 2008 meta-analysis, given that only one death occurred—this gives an approximate background asthma death rate of .03% for a year-long study. The value of $p = 0.0003$ is therefore included in the sample size estimates to provide an approximation of the sample sizes needed to power the trial for an asthma-death endpoint for a one-year study.

The composite endpoint of asthma-related hospitalization, asthma-related intubation, and asthma death is also being considered for the trial design, due to the power problems related to the rarity of asthma-related death alone. From the same meta-analysis, the rate of this composite event across both arms in the LABA and ICS versus ICS trial was approximately 0.38% over a median treatment length of 91 days. Under the same assumptions as with asthma-related death, this gives an estimated rate of 1.5% for a year-long trial, and 0.75% for a half-year trial; these rates are included in the sample size estimation tables. In addition, the rates 0.5% and 2% were chosen to provide bracketing for the estimated values of p , giving a great idea of the approximate sample sizes necessary under different conditions. A rate of

1% was also included to give a more moderate value for comparison.

We note that according to the American Lung Association’s 2009 document on asthma trends, the rate of first-listed hospital discharges for asthma in the United States in 2006 (most recent data available) was approximately 444,000 out of 22.9 million asthmatics, or 1.94%. This is within our bracketing values, and is likely higher than the rate of a clinical trial population, since the population for the ALA document did not necessarily have proper medical care or pharmaceutical treatment for their asthma. This provides some confidence that the spread of estimated rates used in the sample size calculation adequately cover the parameter space of interest for this trial.

Finally, it is necessary to obtain some estimate of the true background rate of hospitalizations in a pediatric population. In the proposal for the pediatric study, OND defined the population of interest as pediatric patients with asthma aged 4 to 12. According to the data used by Levenson for the 2008 meta-analysis, out of 886 subjects aged 4 to 11 in all trials testing LABA with ICS against ICS-alone, 3 had asthma-related hospitalizations. This gives a rate of 0.34% for the studies, which had a median treatment length of 89 days. Assuming a constant rate of pediatric hospitalizations, this gives an approximate annual rate of 1.39% for pediatric events. Thus, 1.39% will be used as the estimate of p for the pediatric population. The National Center for Health Statistics (2006) states that approximately 198,000 pediatrics (aged 0–17) were hospitalized for asthma in 2004; the American Lung Association (2009) reports approximately 6.2 million people under age 18 had asthma during 2004, giving an approximate annual rate of 3.19%. While this rate is likely higher than the true background rate for a clinical trial, it will be included in the tables of estimates in order to provide an upper bracket for pediatric rates. Since this rate is likely too high, it is important to note that the approximate sample size estimates for the background rate of 3.19% are a bare minimum at best, and should not be considered as the most reasonable sample sizes for a pediatrics trial; the estimated rate from the meta-analysis, 1.39%, should provide a more accurate estimate of the sample size.

Sample Size Estimates

Based on the assumptions detailed above, it is possible to obtain estimates of the sample sizes necessary to adequately determine the non-inferiority of a treatment of LABA combined with ICS compared with ICS alone in a two-arm trial. If risk differences are used—that is, if the null and alternative hypotheses are (1) and (2), respectively—then the estimated sample sizes are as given in Table 1. These are calculated using the formula (Chow, Shao, & Wang, 2003)

$$n \approx 2 * \text{ceil} \left(\frac{2p(1-p)(z_\alpha + z_\beta)^2}{\delta^2} \right).$$

If the hypotheses are in terms of risk ratios, as in (3) and (4), then the approximate sample sizes are given by the formula (Chow, Shao, & Wang, 2003)

$$n \approx 2 * \text{ceil} \left(\frac{2}{p(1-p)} \frac{(z_\alpha + z_\beta)^2}{(\log(1 + \delta'))^2} \right),$$

and are shown in Table 2. The sample sizes in both tables are the estimated total sample needed for the trial, assuming that each of the two arms has an equal number of subjects allocated to it. Thus, any sample size estimate should be divided by 2 to obtain the estimated sample size for each arm. Since δ is a non-inferiority margin for risk differences, it is an absolute difference; $\delta = 0.1$, for example, indicates the non-inferiority margin is an increase of 0.1 in the probability of an endpoint. However, δ' is a non-inferiority margin for relative risks and is thus a relative difference, rather than absolute. A δ' of 0.1 indicates, then, an increase of 10% of the control rate, rather than an increase in absolute risk of 0.1. Note also that these sample sizes *do not* contain any adjustment for expected dropout; they will need to be multiplied by 1.1 (for estimated 10% dropout) or 1.2 (for estimated 20% dropout) to make such an adjustment. Also, the sample sizes do not account for heterogeneity across regions and sites.

Variation in Estimates

Sample size estimation is approximate, not only due to its reliance on asymptotic results for easy-to-calculate formulae, but because several assumptions must be made to implement these calculations. Any variation in these assumed values can cause differences in the estimated sample size required, some quite significant. For reference, all of the following may change the results of a sample size estimation to change:

- Different assumed value of α , the maximum tolerable probability of Type I error. While a one-sided α of 0.025 is standard for non-inferiority trials, some may use a one-sided value of 0.05, which would decrease the resulting sample size.
- Different desired power, $1 - \beta$. Increasing the desired power (for example, to 0.95) would result in an increase in the estimated sample size.
- Different δ , the non-inferiority margin. This parameter is quite likely to vary from source to source, as it is a matter of clinical judgment. Increasing the non-inferiority margin—that is, allowing the LABA and ICS treatment to have a larger increase of risk before it is deemed inferior to ICS-alone—results in a smaller estimate of sample size.
- Different estimates for p , the background rate of events. Even assuming that the same endpoints are used (see following point), there is much uncertainty about the “true” rate of endpoint occurrence in the clinical population. Estimates based on the U.S. population as a whole, for example, may not be accurate, as they would not represent the moderate-to-severe asthmatic population of interest to the clinical study, nor would it account for possible regional differences by country in endpoint rates. This

memorandum believes that the 2008 meta-analysis provides some of the most accurate estimates of the true background rate, but estimates based on other sources will vary, causing the resulting sample size approximations to likewise vary. In general, the more rare an event is (i.e. the lower value for p), the larger sample size it will require; if p becomes greater than 0.5, this relationship becomes reversed.

- Different choice in endpoint. Adding surrogates to the endpoint, such as the asthma intubation and asthma hospitalization in the composite endpoint, can increase the background endpoint rate p , leading to a decrease in estimated sample size. This may carry the disadvantage of adding “noise” to the endpoint that is not significantly related to the endpoint of interest (asthma death, in the case of this study). Similarly, narrowing the endpoint will result in increases in the estimated sample size, as can be seen with the estimated sample sizes for death-only trials in Tables 1 and 2.
- Different planned treatment length. The background rates used in Tables 1 and 2 were estimated assuming a year-long or half-year treatment length. Exposing subjects to treatments for greater lengths of time could increase the rate of endpoints, which would result in a greater estimated p and lower resulting sample size approximation.
- Adding assumptions regarding dropout rates. The sample size estimates provided in Tables 1 and 2 assume that there are no dropouts among subjects. As addressed in the previous section, assuming a certain dropout rate requires increasing the sample size estimate accordingly.
- Different methods of sample size calculation. Tables 1 and 2 provide sample size estimates for the asymptotical risk difference and risk ratio methods, which are two common methods of sample size calculation. However, use of methods such as the log-rank test or exact methods could result in different sample size approximations.

Conclusions

This memorandum is meant to provide assistance in the design of a post-marketing safety study on the effects of LABAs added to ICS treatments. The approximate sample size estimates given should be considered by the clinical team and used to help plan a feasible study design. The information on possible deviations and variations in sample sizes may help in understanding other sample size approximations that may be proposed. It is important to remember that any sample size estimates given in this document are approximate at best and should be used with care.

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Table 1: Total Sample Size, Equal Arm Size, Using Risk Difference

Background Rate	NI Margin (Proportion of Rate)	Power	
		0.8	0.9
0.0003 ^a	0.00006 (.2)	2615510	3501424
	0.00009 (.3)	1162450	1556190
	0.00015 (.5)	418482	560228
0.005 ^b	0.001 (.2)	156194	209098
	0.0015 (.3)	69420	92934
	0.0025 (.5)	24992	33456
0.0075 ^b	0.0015 (.2)	103868	139050
	0.0025 (.3)	46164	61800
	0.00375 (.5)	16620	22248
0.01 ^b	0.002 (.2)	77704	104024
	0.003 (.3)	34536	46234
	0.005 (.5)	12434	16644
0.0139 ^c	0.0028 (.2)	55682	74544
	.0042 (.3)	24748	33130
	.0070 (.5)	8910	11928
0.015 ^b	0.003 (.2)	51542	69000
	0.0045 (.3)	22908	30668
	0.0075 (.5)	8248	11040
0.02 ^b	0.004 (.2)	38460	51488
	0.006 (.3)	17094	22884
	0.01 (.5)	6154	8238
0.0319 ^c	0.0061 (.2)	23820	31888
	0.0091 (.3)	10588	14174
	0.0152 (.5)	3812	5104

^a Estimated rate for death-only endpoint^b Estimated rate for composite endpoint^c Estimated rate for hospitalizations in pediatrics aged 4–12

Table 2: Total Sample Size, Equal Arm Size, Using Risk Ratio

Background Rate	NI Margin (Proportion of Rate)	Power	
		0.8	0.9
0.0003 ^a	0.00006 (.2)	3149204	4215890
	0.00009 (.3)	1520784	2035898
	0.00015 (.5)	636752	852430
0.005 ^b	0.001 (.2)	189846	254150
	0.0015 (.3)	91680	122732
	0.0025 (.5)	38386	51388
0.0075 ^b	0.0015 (.2)	126882	169860
	0.0025 (.3)	61274	82028
	0.00375 (.5)	25656	34346
0.01 ^b	0.002 (.2)	95402	127716
	0.003 (.3)	46072	61676
	0.005 (.5)	19290	25824
0.0139 ^c	0.0028 (.2)	68906	92246
	.0042 (.3)	33276	44548
	.0070 (.5)	13934	18652
0.015 ^b	0.003 (.2)	63926	85578
	0.0045 (.3)	30870	41326
	0.0075 (.5)	12926	17304
0.02 ^b	0.004 (.2)	48188	64510
	0.006 (.3)	23272	31154
	0.01 (.5)	9744	13044
0.0319 ^c	0.0061 (.2)	30584	40944
	0.0091 (.3)	14770	19772
	0.0152 (.5)	6184	8280

^a Estimated rate for death-only endpoint^b Estimated rate for composite endpoint^c Estimated rate for hospitalizations in pediatrics aged 4–12



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:

2/9/2010

To:

Badrul Chowdhury, MD, PhD
Director, Division of Pulmonary and Allergy Products
Office of New Drugs
Center for Drug Evaluation and Research

Through:

Gerald Dal Pan, MD, MHS
Director, Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

From:

Ann W. McMahon, MD, MS
Deputy Director, Division of Pharmacovigilance I
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

Subject:

Recommendations for study design of future
manufacturer-sponsored studies of long-acting beta-
agonists in children and adults

Drug Name (NDA numbers):

Advair (021254, 021077)
Foradil (020831, 021279, 021592)
Serevent (020236, 020692)
Symbicort (021929)

Application Type:

NDA

Applicant/sponsor:

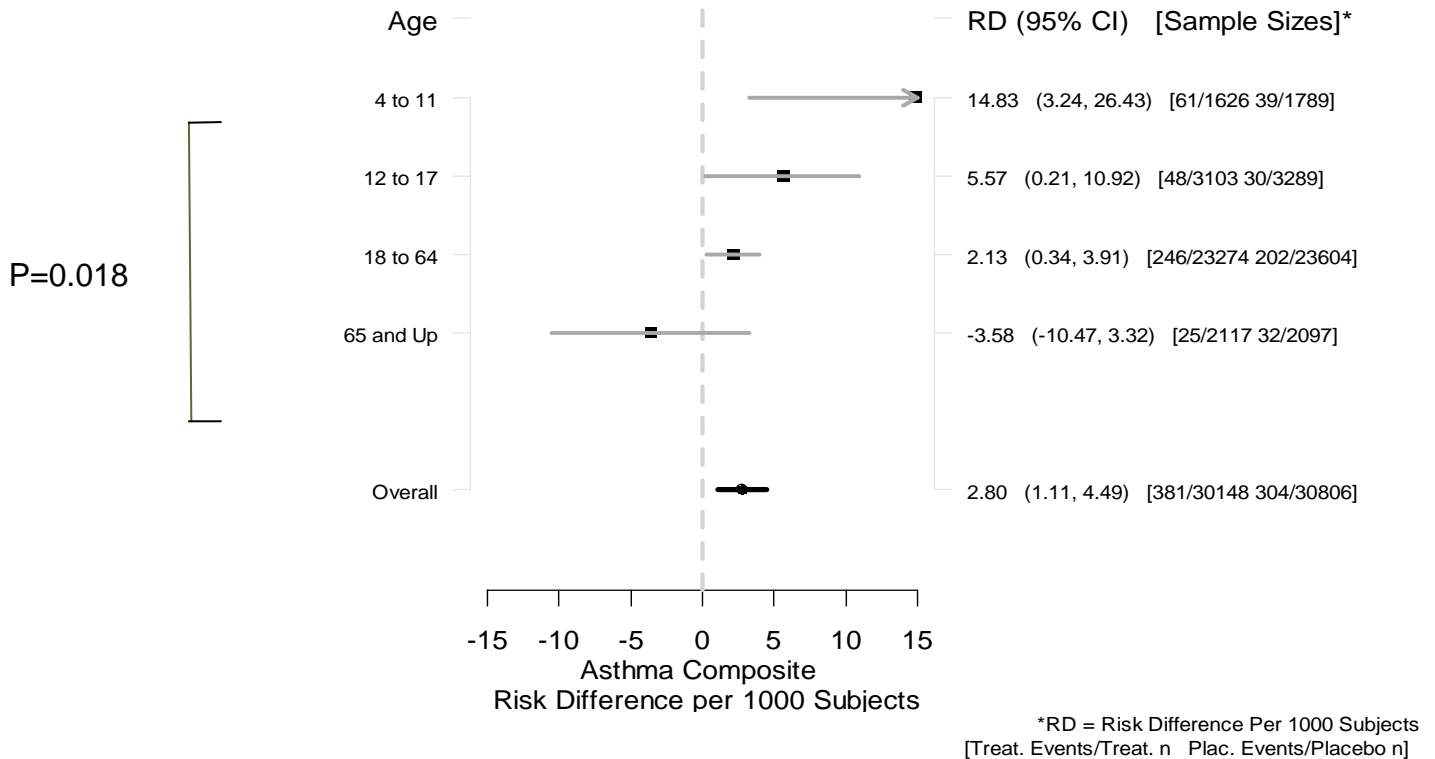
GlaxoSmithKline
Novartis
Astrazeneca

The Office of Surveillance and Epidemiology (OSE), in conjunction with the Office of Biostatistics, was asked by the Division of Pulmonary and Allergy Products in the Office of New Drugs to recommend study designs for FDA-recommended safety studies to be performed by Sponsors of Long-Acting Beta-2 Agonist (LABA) drugs. The following outlines the opinion of OSE regarding the primary issues facing us in early 2010 in assessing the safety of the LABAs.

Background: The single-ingredient LABAs (Serevent in particular) have already been adequately studied with large safety trials in adults so as to establish that these products, used alone, increase the risk of serious asthma outcomes such as asthma-related death and intubation^{1,2} in the populations studied. An unanswered question after these large safety trials was whether serious asthma outcomes are increased in patients receiving LABAs in combination with inhaled corticosteroids (ICS) compared with patients receiving ICS alone. In a recent meta-analysis³, it was noted that there was a statistically significant increased risk of hospitalizations due asthma in adult patients receiving LABA plus ICS compared to ICS alone. But there has never been a large safety trial comparing asthma-related serious outcomes in patients using LABA plus ICS compared to ICS alone.

In children, a striking finding was observed in the FDA meta-analysis conducted in preparation for the 2008 advisory committee meeting. The Figure below shows a significant trend towards the risk difference of asthma-related hospitalizations being higher at younger ages in individuals receiving LABAs compared to individuals not receiving LABAs. Note that ICS may or may not have been used in the LABA and comparator groups in this analysis. However, when ICS were used with LABA in the treatment arm, the control arm also used an identical ICS regimen. The age trend in asthma-related hospitalizations is a key point in the considerations for conducting safety trials for the LABAs.

Figure. Adjusted Overall Risk Differences in Long-Acting Beta Agonists by Age.
Outcome=Asthma Composite Index (Asthma-related death, Asthma-related intubation, Asthma-related hospitalization)



Objective: To assess safety of long-acting beta agonist combination products with ICS (Advair and Symbicort) compared to ICS alone in adults and children.

Hypothesis: In adults, imbalance in randomized clinical trials of subjects receiving Salmeterol compared to subjects receiving placebo^{1,2} was seen using the endpoints of asthma-related death and intubation, but not in the endpoint of asthma-related hospitalization. However, in a recent meta-analysis comparing LABA plus ICS with ICS alone, it was noted that there was a statistically significant increase in asthma-related hospitalizations in the LABA plus ICS arm³. In addition, data on Hospitalizations may be relevant in children, given the age trend dominated by hospitalizations in the FDA meta-analysis (Figure). Therefore, we would recommend considering two hypotheses:

Hypothesis #1:

- LABA + ICS use in moderate to severe asthmatics is associated with a greater rate of asthma deaths and intubations than use of high-dose ICS alone,
- Outcome of interest

- Asthma-related deaths and intubations.

Hypothesis #2:

- LABA + ICS use in moderate to severe asthmatics is associated with a greater rate of asthma-related hospitalizations than use of high-dose ICS alone,
- Outcome of interest
 - Asthma-related hospitalizations.

Arms of the trials:

1. LABA+ICS as one agent (i.e. Advair or Symbicort)
2. High dose ICS as single agent (Flovent or Budesonide)

High dose inhaled corticosteroids (ICS) are recommended in the control arm since this dose of ICS is recommended in the National Heart, Lung, and Blood Institutes Guidelines for the Diagnosis and Management of Asthma as an alternative to the LABA/ICS combination products. Therefore high dose ICS would appear to be an appropriate comparator arm.

Study populations and parameters:

OSE recommends 4 separate trials to obtain the appropriate power in the most significant subpopulations:

Table 1. Four separate trials included in this recommendation.

Drug	Advair		Symbicort	
Population	Pediatrics	Adults	Pediatrics	Adults

Blinding and rescue therapy

- All trials would be double blinded
- Rescue albuterol would be allowed in all arms of the trial

Duration of study observation period

- Since duration of LABA use appears to be correlated with level of risk⁴, and since the exposure period that was previously demonstrated to be unsafe was 24-28 weeks^{1,2}, it seems appropriate from an ethical point of view to recommend limiting the exposure period to LABAs for study participants perhaps to 3 months or approximately half the period in which the elevated risk was observed^{1,2}.

Study design: OSE is of the opinion that a non-inferiority study design is appropriate in this instance. Sample size estimates are provided for different background rates ranging from 0.0005 to 0.01; the non-inferiority margin is set to 0.5 times the respective background rate. Sample sizes assume a one-sided type-I error rate of 2.5%, and either 80% or 95% power. See Table 2 for total sample size estimates for the different study parameters. Total sample sizes assume equal number of patients per treatment arm.

Table 2. Total sample size*.

Background rate	NI margin^	Power	
		0.8	0.95
0.0005	0.00025	251040	415624
0.001	0.0005	125458	207708
0.002	0.001	62666	103750
0.003	0.0015	41736	69098
0.004	0.002	31270	51772
0.005	0.0025	24992	41376
0.006	0.003	20806	34446
0.007	0.0035	17816	29496
0.008	0.004	15574	25782
0.009	0.0045	13828	22894
0.01	0.005	12434	20584

*Reflects observation period of 3 months.

^Noninferiority margin expressed in absolute terms.

The background risk of asthma-related death or intubation in the ICS treatment arm is assessed at < 0.00014 events per 3 month period, based on Dr. Levenson's meta-analysis³. Therefore, if one were attempting to exclude a noninferiority margin of 0.00025 with 80% power (Table 2), the sample size would be larger than 250,000 for a trial comparing asthma-related death or intubation in the treatment and control arms in adults, as was suggested above.

Likewise, the background risk of asthma-related hospitalizations in children and adults was assessed in Dr. Levenson's meta-analysis at 0.0035 events in a 3 month period⁴. Therefore, if one were attempting to exclude a noninferiority margin of 0.0015 with 80% power (Table 2), the sample size would be approximately 40,000 for a pediatric or adult trial comparing asthma-related hospitalizations in the treatment and control arms.

CONCLUSIONS/RECOMMENDATIONS:

OSE has proposed features of a trial design many aspects of which are up for discussion. The following outlines the considerations for such trials:

1. Separate trials should be performed in adults and children, each adequately powered to detect the differences thought to be of primary interest in that population (See Hypothesis Section above).
2. It is important to decide upon an appropriate level of risk to exclude in any LABA plus ICS safety trial.
3. If an adult trial were designed with the primary endpoint of asthma-related deaths and intubations, such a trial would not be feasible due to the large sample size required. A trial with the endpoint of asthma-related hospitalizations may be feasible, and given the recent meta-analysis results suggesting an increased risk of hospitalizations in adults treated with LABA plus ICS compared with ICS alone, it could be an important safety study to perform.
4. A pediatric trial designed to measure asthma-related hospitalizations as an endpoint could be feasible. Since this endpoint in children showed disparity between treatment and control arms in the FDA meta-analysis³, such a study would have the potential to answer important open questions in the field of LABA safety.
5. Consideration should be given to the duration of the observation period in the study(ies) being no longer than 3 months.
6. Consideration should be given to the comparator arms in both the study(ies) being high-dose ICS.

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DIVISION DIRECTOR MEMORANDUM

Date: November 12, 2008

From: Badrul A. Chowdhury, MD, PhD
Director, Division of Pulmonary and Allergy Products, CDER, FDA

To: Members, Pulmonary-Allergy Drugs Advisory Committee (PADAC), Drug Safety and Risk Management Advisory Committee (DSARM), and Pediatric Advisory Committee (PAC)

Subject: Safety and risk-benefit assessment of long-acting beta-agonist bronchodilators for the treatment of asthma

1. Introduction and Background

Thank you for your participation in the upcoming Advisory Committee meeting to be held on December 10 and 11, 2008. As members of FDA Advisory Committees, you provide important expert scientific advice and recommendations to the FDA on various regulatory decision making processes, including those related to the continued assessment of safety and efficacy of drugs marketed in the United States. The objective of the upcoming meeting is to discuss the implications of available data related to the safety of inhaled long-acting beta-agonist bronchodilators (LABAs) in the treatment of asthma. There are two inhaled LABAs marketed in the United States that will be discussed in this meeting. These are salmeterol xinafoate, marketed either as a single ingredient product, or as combination products with the inhaled corticosteroid fluticasone propionate, and formoterol fumarate, marketed either as a single ingredient product, or as a combination product with the inhaled corticosteroid budesonide. Inhaled LABAs are approved for treatment of two diseases, asthma and chronic obstructive pulmonary disease (COPD). Only the asthma indication is the subject of this advisory committee discussion.

The principal benefits patients derive from inhaled LABAs are from bronchodilation, which results in improved pulmonary function, and decreased need for rescue short-acting bronchodilator use for asthma exacerbations. Inhaled LABAs have a duration of bronchodilation of at least 12 hours after dosing. They have adverse effects that are typical of beta-adrenergic agonists. In addition, an important adverse effect that has been observed with these drugs in patients with asthma is the occurrence of asthma-related death. Because of the risk of asthma-related death, all inhaled LABA-containing products have a warning statement in their product labels, including a Boxed Warning as well as a Medication Guide.

Whether the risk-benefit assessment of inhaled LABAs justifies their continued marketing was discussed at a Pulmonary-Allergy Drugs Advisory Committee (PADAC) meeting on July 13, 2005. At the meeting, the Committee recommended via a unanimous vote that both salmeterol and formoterol should continue to be marketed in the United States (1). At a Pediatric Advisory Committee (PAC) meeting held on November 27 and 28, 2007, to discuss

adverse events reports after one year of granting marketing exclusivity for pediatric studies as required by the Best Pharmaceuticals for Children Act (BPCA), there was an expanded discussion on salmeterol. In the briefing material for the PAC meeting prepared by CDER, FDA, opinion was expressed that “salmeterol may have an unfavorable risk-benefit ratio in the treatment of pediatric asthma” (2). There was not an internal FDA consensus on this opinion. At the PAC meeting, an analysis of the available observational epidemiology studies and subgroup analysis of the pediatric population in clinical trials was presented. The Agency stated that further assessment of the role of salmeterol in the treatment of pediatric asthma is warranted and that this issue would be brought to a future advisory committee. At the PAC meeting, Committee members discussed the possibility of removal of salmeterol from the market. The Committee agreed with the Agency that an extensive discussion of the benefits in the context of the risk of salmeterol in pediatric patients was warranted (3). The upcoming December 10 and 11, 2008, meeting is being convened to discuss this risk-benefit analysis. This meeting will discuss both salmeterol and formoterol because the risk-benefit analysis applies to both inhaled LABAs. The discussion will include adult patients as well as pediatric patients, because most of the safety data with inhaled LABAs are in patients 12 years and older, and the risk-benefit analysis will be applicable to both pediatric and adult patients with asthma.

Subsequent sections of this document provide: an overview of asthma and asthma treatment, a summary of the regulatory histories of salmeterol and formoterol and studies that identified asthma-related death for these products, a discussion of asthma-related death with inhaled short-acting beta-agonists (SABAs), a discussion of possible mechanisms of asthma-related death with beta-agonists, a risk-benefit analysis of inhaled LABAs, and finally issues and questions for discussion at this advisory committee meeting.

2. Asthma

Asthma is a chronic inflammatory disease of the airways characterized by varying and recurring symptoms of shortness of breath, chest tightness, wheezing and cough, airflow obstruction, bronchial hyperresponsiveness, and underlying inflammation. In the United States, asthma affects more than 22 million persons. It is one of the most common chronic diseases of childhood, affecting more than 6 million children. Worldwide, about 300 million people are affected (4, 5).

Asthma is classified into four categories based on the level of symptoms, nighttime awakening from symptoms, short-acting beta-agonist bronchodilator use for symptom control, interference with normal activity, and lung function. The four categories of asthma are: Intermittent, Mild Persistent, Moderate Persistent, and Severe Persistent (4, 5). Classification of asthma based on severity is useful when deciding about management at the initial assessment of a patient. When a patient is already on treatment, asthma severity classification reflects both the severity of the underlying disease and its responsiveness to treatment.

a. Medications available for treating asthma

Medications for asthma are categorized into two classes: quick-relief medications used to treat acute symptoms and exacerbations and long-term control medications used to achieve and maintain control of persistent asthma (4). Medications available under prescription for the treatment of asthma in the United States are listed in Table 1.

Table 1. Asthma medications available under prescription in the United States

I. Quick-relief medications (listed in alphabetical order by class)
a. Short-acting beta-agonist bronchodilators (SABAs)
1. Albuterol sulfate inhalation aerosol and inhalation solution
2. Albuterol sulfate tablets and syrup
3. Metaproteronol inhalation aerosol
4. Pirbuterol acetate inhalation aerosol
5. Levalbuterol inhalation aerosol and inhalation solution
b. Systemic corticosteroids
1. Methylprednisolone tablets and injection
2. Prednisolone tablets, oral solution, oral syrup
3. Prednisone tablets, oral solution, oral syrup
II. Long-term control medications (listed in alphabetical order by class)
a. Cromones
1. Cromolyn sodium inhalation aerosol
2. Nedocromil sodium inhalation aerosol
b. Immunomodulators
1. Omalizumab injection
c. Inhaled corticosteroids (ICSs)
1. Beclomethasone dipropionate inhalation aerosol
2. Budesonide inhalation powder and inhalation suspension
3. Ciclesonide inhalation aerosol
4. Flunisolide inhalation aerosol
5. Fluticasone inhalation aerosol and inhalation powder
6. Mometasone inhalation powder
7. Triamcinolone inhalation aerosol
d. Leukotriene modifiers
1. Montelukast tablets, chewable tablets, and oral granules
2. Zafirlukast tablets
3. Zileuton extended release tablets
e. Long-acting beta-agonist bronchodilators (LABAs)
1. Albuterol sustained release tablets
2. Formoterol inhalation powder
3. Salmeterol inhalation powder
f. Methylxanthines
1. Theophylline tablets, extended release capsules, elixir, and solution for injection
g. Systemic corticosteroids
1. Methylprednisolone tablets
2. Prednisolone tablets, oral solution, oral syrup
3. Prednisone tablets, oral solution, oral syrup

To place inhaled LABAs in the proper clinical perspective, it is important to understand the treatment options that are currently available for patients with asthma. In the paragraphs below, all medication classes available for the treatment of asthma in the United States are

briefly described. The reader is referred to the product labels of these drugs for a detailed review of these medications. Expert panel reviews, such as The National Asthma Education and Prevention Program's (NAEPP) Expert Panel Report III and The Global Initiative for Asthma (GINA) Report have recommendations on the use of these medications in the treatment of asthma (4, 5). Some of these recommendations are mentioned with the description of each drug class below. These recommendations, as mentioned in this section and elsewhere in this document, should not be interpreted as endorsement by the FDA.

Short-Acting Beta-Agonists (SABAs)

Inhaled SABAs are the mainstay of therapy for the acute treatment of bronchospasm in both routine outpatient management and in the hospital setting (4). Inhaled SABAs have a relatively quick onset of bronchodilation that lasts for about 6 hours. Adverse reactions of inhaled SABAs are typical beta-adrenergic effects, such as increases in heart rate and blood pressure, muscle tremor, and metabolic effects, such as increase in blood glucose, and decrease in serum potassium. The inhaled SABAs available at present are relatively selective beta₂-agonists and have less pronounced cardiovascular effects.

Oral albuterol has a limited role in acute treatment of bronchospasm because of adverse cardiovascular and other systemic effects, and availability of inhaled formulations that provide better risk-benefit profile.

Cromones

Cromones have an excellent safety profile and have demonstrated efficacy in the treatment of asthma as long-term control medications. NAEPP considers these drugs to have a weak anti-inflammatory effect, show inconsistent efficacy in clinical trials, and generally to be less efficacious than ICS (4). Due to their excellent safety profile, cromones are considered as acceptable treatment options, particularly in younger children, and in those with mild persistent asthma (4, 5). The NAEPP recommends cromones as an alternative, not preferred, treatment option for mild persistent asthma (4).

Omalizumab

Omalizumab is used in the treatment of patients 12 years and older with asthma who have proven sensitivity to aeroallergens and elevated serum IgE levels. Anaphylaxis and malignancy are two serious adverse reactions associated with omalizumab. The NAEPP recommends that omalizumab may be considered as an adjunctive treatment for patients with severe persistent asthma inadequately controlled with a combination of high-dose ICS and LABA (4).

Inhaled Corticosteroids (ICSs)

Inhaled corticosteroids (ICSs) are the most potent and effective anti-inflammatory medications currently available as long-term control medications for asthma. Drugs of this class show consistent efficacy in the treatment of asthma. Adverse reactions with ICSs include localized infection such as oral candidiasis of the mouth and throat, hoarseness, potential worsening of infection, adrenal suppression, decrease in bone mineral density, glaucoma, cataracts, and growth suppression. Most of these adverse reactions are dose-

dependent and not as common with ICS as with systemic corticosteroids. The NAEPP recommends ICS as the preferred treatment for persistent asthma of all severities (4).

Leukotriene Modifiers

Leukotriene modifiers have demonstrated efficacy in the treatment of asthma as a long-term control medication. NAEPP and GINA consider these drugs to provide only a modest improvement in lung function and generally to be less efficacious than ICSs (4, 5). Zileuton, one of the leukotriene modifiers, can cause liver injury and its use requires periodic liver function monitoring for patient safety. The NAEPP recommends leukotriene modifiers as an alternate, not preferred, treatment option for mild persistent asthma, and states that combination therapy of LABA and ICS are preferred over combination therapy of leukotriene modifiers and ICS (4).

Inhaled Long-acting beta-agonists (LABAs)

Inhaled LABAs provide bronchodilation of approximately 12 hours in duration, resulting in improved pulmonary function and decreased rescue short-acting bronchodilator use for asthma exacerbation. The risks of inhaled LABAs include asthma-related death and beta-adrenergic related adverse reactions. NAEPP and GINA recommend inhaled LABAs as the preferred treatment to combine with ICS in patients who need a second long-term control medication (4, 5).

Sustained release albuterol tablets

Sustained release oral albuterol has limited role as a long-term control medication because of limited efficacy, and adverse effects such as cardiovascular stimulation, anxiety, and skeletal muscle tremor (5).

Methylxanthines

Although theophylline has been traditionally classified as a bronchodilator, it also has efficacy as a long-term control medication. Its use has decreased over time with the introduction of newer long-term control medications and concerns regarding theophylline toxicity (e.g. gastrointestinal intolerance, cardiac arrhythmias, seizures, and death) and narrow therapeutic window. Monitoring of blood theophylline levels is necessary for its safe use. NAEPP states that theophylline provides only modest improvement in lung function and less control of asthma than low-dose ICS. The NAEPP recommends sustained-release theophylline as an alternate, not preferred, treatment option for mild persistent asthma (4).

Systemic Corticosteroids

Systemic corticosteroids can be used as a long-term control medication for severely uncontrolled asthma, but their use is limited by significant adverse effects such as hypothalamic-pituitary-adrenal axis suppression, osteoporosis, diabetes, hypertension, cataracts, glaucoma, growth suppression, skin thinning, muscle weakness, and Cushing's syndrome (4, 5). The NAEPP recommends chronic treatment with oral systemic corticosteroids only for the most severe refractory asthma (4).

Despite progress in the understanding of the pathophysiology of asthma, treatment choices remain limited. The medication classes that form the cornerstone of asthma treatment are

inhaled SABAs, ICSs, and inhaled LABAs. The available choices may become further limited in the future due to restriction of the use of stratospheric ozone-depleting chlorofluorocarbons (CFCs) as a propellant in inhalation aerosols. With the CFC phase-out proposed in the United States, the following inhalation aerosols may not be available in the future: both the cromones – cromolyn and nedocromil, flunisolide, triamcinolone, metaproteronol, and pirbuterol (6).

3. Treatment of asthma

The goal of asthma treatment for all ages is to maintain control with the least amount of medication and hence minimal risk of adverse effects. Asthma is treated in a step-wise manner with the dose and number of medications increased as necessary, and decreased when possible. Both the NAEPP and GINA reports provide recommendations for a step-wise approach for asthma management (4, 5). The NAEPP and GINA treatment recommendations for intermittent asthma and persistent asthma are briefly summarized below to familiarize the reader with the current standard of care. The reader is referred to the NAEPP and GINA reports for a through review of these recommendations (4, 5). These recommendations, as mentioned in this section and elsewhere in this document, should not be interpreted as endorsement by the FDA.

a. Intermittent Asthma

Patients with intermittent asthma have symptoms ≤ 2 days per week, nighttime awakening 0 to ≤ 2 times per month, no interference with normal activity, use of SABA ≤ 2 days per week, and lung function (forced expiratory volume in 1 sec, FEV_1) $>80\%$ predicted and normal between exacerbations (4).

NAEPP and GINA recommend inhaled SABAs as the medication of choice for the relief of intermittent asthma. The use of these medications is recommended on an as-needed basis in the lowest dose and frequency required. Increased use, especially daily use, is an indication of deterioration in asthma control.

b. Persistent Asthma

Patients with persistent asthma have symptoms from ≤ 2 days per week to throughout the day, nighttime awakening from ≤ 2 times per month to daily, use of SABAs from ≤ 2 days per week to several times per day, interference with daily activity from none to extreme limitation, and lung function (FEV_1) varying from $>80\%$ predicted to $<60\%$ predicted. Persistent asthma is classified as mild, moderate, or severe based on the severity of these symptoms and signs (4).

NAEPP and GINA recommend that all patients with persistent asthma be treated with long-term control medications. ICSs are the most effective and potent anti-inflammatory medications available for the treatment of persistent asthma and are recommended as the preferred treatment for patients of all ages. For mild persistent asthma, single agent low-dose

ICS is the preferred recommended treatment. With increasing severity from moderate to severe persistent asthma, mid-dose and high-dose ICSs are recommended, respectively. Inhaled LABAs are the other preferred recommended treatment for persistent asthma. Inhaled LABAs do not influence the underlying airway inflammation in asthma, and therefore, are not recommended as monotherapy for the long-term control of asthma. Rather, inhaled LABAs are to be used in combination with ICSs for long-term control and prevention of symptoms in moderate and severe persistent asthma. NAEPP has slightly varying recommendations for use of long-term control medications for patients of different age groups. For patients 12 years of age and older, combined therapy with an ICS and an inhaled LABA is preferred when low-dose or mid-dose ICS alone fails to achieve control of asthma. For patients 5 to 11 years of age, preferred combination therapy with ICS include an inhaled LABA, a leukotriene modifier, or theophylline. For patients 0 to 4 years of age, preferred combination therapy with ICS include an inhaled LABA or montelukast. Per the NAEPP guidelines, inhaled LABAs are less preferred in children younger than 12 years because they have demonstrated less consistent efficacy with regard to some outcome measures in patients 5 to 11 years of age as compared to older patients, and the efficacy of inhaled LABAs has not been adequately established in patients 0 to 4 years of age. For patients of all ages, oral systemic corticosteroids are also listed as an option for the most severe and difficult-to-treat asthma.

It should be noted that the recommended ages mentioned above for various medications are those of the NAEPP and GINA expert panel, and some of these are not in agreement with product labels approved by the FDA. For example, inhaled LABAs are not approved for use in patients below 4 years of age. ICSs in inhalation aerosols and dry powder inhalers are not approved for use in patients below 4 or 5 years of age. One ICS, budesonide, available as an inhalation suspension to be used with nebulizers, is approved for use in patients 1 year of age and older. Montelukast is not approved for asthma in patients below 1 year of age.

4. Regulatory history of LABAs relevant to this meeting

a. Salmeterol-containing products

There are four salmeterol-containing products approved for marketing in the United States for the treatment of asthma. These are Serevent (salmeterol xinafoate) Inhalation Aerosol approved in 1994, Serevent Diskus (salmeterol xinafoate inhalation powder) approved in 1996, Advair Diskus (fluticasone propionate and salmeterol inhalation powder) approved in 2000, and Advair HFA (fluticasone propionate and salmeterol) Inhalation Aerosol approved in 2006. GlaxoSmithKline (GSK) has discontinued marketing of the CFC- propelled Serevent Inhalation Aerosol in the United States. The approved age ranges for the asthma indications for these products are as follows: Serevent Diskus and Advair Diskus are for patients 4 years of age and older; Advair HFA Inhalation Aerosol is for patients 12 years of age and older; Serevent Inhalation Aerosol was for patients 12 years of age and older prior to its removal from the market because of the CFC phase-out.

The clinical development program conducted by GSK to support an asthma indication for salmeterol was typical of a drug in this class. The Serevent Inhalation Aerosol phase 3 program included two placebo- and active-controlled (albuterol inhalation aerosol) 12-week studies in patients 12 years of age and older (n=556). The Serevent Diskus phase 3 program included two placebo- and active-controlled (albuterol inhalation aerosol) 12-week studies in patients 12 years of age and older (n=451), one placebo-controlled 12-week study in patients 4 years of age and older (n=449), and four studies in patients with asthma on concomitant ICS to assess the effect of adding salmeterol (n=1,922). The latter studies utilized the inhalation aerosol formulation of salmeterol for a treatment period of 6 months. The Advair Diskus phase 3 program included three 12-week studies in patients 12 years of age and older, where Advair Diskus was compared to its individual components fluticasone and salmeterol, and to placebo (n=1,208), and one 12-week study in patients 4 to 11 years of age where Advair Diskus was compared to fluticasone (n=203). The Advair HFA Inhalation Aerosol phase 3 program included four 12-week studies in patients 12 years of age and older where Advair HFA was compared to its individual components fluticasone and salmeterol (n=1517). These studies supported the efficacy and safety of salmeterol both as a single ingredient product and as a combination product with fluticasone in patients with asthma. These studies did not show safety signals of asthma-related death or severe asthma exacerbations.

Serevent Inhalation Aerosol, approved in 1994, was the first salmeterol-containing product approved for marketing in the United States for use in patients with asthma. At that time, there were concerns that the chronic use of beta-agonists in patients with asthma may worsen asthma control in some patients. Although the clinical program conducted to support registration of Serevent Inhalation Aerosol did not show any signal of acute exacerbation or asthma worsening, there were literature reports suggesting that chronic use of salmeterol may worsen asthma. The Serevent Nationwide Surveillance Study (SNS study), published in 1993, involved approximately 25,000 patients with asthma (16,787 on salmeterol and 8,393 on albuterol) and showed that chronic use (16 weeks) of salmeterol was associated with a small and statistically non-significant excess of asthma-related deaths compared with chronic use of albuterol (0.07% compared to 0.02%, a relative risk of 3) (7). Early post-marketing adverse reports also suggested that salmeterol use may lead to severe adverse asthma outcomes, including death. However, in such cases where the adverse event of interest is a manifestation of the disease being treated, spontaneous adverse event reporting alone cannot establish causality. Due to accumulating concerns regarding the safety of chronic, regular use of beta-agonists in general and salmeterol specifically, FDA worked with GSK to have them conduct a large, controlled, prospective safety study to address this issue. As a result, GSK initiated the Salmeterol Multicenter Asthma Research Trial (SMART) in 1996 and halted the study in 2003. The study is published in the literature along with a number of commentaries and perspectives and is briefly described below (8-12).

The SMART was a randomized, double-blind study that enrolled patients 12 years of age and older with asthma not currently using LABAs (average age of study subjects was 39 years; 71% Caucasian, 18% African American, 8% Hispanic) to assess the safety of salmeterol (Serevent Inhalation Aerosol, 42 mcg twice daily for 28 weeks) compared to placebo when added to usual asthma therapy. The study consisted of one clinic visit during which baseline

demographic information, medical history, asthma history, concomitant medication use, vital signs, and peak expiratory flow measurements were obtained. To be enrolled, patients were required to have a diagnosis of asthma, be treated with prescription asthma medications other than a LABA, and be free of significant systemic diseases. Study medication was dispensed at the clinic visit, and the patients were contacted by phone at approximately weeks 4, 8, 12, 16, 20, 24, and 28. Due to practical issues of powering such a study to detect important differences in a very rare event, the primary endpoint was defined as the combined number of respiratory-related deaths or respiratory-related life-threatening experiences (intubation and mechanical ventilation). Despite this primary endpoint, the interest of the Agency was to look specifically at issues of mortality, specifically asthma-related death. The study initially was intended to enroll 30,000 patients, with 15,000 patients per treatment arm, to detect relative-risk differences of 1.4 between salmeterol and placebo for the primary endpoint and 3 for asthma-related death. After approximately 15,000 patients had been enrolled, the Data Safety Monitoring Board noted that the observed occurrence of the primary endpoint overall was approximately half of what had been expected. As a result, the sample size was then revised to enroll 60,000 patients, or 30,000 patients per treatment arm. GSK halted the study prematurely in January 2003, after approximately 30,000 patients had been enrolled, because a planned interim analysis suggested that salmeterol may be associated with an increased risk of severe asthma exacerbations including asthma-related death, particularly in African Americans. In addition, difficulty in enrolling patients would have precluded completing the study within an acceptable time frame.

GSK submitted preliminary summary results of the SMART to the Agency in February 2003. Subsequent to discussion with the Agency, in August 2003, GSK incorporated preliminary results of the SMART into all salmeterol-containing product labels, including the addition of a boxed warning cautioning the use of salmeterol in patients with asthma. Due to the seriousness and importance of the findings, the labeling changes were performed expeditiously before a full Agency review of the SMART data. Following a comprehensive FDA review of the complete study results, in September 2004, there were additional changes in both the data content and the language in the product label. Changes were again made to the labeling language after the July 13, 2005, PADAC meeting.

There are two important points regarding GSK's analysis of the SMART data that should be noted. First, GSK decided to include the spontaneously reported post-study adverse events for 6 months beyond the 28 weeks controlled portion of the study, and second, GSK decided to include data from a National Death Index (NDI) search to capture as many of the outcome events as possible. The protocol did not pre-specify inclusion of the NDI data or the 6 month post-study adverse events data in the analysis data set. The Agency disagreed with GSK's position of including events beyond the protocol-specified 28-week study period in the analysis because this post-study period was not controlled, and it was possible that patients could take approved treatments for asthma, including salmeterol, once they had completed the 28 weeks of protocol-specified treatment. Table 2 shows the results of the primary endpoint and asthma-related death in SMART, with asthma-related death being the endpoint of interest. The analysis shown in the table does not include events that occurred beyond the 28-week treatment period, but does include events identified in the NDI search.

Table 2. Overall incidence of primary endpoint and asthma-related death (SMART)

	Serevent MDI (n=13,176)	Placebo (n=13,179)	Relative Risk (95% CI)
Primary Endpoint: Respiratory-related deaths or life-threatening experiences			
Total	50 (<1%)	36 (<1%)	1.40 (0.91, 2.14)
Caucasians	29 (<1%)	28 (<1%)	1.05 (0.62, 1.76)
African Americans	20 (<1%)	5 (<1%)	4.10 (1.54, 10.90)
Secondary Endpoint: Asthma-related death			
Total	13 (<1%)	3 (<1%)	4.37 (1.25, 15.34)
Caucasians	6 (<1%)	1 (<1%)	5.82 (0.70, 48.37)
African Americans	7 (<1%)	1 (<1%)	7.26 (0.89, 58.94)

While there is interest in assessing the influence of concomitant ICS use on the effect of salmeterol, the SMART study was not adequately designed to assess this issue for several reasons. For instance, use of ICS was not randomly assigned and the data for ICS use was collected only at baseline, not throughout the treatment period. Furthermore, data for ICS use at baseline did not contain detailed information on the type of ICS or the dose of the ICS reported to be used. Nevertheless, the data were analyzed based on baseline ICS use (Table 3). The numbers of events in the subgroups were too small to form the basis of any firm conclusion. However, reported use of ICS at baseline did not appear to have any notable “protective” effect in the African American cohort in whom the signal of concern was most noticeable.

Table 3. Primary and selected secondary outcomes by baseline inhaled corticosteroid use (SMART)

	Inhaled Corticosteroids at baseline			No Inhaled Corticosteroids at baseline		
	Serevent	Placebo	Relative Risk	Serevent	Placebo	Relative Risk
Number of patients						
Total	6127	6138		7049	7041	
Caucasians	4586	4637		4695	4724	
African Americans	906	875		1460	1444	
Primary Endpoint: Respiratory-related deaths or life-threatening experiences						
Total	23	19	1.21 (0.66, 2.23)	27	17	1.60 (0.87, 2.93)
Caucasians	13	15	0.88 (0.42, 1.84)	16	13	1.25 (0.60, 2.60)
African Americans	9	3	3.02 (0.82, 11.11)	11	2	5.61 (1.25, 25.26)
Secondary Endpoint: Asthma-related death						
Total	4	3	1.35 (0.30, 6.04)	9	0	
Caucasians	1	1	0.96 (0.06, 15.35)	5	0	
African Americans	3	1	3.12 (0.33, 29.92)	4	0	

The labeling changes based on the SMART data, including the boxed warning, were applied to all salmeterol-containing products, including Advair Diskus and Advair HFA Inhalation Aerosol (fluticasone propionate and salmeterol) labels because there were no clinical trial data to show that fluticasone ameliorated the risk of salmeterol. Further, there was no mechanistic basis of interaction between the two drugs at a cellular or sub-cellular level that could explain how fluticasone would negate the effect of salmeterol. Although the SMART study was conducted in patients 12 years of age and older, the labeling language was applied to all approved ages (i.e. patients 4 years of age and older), because there was no reason to

believe that the safety signal seen in SMART in patients 12 years of older would not apply to younger children.

b. Formoterol-containing products

There are two formoterol-containing products approved and marketed in the United States for the treatment of asthma. These are Foradil Aerolizer (formoterol fumarate inhalation powder) approved in 2001, and Symbicort (budesonide and formoterol fumarate) Inhalation Aerosol approved in 2006. Foradil Aerolizer is approved for use in patients with asthma 5 year of age and older; the recommended dose is 12 mcg every 12 hours. Symbicort is approved for use in patients with asthma 12 years of age and older.

The clinical development program conducted by Novartis to support the asthma indication for Foradil Aerolizer was typical of a drug in this class. The Foradil Aerolizer phase 3 program included two placebo- and active-controlled (albuterol inhalation aerosol) 12-week studies in patients 12 years of age and older with mild-to-moderate asthma (n=1,095), and one placebo-controlled 1-year study in patients 5-12 years of age with asthma (n=518). In each of the three studies, two different doses of formoterol were used: 12 mcg every 12 hours and 24 mcg every 12 hours. The three studies supported the efficacy of formoterol; however, there did not seem to be an additional benefit with the higher dose.

The clinical development program conducted by AstraZeneca to support the asthma indication for Symbicort Inhalation Aerosol was typical of a drug in this class. The Symbicort phase 3 program included one placebo- and active-controlled (budesonide, and formoterol) 12-week study in patients 12 years of age and older with moderate-to-severe asthma (n=596), and one 12-week study in patients 12 years of older with mild-to-moderate asthma (n=480). The two studies supported the efficacy and safety of Symbicort in patients with asthma.

In the safety assessment of the Foradil Aerolizer studies, it was noted that formoterol 24 mcg every 12 hours tended to be associated with more episodes of serious asthma exacerbations as compared to formoterol 12 mcg every 12 hours (Table 4). A serious asthma exacerbation was defined as an asthma exacerbation that resulted in a life-threatening experience, inpatient hospitalization or prolongation of hospitalization, persistent disability or incapacity, or death. Because of the safety concerns with asthma exacerbations seen consistently across the pivotal phase 3 studies with formoterol 24 mcg, and due to the absence of clear benefits of 24 mcg over the 12 mcg dose, only the 12 mcg every 12 hours dose of formoterol was approved for marketing in the United States (13).

Table 4. Occurrence of serious asthma exacerbations* in three asthma studies with formoterol, results expressed as number of patients with serious asthma exacerbation/total patients in the study (%)

	Placebo	Albuterol 180 mcg BID	Formoterol 12 mcg BID	Formoterol 24 mcg BID
12-wk study in adults and adolescents (study 040)	0/136 (0%)	2/134 (1.5%)	0/136 (0%)	4/135 (3%) [†]
12-wk study in adults and adolescents (study 041)	2/141 (1.4%)	0/138 (0%)	1/139 (0.7%)	5/136 (3.7%) [‡]
1-yr study in 5-12 year old children (study 049)	0/176 (0%)	NA	8/171 (4.7%)	11/171 (6.4%)

	Placebo	Albuterol 180 mcg BID	Formoterol 12 mcg BID	Formoterol 24 mcg BID
* Life-threatening experience, hospitalization, prolongation of hospitalization, persistent disability, or death				
† 1 patient required intubation				
‡ 2 patients had respiratory arrest, 1 of the patients died				

As a result of concerns arising from the possibility of acute exacerbation and worsening of asthma with the use of the long-acting beta-agonist, salmeterol, and the findings of the formoterol phase 3 studies, the Agency asked Novartis to perform a phase 4 clinical study to further investigate the relative safety of the two different doses of formoterol. The study was started in 2002 and completed in 2004. The study is published in the literature (14). The study is briefly described below.

The formoterol phase 4 study was a randomized, blinded, placebo-controlled study of 16 weeks duration in 2,307 patients 12 years of age and older with mild-to-moderate persistent asthma (average age 38 years; 79% Caucasian, 13% African American). The study consisted of one baseline visit and subsequent visits in weeks 1, 4, 8, 12, and 16, during which vital signs, physical examination, pre-and 2-hour post-dose spirometry, and concomitant medication use were recorded, and adverse events were solicited. This study allowed liberal use of anti-inflammatory medications. More patients enrolled in this phase 4 study received ICS during the study than those in the phase 3 studies (58% vs. 47%). Patients were randomized approximately equally to receive Foradil Aerolizer 12 mcg BID, Foradil Aerolizer 24 mcg BID, Foradil 12 mcg BID with up to two additional on-demand 12 mcg doses per day, and placebo. The Foradil fixed-dose groups and placebo group were treated in double-blind fashion, and the Foradil on-demand group was open-label. There were no deaths in this study. Key safety findings of interest are shown in Table 5.

Table 5. Occurrence of asthma exacerbations, results expressed as number of patients with event (%)

	Formoterol 12 mcg BID (n=527)	Formoterol 24 mcg BID (n=527)	Placebo (n=514)	Formoterol Open-label (n=517)
Serious asthma-related adverse events	5 (0.9%)	2 (0.4%)	1 (0.2%)	1 (0.2%)
Serious asthma exacerbations *	3 (0.6%)	2 (0.4%) †	1 (0.2%)	1 (0.2%)
* Life-threatening experience, hospitalization, prolongation of hospitalization, persistent disability, or death				
† 1 patient required intubation				

The patients who had serious asthma-related adverse events satisfied the criteria by virtue of requiring hospitalization. The information about serious asthma exacerbations was generated by the Agency following the criteria that were used in the phase 3 program. Two patients had serious asthma exacerbations, one in the Foradil 12 mcg BID group and one in the Foradil 24 mcg BID group; one patient required intubation. The overall rates of events of interest in this relatively small study were too low to draw any firm conclusion, although the trends were in the direction of the phase 3 study finding. The lower age bound of this phase 4 study was 12 years, whereas in the phase 3 clinical program a numerically stronger signal was seen in the pediatric study that enrolled children 5 to 12 years of age (Table 4).

At the July 13, 2005, PADAC meeting, the Committee reviewed the data on salmeterol and formoterol presented above, and recommended via unanimous vote that formoterol-containing product labels should include warning statements similar to salmeterol (1). This recommendation was made because both salmeterol and formoterol belong to the same class of drugs, and without convincing negative safety data with formoterol, the safety finding seen with salmeterol should be applied to formoterol. Furthermore, the signal of serious asthma exacerbation seen with formoterol in considerably smaller studies was concerning. Following the PADAC recommendation, the labels for all formoterol-containing products were changed to include a warning statement, including a boxed warning regarding asthma-related death.

Asthma exacerbations with formoterol were also seen in the phase 3 studies conducted by AstraZeneca to support approval of Symbicort (budesonide and formoterol fumarate). As stated above, Symbicort was approved in 2006 based on two phase 3 studies. Study 1 was conducted in patients with moderate-to-severe asthma where Symbicort 160/4.5 was used, and study 2 was conducted in patients with mild-to-moderate asthma where Symbicort 80/4.5 was used. Both studies required that patients who satisfied pre-defined asthma worsening criteria be withdrawn. The pre-defined asthma withdrawal criteria were a clinically important decrease in FEV₁ or PEF, increase in rescue albuterol use, nighttime awakening due to asthma, emergency intervention or hospitalization due the asthma, or requirement of asthma medication not allowed in the protocol. The percentages of patients meeting the withdrawal criteria in the two studies are shown in Table 6. There were more patients in the formoterol-alone treatment arm, compared to other active treatment arms, satisfying the total pre-defined asthma withdrawal criteria. When each of the criteria was examined individually there were more patients in the formoterol-alone treatment arm with a decrease in FEV₁, decrease in PEF, and clinical asthma exacerbation. In study 1, the study in patients with more severe asthma, the frequency of patients satisfying these criteria were similar for the formoterol-alone and placebo arms.

Table 6. Number (percentage) of patients meeting asthma withdrawal criteria *

Study 1	Symb n = 124	Bud n = 109	For n = 123	Bud + For n = 115	Pbo n = 115
Total [†]	37 (29.8)	48 (44.0)	68 (55.3)	24 (20.9)	84 (67.2)
-- Decrease in FEV1	4 (3.2)	7 (6.4)	15 (12.2)	8 (7.0)	14 (11.2)
-- Rescue medication use	2 (1.6)	3 (2.8)	3 (2.4)	0 (0.0)	7 (5.6)
-- Decrease in AM PEF	2 (1.6)	5 (4.6)	17 (13.8)	5 (4.3)	15 (12.0)
-- Nighttime awakening [‡]	24 (19.4)	29 (26.6)	32 (26.0)	11 (9.6)	49 (39.2)
-- Clinical exacerbation	7 (5.6)	5 (4.6)	17 (13.8)	6 (5.2)	16 (12.8)
Study 2	Symb n = 123	Bud n = 121	For n = 114	-	Pbo n = 122
Total [†]	23 (18.7)	26 (21.5)	48 (42.1)	-	69 (56.6)
-- Decrease in FEV1	3 (2.4)	3 (2.5)	11 (9.6)	-	9 (7.4)
-- Rescue medication use	1 (0.8)	3 (2.5)	1 (0.9)	-	3 (2.5)
-- Decrease in AM PEF	3 (2.4)	1 (0.8)	8 (7.0)	-	14 (11.5)
-- Nighttime awakening [‡]	17 (13.8)	20 (16.5)	31 (27.2)	-	52 (42.6)
-- Clinical exacerbation	1 (0.8)	3 (2.5)	5 (4.4)	-	20 (16.4)
* Assessed on a daily basis with the exception of FEV ₁ , which was assessed at each clinic visit					

[†] Individual criteria are shown for patients meeting any predefined criteria regardless of withdrawal status

^{*} Patients allowed to remain in the study at investigator discretion if none of the other criteria were met

5. Asthma-related death with chronic use of inhaled short-acting beta-agonists (SABA)

Concerns of asthma-related death with inhaled beta-agonist bronchodilators are not unique to LABAs. It has been known for some time that SABAs can also worsen asthma and cause asthma-related death in some patients (Figure 1). During the 1940s and 1950s there was a slight rise in asthma-related death and concerns about a possible link to inhaled epinephrine were raised (15). The increase in death was small and the cause unclear, and new inhalation aerosols were introduced to the market in many countries in the 1950s and 1960s. At that time another non-selective (beta1 and beta2) SABA, isoproterenol, was suspected in the development of refractory asthma and asthma-related death in patients who used it in excess (16, 17). In the 1960s there was a substantial increase in asthma-related deaths in the UK, Australia, and New Zealand, which coincided with market introduction of the inhalation aerosol, isoproterenol forte, which contained 2-8 times more isoproterenol per administration than the standard preparation. During the same time period, asthma-related deaths did not increase in countries like the Netherlands, where isoproterenol forte was introduced late and sales volume was low, or in the USA and Canada, where isoproterenol forte was never marketed. This was despite an approximate 3-fold increase in per capita alternate inhaled bronchodilator use in the United States (18). In the mid 1970s, there was another substantial increase in asthma-related deaths in New Zealand. The increase coincided with market introduction and rising sales of inhaled fenoterol, another relatively non-selective SABA (19-21). A subsequent cohort study from Saskatchewan, Canada, showed that the chronic use of high-dose inhaled fenoterol was associated with an increased risk of asthma-related death compared with albuterol (22, 23). The same study also suggested a more general association between inhaled beta-agonists, including inhaled albuterol, and asthma-related death (23). However, the conclusion regarding inhaled albuterol remained controversial (24).

Subsequent prospectively designed controlled studies with inhaled albuterol did not show any beneficial or harmful effects with scheduled inhaled albuterol treatment. A study comparing regular inhaled albuterol use and as needed albuterol use for 16 weeks showed no difference in various measures of asthma control (25). Another study comparing regular use of inhaled albuterol and regular use of inhaled albuterol with ICS for 12 months showed no difference in asthma exacerbation between the two groups (26). Based on the available data, both NAEPP and GINA do not recommend daily, scheduled, long-term use of any SABAs, including inhaled albuterol (4, 5).

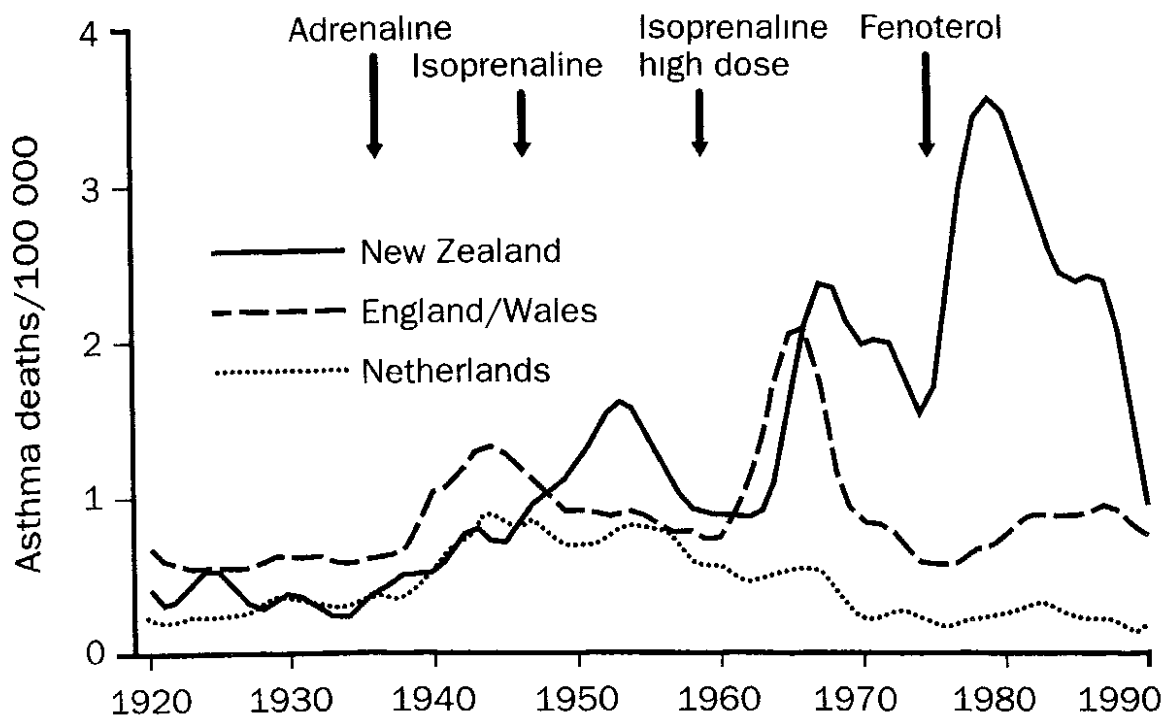


Figure 1. Changes in asthma mortality (5-34 age group) in three countries in relation to the introduction of some inhaled asthma medications (from reference 27)

6. Possible mechanism of asthma-related death with inhaled beta-agonists

The mechanisms by which inhaled SABAs and LABAs may cause asthma-related death are not known. It is reasonable to assume that the mechanisms are similar, as the basic pharmacological actions of both medication classes are the same. Both SABAs and LABAs directly relax airway smooth muscle by stimulation of beta2-receptors, which increases cyclic AMP and produces functioning antagonism to bronchoconstriction. Both SABAs and LABAs are devoid of any clinically apparent anti-inflammatory activity. The principal difference between the two classes is the longer duration of bronchodilation offered by LABAs as compared to SABAs.

Both the controlled and epidemiological studies described in sections 4 and 5 were not designed to identify the underlying mechanism(s) by which these drugs increase asthma-related death. However, these studies did point to two possible contributing factors: (1) use of high doses of the drugs, as was seen with isoproterenol, fenoterol, and formoterol; and (2) use of less selective beta-agonist drugs, as was seen with epinephrine, isoproterenol, and fenoterol.

Two fundamental mechanisms have been hypothesized as the cause of asthma-related death with SABAs and LABAs: (1) Beta-agonists are known to reduce protection against bronchoconstricting stimuli, which may paradoxically result in more severe obstruction in patients on chronic SABA or LABA therapy when exposed to bronchoconstricting stimuli, as

compared with patients not on these drugs. Reduced protection against bronchoconstricting stimuli by beta-agonists has been observed with a wide range of such stimuli, including methacholine, histamine, adenosine monophosphate, exercise, cold air, and allergens (28-32). Reduced protection against bronchoconstrictor stimuli by beta-agonists is not prevented by the co-administration of ICS (33). (2) Effective bronchodilation achieved through chronic beta-agonist therapy may mask symptoms of deteriorating asthma, leading to a delay in seeking appropriate medical attention and catastrophic increase in airway obstruction.

To date, genetic studies conducted to understand the cause(s) of serious asthma exacerbation and asthma-related death with chronic use of SABAs and LABAs are limited, and have not produced conclusive results. However, some useful data have been generated with inhaled albuterol. Genetic studies have mostly focused on codon 16 of the beta2-receptor, which is known to be polymorphic, with the common type being homozygous for glycine (Gly/Gly 16) and the rare type being homozygous for arginine (Arg/Arg 16). One study showed that with chronic albuterol treatment, patients with the Arg/Arg 16 genotype experienced more exacerbations compared to patients with the Gly/Gly 16 genotype (34). Two studies, one retrospective and the other prospective, showed that with chronic albuterol treatment, patients with the Arg/Arg 16 genotype were more likely than patients with the Gly/Gly 16 genotype to experience a decline in lung function (35, 36). It is not known if the patients in whom lung function declines with albuterol are the same patients who develop serious asthma exacerbation and asthma-related death. Genetic studies with LABAs assessing the role of polymorphism of codon 16 of the beta2-receptor have produced inconclusive results. One study showed that with chronic salmeterol and ICS combined treatment, patients with the Arg/Arg 16 genotype had poor clinical response compared to patients with Gly/Gly 16 (37). Two other studies showed that with chronic salmeterol and ICS combined treatment, there was no difference in the clinical response between Arg/Arg 16 and Gly/Gly 16 genotypes (38, 39).

7. Risk-benefit analysis of chronic use of inhaled LABAs in the treatment of asthma

Risks, benefits, and risk-benefit analysis of inhaled LABAs for both adults and children are discussed in the following sections. The discussion regarding the use of inhaled LABAs in adults is more detailed, as most of the available data are in adult and adolescent patients 12 years of age and older.

a. Risks of inhaled LABAs in adults

The main risk of inhaled LABAs in patients with asthma is asthma-related death as discussed in section 4 above. Large controlled studies with salmeterol have clearly shown an increased risk of asthma-related death in patients using salmeterol. Studies with formoterol were smaller compared to the studies with salmeterol, but even these smaller studies revealed concerning findings regarding serious asthma exacerbations with formoterol. Though there are some differences between the two drugs, salmeterol and formoterol belong to the same pharmacological class and as a result, we have treated them equally from a safety perspective. There is neither compelling data nor scientific rationale to suggest that the

safety profiles of the two drugs would differ. In fact, available data suggest that the safety risk of asthma-related death for the two drugs is qualitatively similar. Subsequent to the July 13, 2005, PADAC discussion of the salmeterol and formoterol studies and publication of these studies in the literature, two major meta-analyses investigating the association of asthma-related death and serious asthma exacerbation with salmeterol and formoterol were published (40, 41). These meta-analyses further support the association of asthma-related death with use of both of these LABAs, and are briefly described below.

One meta-analysis combined data from 19 studies with salmeterol and formoterol involving a total of 33,826 patients (40). This meta-analysis showed that inhaled LABAs increased asthma-related death (odds ratio 3.5, 95% confidence interval 1.3, 9.3; relative risk 4.4, 95% confidence interval 1.3, 15.3), increased life-threatening asthma exacerbations (odds ratio 1.8, 95% confidence interval 1.1, 2.9), and increased hospitalizations for asthma exacerbation (odds ratio 2.6, 95% confidence interval 1.6, 4.3). In this meta-analysis, the majority of the data from which the increase in asthma-related death was derived originated from SMART. SMART data also accounted for 80% of the data used to conclude that inhaled LABAs lead to an increase in life-threatening asthma exacerbations. Hospitalization data were from other studies because SMART did not capture hospitalization events.

A Cochrane Library systematic review combined data from 26 studies comparing salmeterol to placebo and 8 studies comparing salmeterol to albuterol. The two sets of studies involved a total of 62,630 patients, including 2,380 children (41). This meta-analysis showed results similar to the meta-analysis discussed above. To ascertain the possible effect of ICSs, the authors combined individual patient data from the SNS and SMART studies based on baseline ICS use, which was the only information on ICS available from these studies. The authors concluded that asthma-related death in patients not taking ICS at baseline was increased (odds ratio 9.52, 95% confidence interval 1.24, 73.09). The authors could not rule out an increase in asthma-related death in patients taking ICS at baseline because the confidence interval was too wide (odds ratio 1.52, 95% confidence interval 0.51, 4.49). The authors acknowledge that it is not possible to draw firm conclusion about the risk of salmeterol when used with ICS, as the patients in these two studies were not randomized to ICS treatment. The authors state that their meta-analysis neither demonstrates that ICS abolish the risk of asthma-related death in patients taking salmeterol, nor can they assume mortality rate might not even be lower if ICS were taken alone (41).

Other safety concerns of LABAs are typical of inhaled beta-agonists. Like other sympathomimetic drugs, inhaled LABAs can cause cardiovascular effects, such as increased heart rate and increased blood pressure; metabolic effects, such as increased blood glucose and decreased serum potassium; direct muscle effects manifested as tremor and CNS excitability. These events are rare with inhaled LABAs because the inhaled doses that are approved for use are much lower than the doses known to cause systemic effects. Patients taking inhaled LABAs rarely experience ear, nose, and throat irritation, and respiratory irritation, such as cough, tracheitis, and bronchitis. These events are described in the product labels of these drugs.

b. Risks of inhaled LABAs in children

The risk of inhaled LABAs as discussed above for adults also applies to children 12 years of age and older because most of the clinical studies that evaluated safety were conducted in this age cohort. These include the two large controlled studies with salmeterol, the SNS study and the SMART, and the controlled formoterol studies. In these studies a reasonable number of children 12 years of age and older were enrolled. Based on these studies, there were no remarkable differences in the safety findings between adults and children 12 years of age and older.

Reasonable safety data are available in children 4 to 11 years of age. Although there are no controlled studies of the magnitude of SNS and SMART that included children below 12 years of age, there are a number of smaller controlled studies. Phase 3 controlled studies conducted for product registration in the United States included one 12-week study with Serevent Diskus in patients 4 years of age and older (n=449), one 12-week study with Advair Diskus in patients 4 years of age and older (n=203), and one 1-year study with Foradil Aerolizer in patients 5 years of age and older (n=518). There were no asthma-related deaths in these three controlled studies. Serious asthma exacerbation was more frequent with formoterol compared to placebo in the formoterol pediatric study (Table 4). The Cochrane Library systematic review of salmeterol described above also presented data for adults and children separately (41). The authors state that the number of children contributing to various outcomes of interest was small, which makes the results considerably uncertain. Asthma-related death was rare in children. For the non-fatal serious adverse reactions, the numerical trends for children were similar to adults. The overall data do not appear to suggest that the safety risk with LABAs is higher in children 4 to 11 years of age compared to older children and adults. The pathophysiology of the disease is the same, response to LABAs are expected to be the same, and the target of LABAs, the beta-receptors, also function similarly in the two age cohorts. Therefore, the products carry the same labeling warning irrespective of age, with the conclusion that the asthma-related death risk seen in studies conducted in adult and adolescent patients 12 years of age and older also applies to children 4 to 11 years of age.

Specific risk discussion for patients below 4 years of age is not relevant because inhaled LABA-containing products are not approved for use in this age group.

c. Benefits of inhaled LABAs in adults

Inhaled LABAs are clearly effective and beneficial in the treatment of asthma. The principal benefits patients derive from these drugs are from bronchodilation that results in improved pulmonary function, and decreased need for rescue short-acting bronchodilator use for asthma exacerbations. The labeled indications (see the Indication and Usage section of product labels containing salmeterol or formoterol) of inhaled LABAs are for maintenance treatment of asthma and in the prevention of bronchospasm, including symptoms of nocturnal asthma, and for prevention of exercise-induced bronchospasm.

For U.S. registration of single-ingredient products containing either salmeterol or formoterol, companies performed placebo-controlled, active-controlled, or both types of studies to show superiority of these drugs over placebo (studies are summarized in Sections 4.a. and 4.b. above, and the studies and results are described in the product labels of these drugs). In all of these studies, inhaled LABAs showed significant post-dose bronchodilation (as measured by serial FEV₁ for 12 hours post-dose) without tachyphylaxis to the bronchodilator effect. LABAs also improved morning and evening peak expiratory flow rate (PEFR), reduced nocturnal awakening from asthma, and reduced rescue medication use.

For U.S. registration of combination products containing either salmeterol or formoterol with ICS, companies performed factorial design studies to show the contribution of each component to the efficacy of the combination product. Typical treatment arms were LABA+ICS, LABA, and ICS. In these studies, LABA+ICS was compared to LABA on pre-dose trough FEV₁ or on pre-defined asthma worsening criteria (comprised of pre-defined decrease in FEV₁ or PEFR, increase in rescue albuterol use, increase in nighttime waking due to asthma, emergency intervention or hospitalization) to show contribution of the ICS; LABA+ICS was compared to ICS on post-dose FEV₁ to show contribution of the LABA. Some studies had placebo comparator arms as well (studies are summarized in sections 4.a. and 4.b. above, and the studies and results are described in the product labels of these drugs). In these studies, combination products improved pre-dose FEV₁, asthma worsening, and post-dose serial FEV₁, compared to either single ingredient products, which would be expected with the presence of both ICS and LABA in the same product. The LABA+ICS combination products also showed a clinically meaningful improvement in the overall Asthma Quality of Life Questionnaire (AQLQ) score compared to placebo. The clinically meaningful improvement was defined as a 0.5 point or more increase (0.5 point is recognized as the minimally important difference for the AQLQ instrument) from baseline to the end of treatment with LABA+ICS combination product over the increase from baseline to the end of treatment with placebo. Combination products containing LABA+ICS are the only products for asthma that show a clinically meaningful improvement in the AQLQ score.

To further investigate the effect of LABA monotherapy and LABA+ICS combination therapy, some large studies conducted with industry or public funding have been published in the literature (42-47). These studies have further demonstrated the efficacy of LABAs either alone or in combination with ICS. These studies generally have shown superior efficacy of LABA+ICS combination therapy over either LABA or ICS alone, at the same dose of ICS used in the combination therapy (42-47). The NAEPP and GINA recommendations on LABAs were informed by these studies, the efficacy and safety studies conducted for product registration, and the safety studies reviewed in Section 4 above.

d. Benefits of inhaled LABAs in children

The benefits of inhaled LABAs discussed for adults apply to children 12 years of age and older because most of the clinical studies that evaluated efficacy were conducted in patients 12 years of age and older. This includes all the studies, with the exception of dedicated pediatric studies (< 12 years of age), conducted for U.S. product registration (discussed in Section 4 and 5c above), and most of the large studies conducted with industry or public

funding that are published in the literature (43-47). The efficacy findings were consistent when examined across different age groups in these studies.

Reasonable efficacy data are available in children 4 to 11 years of age. As discussed in section 4, dedicated phase 3 studies were conducted in children of these ages with salmeterol and formoterol. These included one 12-week study with Serevent Diskus in patients 4 years of age and older (n=449), one 12-week study with Advair Diskus in patients 4 years of age and older (n=203), and one 1-year study with Foradil Aerolizer in patients 5 years of age and older (n=518). Efficacy findings in these studies were consistent with studies conducted in patients 12 years of age and older. One of the aims of the dedicated pediatric studies was to show that the selected dose was efficacious in patients 4 to 11 years of age, as efficacy of drugs acting locally in the lung cannot be convincingly shown by other means such as plasma drug concentration. These studies have identified effective doses for children 4 to 11 years of age.

Specific benefit discussion for patients below 4 years of age is not relevant because inhaled LABA-containing products are not approved for use in this age group.

e. Risk-benefit analysis of inhaled LABAs in adults

Inhaled LABAs have a serious and significant safety risk of asthma-related death and serious asthma exacerbations. The magnitude of risk in an individual patient is difficult to ascertain because asthma-related death and serious asthma exacerbations caused by inhaled LABAs are difficult to separate from the natural history and progression of the disease. In a risk-benefit assessment of inhaled LABAs, one has to accept the existence of the risks of asthma-related death and serious asthma exacerbations, and make a judgment as to whether the benefits outweigh the risks.

The risk of asthma-related death with inhaled LABAs is numerically small. In the SMART, the number of deaths was 13 out of 13,176 for patients on salmeterol versus 3 out of 13,179 for patients on placebo. Excess death per 10,000 patients for the 28-week treatment period was 8 [95% confidence interval 3, 13]. On a population basis, the risk does not seem to have translated to an overall increase in asthma death in the United States. In fact, there has been no increase in asthma deaths in the United States since the introduction of inhaled LABAs in 1994. Rather, the asthma death rate flattened in the late 1990s and has shown a recent decline [see Figure 2] (48), despite the increased use of inhaled LABAs since their approval.

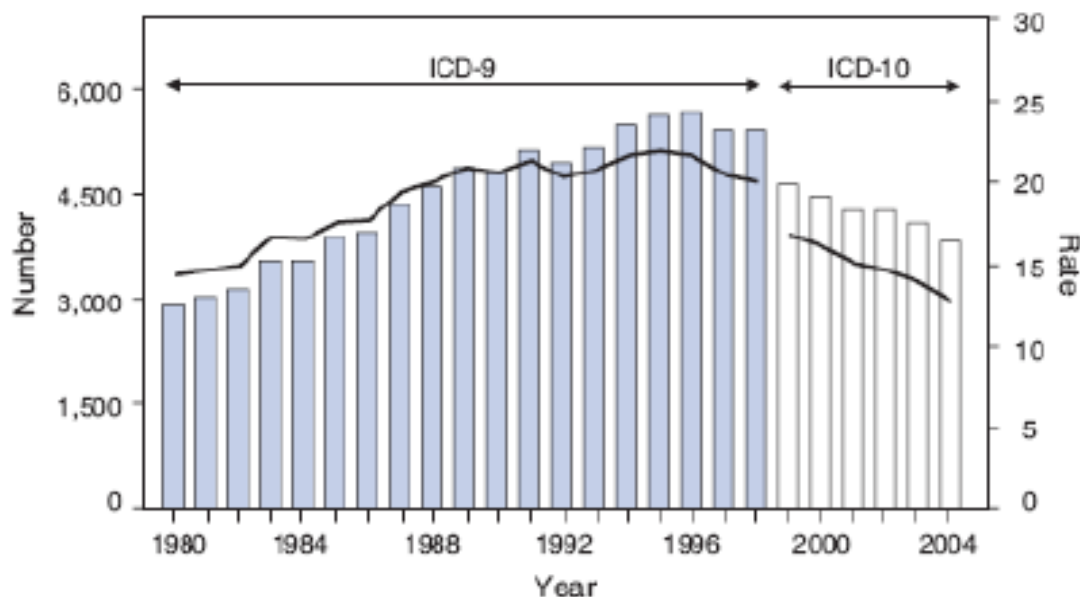


Figure 2. Number and rate (per million population, age-adjusted to 2000 US population) of asthma death in the United States, by year and International Classification of Disease (ICD). (from reference 48)

On the benefit side, most patients who take inhaled LABAs derive symptomatic clinical benefits in the form of improved lung function, reduced nocturnal awakening from asthma symptoms, and decreased need for rescue short-acting bronchodilator for asthma exacerbations. These benefits are not trivial for patients. Therefore, the balance is the risk of asthma-related death in a small number of patients versus the symptomatic benefit achieved in most patients. Removal of inhaled LABAs from the market as a treatment for asthma is a way of managing the risk of these drugs, but would be an extreme approach that could be problematic as discussed below.

Patients, health care providers, and society at large have accepted serious adverse reactions, and even death, in a small number of patients, for symptom control in a large number of patients. Examples include use of acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) for minor aches and pains. Both of these drugs are available over-the-counter in the United States. Acetaminophen can cause serious liver injury and even death in some patients taking doses within therapeutic range (49). Similarly, NSAIDs can cause serious gastro-intestinal bleeding and death in some patients taking doses within therapeutic range (50). For inhaled LABAs, the Agency has taken the approach to manage the safety risk through labeling, which is designed to inform patients and health care providers of the risk, thereby directing use of inhaled LABAs to the appropriate patient populations. This approach is consistent with the recommendation from the July 13, 2005, PADAC meeting, which recommended leaving the LABAs on the market with strengthened labeling. The product labels of all LABA-containing drugs have warning statements, including boxed warnings and Medication Guides. The major asthma management guidelines, such as NAEPP and GINA, also highlight the risk of asthma-related death with inhaled LABAs and recommend appropriate conditions for their use.

Since the availability of SMART data and other data, the indication of all LABA-containing products has been changed to ensure that they are used only when they are necessary. The Indication and Usage of LABA containing product labels reads as follows:

“[Product Name] is indicated for long-term, twice-daily (morning and evening) administration in the maintenance treatment of asthma and in the prevention of bronchospasm in patients [x] years of age and older with reversible obstructive airway disease, including patients with symptoms of nocturnal asthma. Long-acting beta2-adrenergic agonists, (such as salmeterol, [one of] the active ingredient in Serevent Diskus [Advair Diskus] [Advair HFA Inhalation Aerosol],) may increase the risk of asthma related death (see Warnings). Therefore, when treating patients with asthma, [Product Name] should only be used as additional therapy 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 2 maintenance therapies, including [Product Name]. It is not indicated for patients whose asthma can be managed by occasional use of inhaled, short-acting beta2-agonists or 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.”

The NAEPP and GINA recommendations on inhaled LABAs are consistent with the product labels for these drugs (4, 5). The NAEPP states that “LABAs are to be used in combination with ICS for long-term control and prevention of symptoms in moderate or severe persistent asthma,” and “LABAs are not to be used as monotherapy for long-term control of asthma.” Acknowledging the safety issue of asthma-related death with inhaled LABAs, NAEPP recommends that for “patients inadequately controlled on low-dose ICS, the option to increase the ICS dose should be given equal weight to the addition of LABA.” These statements and recommendations are intended to ensure that inhaled LABAs are used only when they are necessary and in the appropriate patient populations.

For patients inadequately controlled on a dose of ICS, the option is either to increase the dose of ICS, or to maintain the dose of ICS and add an inhaled LABA. The option chosen is informed by the profile of the patient. The circumstances of each patient will be variable, and the risk-benefit for one choice versus the other will also vary from patient to patient; therefore, the preferred option is to have the choices available to providers and patients and allow this important decision to be made at the point of health care delivery.

The NAEPP recommends inhaled LABAs as the preferred treatment to combine with ICS in patients 12 years of age and older, and as one of the preferred treatment to combine with ICS in patients younger than 12 years of age (4).

Removal of inhaled LABAs from the market would lead to the removal of one of the preferred long-term control medication classes for asthma and reduce choices for clinicians unable to control patients’ asthma on ICS alone. If inhaled LABAs were to be removed, patients who are not adequately controlled on ICS would require either inhaled SABAs chronically at high dose or another long-term control medication (See Section 2a; Table 1). Chronic use of inhaled SABAs may itself lead to asthma-related death as discussed in section 5 above. The available alternates to add to ICSs include cromones, omalizumab, leukotriene

modifiers, sustained release albuterol tablets, theophylline, and oral steroids. All of these therapies have shortcomings and limitations (See Section 2a).

One question that often arises is whether the single-ingredient inhaled LABA products should be removed from the market for the treatment of asthma in favor of fixed dose combination products containing a LABA+ICS. There are two points one needs to consider when entertaining such a scenario as discussed below.

First, removal of single ingredient inhaled LABAs in favor of fixed dose combination products containing an inhaled LABA and an ICS would restrict the choice of ICS for patients with asthma who need treatment with an ICS and an inhaled LABA. Patients would be forced to use either fluticasone with salmeterol, or budesonide with formoterol. Removal of choices of asthma controller therapies is not ideal when the choices of medications are already limited as discussed above in section 3. Availability of single ingredient medications allow health care providers to decide which specific ICS and inhaled LABA is ideal for an individual patient. Furthermore, in some instances, a health care provider may not want to use ICS for a patient for a particular reason, but may want to combine an inhaled LABA with another long-term control medication. Removal of single ingredient inhaled LABAs would prohibit individualized combination use and hinder physician choice and, potentially, patient care.

Second, there is no data from prospectively designed, controlled studies to show that combination products containing an inhaled LABA and an ICS abolish the risk of asthma-related death with inhaled LABAs. Controlled studies and meta-analyses do suggest that the number of asthma-related deaths is lower in patients taking LABA+ICS compared to LABA alone. This could be because a rare safety signal related to the underlying disease, such as asthma-related death, is more difficult to show in a group of patients who are better controlled (i.e., by being on an ICS). Additionally, the number of deaths in patients taking LABA plus ICS may not be negligible. The Cochrane Library systematic review that combined two large controlled studies with salmeterol, the SNS study and SMART, showed that the point estimate of the odds ratio of asthma-related death in patients taking ICS at baseline was higher in the salmeterol-treated group compared to the placebo treated group (odds ratio 1.52, 95% confidence interval 0.51, 4.49). The authors concluded that their analysis could not confirm that ICS abolish the risk of asthma-related death from inhaled LABA (41). Furthermore, there is no mechanistic basis of interaction between LABAs and ICSs at a cellular or sub-cellular level that could explain how an ICS would negate the risk of a LABA. Although the mechanism of asthma-related death caused by LABAs is not known, it is hypothesized that they reduce protection from bronchoconstrictor stimuli. If this mechanism has some role, then ICS would not be expected to be protective, as one study showed that ICS did not prevent the reduced protection from bronchoconstrictor stimuli due to a LABA (33).

If inhaled LABAs are to be removed from the market for asthma because of the asthma-related death safety risk, it may follow that the combination products containing inhaled LABAs and ICS should also be removed from the market because of the same qualitative safety risk.

While entertaining the option of removing products containing inhaled LABAs from the market in the United States, one needs to consider how this could be operationalized and what it really means for the treatment of asthma. Removal of inhaled LABAs from the market in the United States for asthma will, for all practical purposes, translate to the removal of the asthma indication for products containing salmeterol and formoterol. The actual products will remain in the market because of the COPD indication that these products carry. Therefore, health care providers and patients will still have access to these medications and there is no assurance that use of these products for asthma will not continue (i.e. off-label use). In addition, because the labeled indication for asthma with the specific recommendations regarding appropriate use would be removed, there would be even more concern that inhaled LABAs could be used inappropriately in patients with asthma.

f. Risk-benefit analysis of inhaled LABAs in children

The risk-benefit analysis of inhaled LABAs discussed above for adults applies to children 12 years of age and older because most of the clinical studies that inform this analysis were conducted in patients 12 years of age and older.

For patients 4 to 11 years of age the same risk-benefit analysis also applies because there are no data to show that the risk in patients 4 to 11 years of age is higher than patients 12 years of age and older or that the benefit in this age group is less. Rather, the scientific rationale and existing data suggest that the risk and benefit in patients 4 to 11 years of age is similar to those in patients 12 years of age and older. The current labeling, including Boxed Warning and recommendation for appropriate use, applies to children 4 years of age and older.

Specific risk-benefit analysis for patients below 4 years of age is not relevant because inhaled LABA-containing products are not approved for use in this age group.

8. Issues and questions for discussion

At the July 13, 2005, PADAC meeting the Committee discussed the risk-benefit of inhaled LABAs and recommended on unanimous vote that both salmeterol and formoterol containing products continue to be marketed in the United States. The Committee also recommended on unanimous vote that all salmeterol and formoterol containing products should have similar warning statements, including boxed warning statement (1). Since the July 13, 2005, PADAC meeting, there have been no large controlled safety studies conducted, and, therefore, there are no new original data to consider when making a risk-benefit analysis. As discussed in section 7.a. above, meta-analyses using existing data published since the July 13, 2005, PADAC meeting has confirmed the previous safety concerns of asthma-related death with LABAs. Sub-group analyses of pediatric data from the existing safety data presented at the November 27 and 28, 2008, PAC meeting has not shown any new or unique safety signal for pediatric patients. At the PAC, opinion was expressed that “salmeterol may have an unfavorable risk-benefit ratio in the treatment of pediatric asthma” (2), and Committee members discussed the possibility of removal of salmeterol from the market, but

it was concluded that an extensive discussion of the benefits in the context of risk was warranted (3).

This advisory committee meeting of the PADAC, DRASM, and PAC is convened to have a thorough and fully informed discussion of risks and benefits of inhaled LABAs, and advise the Agency on the basis of a risk-benefit assessment whether inhaled LABAs should continue to be marketed for the treatment of asthma for adult patients and for pediatric patients.

Below are issues for discussion, and questions for discussion and voting. These are tentative and may change prior to the meeting.

1. Discuss the risks of using LABAs for the treatment of asthma, including the possible effects of concomitant controller therapy, e.g. inhaled corticosteroids.
 - in adults and adolescents 12 years of age and older
 - in children 4 to 11 years of age
2. Discuss the benefits of using LABAs for the treatment of asthma, including the possible effects of concomitant controller therapy, e.g. inhaled corticosteroids.
 - in adults and adolescents 12 years of age and older
 - in children 4 to 11 years of age
3. Discuss and then vote on the following:
Based upon a risk benefit assessment, should LABAs continue to be marketed for the asthma indication?
 - in adults and adolescents 12 years of age and older
 - in children 4 to 11 years of age
4. If LABAs remain on the market for the treatment of asthma, are there any labeling changes or other risk mitigation strategies recommended?
 - in adults and adolescents 12 years of age and older
 - in children 4 to 11 years of age

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: **11/12/08**

To: Joint Meeting of the Pulmonary-Allergy Drugs Advisory Committee, Drug Safety and Risk Management Advisory Committee and Pediatric Advisory Committee on December 10-11, 2008

Through: Henry Francis, MD, MS
Deputy Director, Office of Surveillance and Epidemiology

From: Ann W. McMahon, M.D., M.S., Acting Director
Division of Pharmacovigilance II
and
Andrew D. Mosholder, MD, MPH
Shewit Bezabeh, MD, MPH
Division of Epidemiology
and
David J. Graham, MD, MPH
Office of Surveillance and Epidemiology

Subject: Risks and Benefits of Long-Acting Beta Adrenergic Agonists in the Treatment of Asthma

Drug Name (NDA numbers): Advair (021254, 021077)
Foradil (020831, 021279, 021592)
Serevent (020236, 020692)
Symbicort (021929)

Application Type: NDA

Applicant/sponsor: GlaxoSmithKline
Novartis
Astrazeneca

OSE RCM #: [2008-1042](#)

I. Introduction

Asthma is a chronic inflammatory disorder of the airways, with episodes of intermittent airway hyperresponsiveness and reversible airway obstruction. From 1980 to 1996, the prevalence of asthma in the United States increased. Although the pathophysiology of asthma is relatively well understood, the reason for the increased prevalence, and the exact etiology of the disease remain unclear. The prevalence of asthma within subpopulations in the United States varies somewhat, according to a Centers for Disease Control and Prevention Morbidity and Mortality Weekly Report (<http://www.cdc.gov/mmwr/preview/mmwrhtml/ss5608a1.htm>). The asthma prevalence in children (8.5%) was greater than adults (6.7%), and was higher in females (8.1%) than males (6.2%). African Americans had a higher prevalence than Caucasians, in children (12.5% versus 7.7%), but less so in adults (7.6% versus 6.7%).

For most of the last century, a mainstay of the treatment of asthma was the use of epinephrine, usually given subcutaneously. In the 1940's in Europe, the use of inhaled isoproterenol, which was more selective for the beta as opposed to alpha adrenoreceptors, was reported, though adverse effects including palpitations were still a problem. In the late 1960's, more selective beta-2 agonists, such as terbutaline and salbutamol (albuterol) became available. Given the relatively short acting effect of albuterol, in the late 1980's, efforts were made to develop long acting compounds. Two long-acting beta-2 agonists (LABAs) were developed: Salmeterol (GlaxoSmithKline) and Formoterol (AstraZeneca and Novartis). Given previous concerns about the safety profile of some of the short acting beta-2 agonists, salmeterol, but not formoterol, was the subject of large safety trials (see below).

The purpose of this review is to discuss the risks of LABA use for the asthma indication, and to pose the question of which benefits might outweigh those risks. Initially, a brief summary of the public data related to these drugs will be presented. Thereafter, a recent FDA meta-analysis of the data related to risk will be presented. This will be followed by an analysis of the pivotal studies related to drug approval, with the goal of distilling the data on the benefits of the products in the context of the risks.

A. History of approvals

There are currently four drugs containing long-acting beta adrenergic agonist (LABA) licensed for the indication of asthma in the United States. Some were approved in several formulations. Specifically, there are five marketed LABAs, either alone or in combination (with an inhaled corticosteroid), approved for the asthma indication in the U.S.: Serevent Diskus, Advair Diskus, Advair HFA, and Foradil Aerolizer. Foradil Certihaler and Serevent MDI are approved but not marketed. Below is a table listing the salient features of the LABA products approved for use in the United States for the treatment of asthma (Table 1).

Table 1. Summary of Long-Acting Beta Agonist Approvals in the United States for the asthma indication

Product Name	NDA	Year of Approval	Long-Acting Beta-Agonist	Corticosteroid	Current Age Range Approved (yrs)
Serevent MDI	20-236	1994	Salmeterol xinofoate	None	≥12
Serevent Diskus	20-692	1997	Salmeterol xinofoate	None	≥12
Advair Diskus	21-077	2000	Salmeterol xinofoate	Fluticasone	≥4
Advair HFA	21-254	2006	Salmeterol xinofoate	Fluticasone	>12
Foradil Aerolizer	20-831	2001	Formoterol fumarate	None	≥5
Foradil Certihaler	21-592	2006	Formoterol fumarate	None	≥5
Symbicort	21-929	2006	Formoterol fumarate	Budesonide	≥12

B. Large randomized controlled trials studying the safety of LABAs

Serevent Nationwide Surveillance (SNS) study

The concern about asthma-related morbidity and mortality with use of the LABAs has been discussed and studied for many years. In the early 1990s, a large study was performed in the United Kingdom called the Serevent Nationwide Surveillance (SNS) study (1), published in 1993. Table 2 and the bullet points below summarize the key parameters and outcome measures of the study:

- The trial was a randomized double-blind study.
- Subjects were over the age of 12 years.
- There were 25,180 patients randomized in a 2:1 ratio.
- Randomized to receive Salmeterol 50ug BID or Salbutamol (Albuterol) 200ug QID, in a 2:1 ratio.
- The trial duration was 4 months.
- The severity of asthma as classified by the practitioners was similar in the Salmeterol (17.6% severe) versus the Salbutamol (17.7% severe) on entry to the study.
- At entry, 69% of both treatment groups were taking inhaled corticosteroids (ICS). The study was not designed to assess the impact of ICS use on LABA-associated morbidity or mortality.

Table 2. Summary of Outcomes of the Serevent Nationwide Surveillance (SNS) study.

Study	Outcome	Population	Number Salmeterol treated with outcome/population at risk	Number Salbutamol with outcome/population at risk	Relative Risk (95% CI)
SNS	Deaths from asthma	General practices in United Kingdom	12/16,787	2/8,393	3.0 (0.7-20)

Salmeterol Multicenter Asthma Research Trial (SMART)

The Salmeterol Multicenter Asthma Research Trial (SMART), initiated in 1996 in the US, was another large controlled trial (2). The bullets and Table 3 summarize key parameters and outcome measures of the study:

- The trial was a randomized double-blind study.
- Subjects were over the age of 12 years.
- Randomized to receive Salmeterol 42ug BID by metered dose inhaler (MDI) and “standard of care” or placebo MDI BID and “standard of care”.
- The trial duration was 7 months.
- Asthma treatment profiles were similar at baseline in the placebo and Salmeterol groups (92% Salmeterol versus 91% placebo receiving inhaled or oral beta-2 agonists at baseline)
- At entry, 47% of both treatment groups were taking ICS. The study was not designed to assess the impact of ICS use on LABA-associated morbidity or mortality.
- This trial was halted prematurely because of concerning findings in a planned interim analysis and difficulties with declining patient enrollment. This interim analysis was performed after 25,858 of a planned 60,000 patients ages 12 years of age or older had been enrolled, and showed that Salmeterol had a point estimate of 3.25 (95% CI 0.86-12.27) for asthma-related deaths, and that the subpopulation of African Americans may be particularly at risk. SMART was subsequently terminated early by the Sponsor on January 23, 2003 with a total of 26,355 subjects evaluated. In January, 2006, the results of this study were published.
- Although the African American population had a higher relative risk of respiratory-related deaths (see Table 3) and other outcome measures, this difference was not statistically significant, and the African American population in this study was also shown to be at higher risk at baseline (e.g. 8/4,685 African American had at least one previous intubation versus 4/18,642 Caucasians) (2).

Table 3. Summary of Outcomes of the Salmeterol Multicenter Asthma Research Trial (SMART).

Study	Outcome	Population	Number Salmeterol treated with outcome/population at risk	Number Placebo/Standard of Care with outcome/population at risk	Relative Risk (95% CI)
SMART		United States, multicenter			
	Deaths from asthma	Overall	13/13,176	3/13,179	4.37 (1.25-15.34)
	Respiratory-related deaths	Overall	24/13,176	11/13,179	2.16 (1.06-4.41)
	Respiratory-related deaths	African Americans	8/2,366	2/2,319	3.88 (0.83-18.26)
	Respiratory-related deaths	Caucasians	16/9,281	7/9,361	2.29 (0.94-5.56)

After the SMART study was terminated, the Division of Pulmonary and Allergy Products in the Office of New Drugs, CDER requested the Sponsor to revise the product label to include the important new information from the SMART study. A boxed warning was approved on August 11, 2003 citing the information on asthma-related deaths and suggesting that the risk may be greater in African Americans. Language in the Boxed Warning of Serevent and Advair follows:

“WARNING: Data from a large placebo-controlled US study that compared the safety of salmeterol (SEREVENT Inhalation Aerosol) or placebo added to usual asthma therapy showed a small but significant increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,174 patients treated for 28 weeks) versus those on placebo (4 of 13,179). Subgroup analyses suggest the risk may be greater in African-American patients compared to Caucasians...”

There was a Boxed Warning added to the Foradil label June 19, 2006 (and a similar Boxed warning on Symbicort at approval in July, 2006):

“WARNING: Long-acting beta2-adrenergic agonists may increase the risk of asthma-related death. Therefore, when treating patients with asthma, FORADIL AEROLIZER should only be used as additional therapy 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, including FORADIL AEROLIZER. 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),

the active ingredient in FORADIL AEROLIZER (see WARNINGS).”

C. Selected meta-analyses of controlled clinical trials of LABA use versus a comparator

Since the SMART study was published, there has remained considerable interest in the assessment of and attempt to quantify risks of LABAs. The meta-analyses listed in Tables 4A-B below are some of the major studies attempting to quantify the risks of the LABAs. The following are some salient features of Table 4A-B:

- Table 4 is stratified by specification of the central tendency of trial duration. Among the studies that specified mean or median trial duration (Table 4B), the only one whose mean or median duration was under 4 months was the one performed by Bateman et al. (median duration 3 months).
- Notice that most of the studies in Table 4 compared LABA+ ICS to ICS, though several compared LABA with placebo. Note that these meta-analyses were not designed to measure the impact of concomitant ICS use on LABA-associated morbidity/mortality since there was rarely, if ever, a LABA arm compared to LABA+ICS compared to placebo. This type of comparison is likely not to occur, given the current practice guidelines and labeling.
- Although children <12 years of age were included in some analyses, none of the analyses had an estimate of asthma-related deaths in children of this age.
- When there was an Odds Ratio estimate of asthma-related hospitalization for children <12 years of age, it tended to be higher than the overall Odds Ratio, though this difference did not in any instance reach statistical significance.

Table4A. Summary of risk information from select meta-analyses of the long-acting beta agonists for the indication of asthma.

Meta-analyses analyzed for this review with mean or median duration of observation not specified

First Author	Number of trials adults (≥12 years) /children (<12 years)	Total N	Duration of trials (months)	LABA and comparator ¹	Limited to USFDA approved doses	Odds Ratio ² (CI) for asthma exacerbation	Odds Ratio ² (CI) Overall Asthma-related deaths
Sears, 2008 (3)	64/none	68,004	3-12=range, mean not specified	Formoterol and ICS or other or no comparator	No	N/A ³	1.57 (0.31-15.1)
Jaeschke, 2008 (4)	62/none	29,401	3-12=range, mean not specified	Salmeterol +ICS or formoterol + ICS and ICS	No	0.74 (0.53-1.03)	1.26 (0.58-2.74) Total mortality
Chroinin, 2004 (5)	9/none	1,061	≥1	Salmeterol+ICS or Formoterol+ICS and ICS alone	Yes	1.2 (0.8-1.9) exacerbations requiring oral steroids	N/A
Gibson, 2005 (6)	10/none	2,625+1,776	3-12=range, mean not specified	Salmeterol+Fluticasone and Fluticasone, Formoterol+budesonide and Budesonide	No	1.0 (0.76-1.32) exacerbations requiring oral steroids	N/A
Chroinin, 2005 (7)	18/8	8,147	≥1	Salmeterol+ICS or Formoterol+ICS and ICS	No	0.81 (0.73-0.90) overall, 0.90 (0.57-1.42) children exacerbations requiring oral steroids	N/A
Walters, 2007 (8)	56/11	42,333	1-13=range	Salmeterol+/-ICS or Formoterol+/-ICS and placebo	No	0.73 (0.64 - 0.84) overall ; 1.22 (0.92 - 1.62) children serious asthma exacerbations	N/A
Cates, 2008 (9)	25/7	62,630	3-13=range, mean not specified	Salmeterol and placebo or Salbutamol	No	1.48 (0.97, 2.27) overall; 1.45 (0.81-2.57) children nonfatal serious adverse events in Salmeterol versus placebo	9.52 (1.24-73.09) with no ICS ⁴

¹These are the drugs and comparators included in the overall analysis.

²Odds Ratios were calculated for overall meta-analysis datasets, including more than one drug and comparator.

³Not Applicable. This means that this endpoint was not specified or an Odds Ratio for that endpoint was not estimated in the meta-analysis.

⁴“Individual patient data from the SNS study have been combined with the results of the SMART study; in patients who were not taking inhaled corticosteroids, compared to regular salbutamol or placebo, there was a significant increase in risk of asthma-related deaths.” from Cates CJ, Cates MJ. Regular treatment with salmeterol for chronic asthma: serious adverse events. *Cochrane Database of Systematic Reviews* 2008, Issue 3. Art. No.: CD006363. DOI: 10.1002/14651858.CD006363.pub2 (reference 9).

Table4B. Summary of risk information from select meta-analyses of the long-acting beta agonists for the indication of asthma.							
Meta-analyses analyzed for this review with mean or median duration of observation specified							
First Author	Number of trials adults (≥12 years) /children (<12 years)	Total N	Duration of trials (months)	LABA and comparator ¹	Limited to USFDA approved doses	Odds Ratio ² (CI) for asthma exacerbation	Odds Ratio ² (CI) Overall Asthma-related deaths
Bateman, 2008 (10)	66/none	20,966	3= median	Salmeterol + ICS and ICS	Yes	1.07 (0.66-1.73)	N/A One asthma-related death
Cates, 2008 (11)	17/5	8,032	4=mean	Formoterol and placebo or salbutamol	No	1.57 (1.05-2.37) overall; 2.92 (1.26-6.74) children nonfatal serious AEs	N/A, 3 deaths in treatment, not statistically signif.
Salpeter, 2006 (12)	13/6	33,826	6=mean	Salmeterol or formoterol and placebo	No	2.6 (1.6-4.3) overall ;3.9 (1.7-8.8) children	3.5 (1.3-9.3)
Levenson, 2008*	104/6	60,954	5.6=median	Serevent and non-laba treatment or placebo, Foradil and non-laba treatment or placebo, Advair and Fluticasone, Symbicort and Budesonide	Yes	1.27 (1.09-1.48)	4.00 (1.41-13.92)

¹These are the drugs and comparators included in the overall analysis.

²Odds Ratios were calculated for overall meta-analysis datasets, including more than one drug and comparator.

³Not Applicable. This means that this endpoint was not specified or an Odds Ratio for that endpoint was not estimated in the meta-analysis.

*Current FDA meta-analysis, not published.

D. Observational studies

Several observational and epidemiological studies have been undertaken to address the emerging concerns regarding safety of LABAs. We summarize some of the relevant studies here.

GlaxoSmithKline undertook a feasibility study to determine if a case-control study of asthma deaths could evaluate whether there is an association between salmeterol use and death from asthma, and whether such an effect might be ameliorated by concomitant ICS. They planned to use five years of Medicaid data from six different states. They determined that the level of use of salmeterol, and the number of asthma deaths in these databases, were insufficient to provide statistical power, and accordingly they abandoned this study (13). A case-control study of non-fatal asthma episodes requiring intensive care unit (ICU) admission, with 48 cases and 185 controls, showed an association between salmeterol use and ICU admission (unadjusted relative risk 2.32, 95% CI 1.05-5.16), but this association appeared to be due to more frequent use of salmeterol by patients with more severe asthma (14). With respect to studies not focused specifically on salmeterol, findings from case-control studies have included an association between asthma deaths and life-threatening asthma attacks with use of beta-2 agonists in Japan (15). A case-control study of 532 patients who died from asthma (and an equal number of controls) found an association between asthma deaths and use of short acting beta-2 agonists in the period 1-5 years prior to death. However, for use of long-acting beta-2 agonists during the same period, there was a reduction in the risk of asthma deaths that almost reached statistical significance (16).

A cohort study of health care insurance claims compared emergency asthma care, hospitalization, and intensive care unit stays for 2708 patients prescribed salmeterol and 3825 patients receiving theophylline. This study failed to find any differences in outcomes, although there was evidence that salmeterol was prescribed for patients with more severe asthma (17). This study did not examine asthma deaths. Another observational study used the UK's General Practice Research Database (GPRD) to assess respiratory mortality with salmeterol, ipratropium, and theophylline. No differences between drugs were found, but there were only 5 deaths from respiratory causes among salmeterol patients, and the relative risk estimates had very wide confidence limits, suggesting a lack of statistical power (18). A case-control study of asthma deaths using GPRD data showed the strongest association with heavy use of short acting beta agonists, and a relative risk for heavy users of long acting beta agonists of 3.2 (which was not statistically significant) (19).

Finally, a Kaiser-Permanente retrospective cohort study showed higher mortality among asthma patients receiving LABAs, with or without ICS, but this study has been published in abstract form only (20).

Conclusions from observational studies: Findings regarding the safety of LABAs from health care claims databases and case-control studies have been mixed. Using observational methods has been challenging, because patients prescribed LABAs almost

certainly differ from other asthma patients, and because deaths from asthma are relatively rare, and thereby difficult to study.

E. Advisory Committees on the subject of Long-Acting Beta Agonists

CDER has convened the following Advisory Committees on the subject of Long Acting Beta Agonists used to treat asthma:

February 26, 1993 Pulmonary-Allergy Drugs Advisory Committee Meeting on Serevent NDA

November 23, 1999 Pulmonary-Allergy Drugs Advisory Committee Meeting on Advair NDA

July 13, 2005- Pulmonary-Allergy Drugs Advisory Committee Meeting

An overview of the LABAs was discussed, including data from the SMART and Phase 4 Formoterol studies and revised labeling information. At the time of that AC, there was a Boxed Warning on Serevent and Advair, but not a Boxed Warning on Foradil. The voting questions for the committee were:

- “Based on currently available information, do you agree that salmeterol should continue to be marketed in the US?”
 - Yes-13, No-0, Abstain-0
- “Based on currently available information, should the label of the formoterol containing products include warnings similar to those in the salmeterol label?”
 - Yes-12, No-1, Abstain-1
- “Based on currently available information, do you agree that formoterol should continue to be marketed in the US?”
 - Yes-13, No-0

The July, 2005 AC also put forward recommendations that:

- Boxed Warnings be modified to discourage monotherapy and encourage co-administration with an ICS
- Boxed Warnings be maintained on all salmeterol containing products
- FDA request LABA manufacturers to update product labels with new warnings for all LABA products

FDA actions after July, 2005 AC:

- FDA request Medication Guide for each LABA product
- Healthcare Professional Sheet be issued (done November 2005)
 - salmeterol (Serevent Diskus)
 - salmeterol and fluticasone (Advair Diskus)
 - formoterol (Foradil Aerolizer)

The decision was made to label for the mortality risk for LABAs as a class (see section 1.B.), such that all US-approved LABAs for the asthma indication were labeled with a boxed warning relating to the risk of asthma-related mortality, and the possibility of a greater risk in the African American than the Caucasian population. In the Warnings section is stated that LABAs “should only be used as additional therapy 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 2 maintenance therapies...”

November 28, 2007- Pediatric Advisory Committee (PAC) Meeting

The PAC meeting took place 1 year following the granting of pediatric exclusivity for Salmeterol. Salmeterol was one of many products discussed, but there was an expanded discussion due to salmeterol’s known safety profile. There was a concern raised regarding the risk-benefit ratio in pediatric patients. FDA committed to discuss this issue at a future advisory committee. The December 10-11, 2008 advisory committee meeting will be the follow-up to the PAC. There were no voting questions on salmeterol at the PAC. Topics discussed included:

- the possibility of removal of salmeterol from the market, but it was agreed that more discussion was needed.
- Request for a report back after additional review of the data.
- An urgent concern was expressed about the safety of LABA products from a public health perspective.
- An update to the labeling identifying pediatric risks, including hospitalizations.

D. Benefits versus Risks of the Long Acting Beta Agonist drugs marketed for the asthma indication

Considering the background on the LABAs outlined above, including the SNS and SMART studies, the meta-analyses outlined above, and the previous LABA advisory committees, the following are essential questions that remain about the LABAs:

- What are the benefits, and do they outweigh the risks of salmeterol for the treatment of asthma, including the possible effects of concomitant controller therapy, e.g. inhaled corticosteroids?
 - in adults [≥ 18 years of age]
 - in adolescents [12-17 years of age]
 - in children [4-11 years of age]
- What are the benefits, and do they outweigh the risks of formoterol for the treatment of asthma, including the possible effects of concomitant controller therapy, e.g. inhaled corticosteroids?
 - in adults [≥ 18 years of age]
 - in adolescents [12-17 years of age]
 - in children [5-11 years of age]
- Are there further risk mitigation strategies for LABAs that would be advisable?
- What future studies, if any, would be critical to bring us to the next public health decision regarding LABA use?

The following review outlines the pivotal studies leading to the approval of the 4 US-marketed LABAs for the indication of asthma, and provides the highlights of a meta-analysis performed by the Agency to quantify the risks of these drugs. Finally, the subject of weighing benefits and risks of LABAs is discussed.

II. Methods

A. Meta-analysis (Meta-analysis by Dr. Mark Levenson from Division of Biostatistics 6, CDER, FDA) of randomized clinical trial data for the asthma indication submitted to the Agency from the Sponsors of the 4 LABA drugs

The Agency requested data from all sponsors of LABAs approved for the asthma indication. The data requested was not limited to US data nor age of subject. All randomized data for the asthma indication were requested.

For inclusion in the meta-analysis, the trials and subjects had to meet the following criteria:

1. Subjects were treated with a US-approved dose of the LABA.
2. Subjects were of age for which the LABA is approved in the US.
3. There were at least 20 patients per arm of the trial.
4. The trial was at least 7 days blinded duration.
5. Any additional therapy in the LABA group was present in the non-LABA group.

The primary endpoints were the following:

1. Asthma-related death
2. Asthma-related death or intubation
3. Asthma-related hospitalization
4. Asthma composite, which includes death, intubation, or hospitalization

Secondary endpoints were the following:

1. Rescue medicine episodes per 28 days of therapy
2. All-cause death

Comparisons were between:

1. Patients assigned LABA versus patients assigned non-LABA therapy.
2. Patient assigned LABA without assigned ICS versus patients assigned non-LABA therapy
3. Patient assigned LABA and ICS versus patient assigned ICS therapy

The analysis was conducted by calculating the “risk difference per 1000 subjects” which essentially meant the difference between the incidence of a particular adverse event in a subject receiving LABA therapy and the incidence of that same adverse event in a subject receiving nonLABA therapy for every 1,000 subjects treated, over the duration of the trial, which was usually less than 6 months. The analysis adjusted for different background rates among the trials. Subgroups based on age, race, gender, center location, ICS use, and trial duration were considered.

B. Summary of the Efficacy Endpoints of Trials Used in the approval of the LABAs for the indication of asthma

The pivotal trials constituting the US approval of the 4 LABAs were reviewed, describing a summary of the sizes, composition, and primary and secondary endpoints for each of

the trials. This summary is not a comprehensive review of the randomized clinical trials of the LABA drugs, but is meant to highlight some of the information leading to approval. In the Results section is a brief summary of some of the key findings.

III. Results

A. Brief summary of the highlights of FDA’s meta-analysis of measures of risk with US-marketed Long Acting Beta Agonists for the asthma indication

Table 5. Characteristics of the Trials, Treatments, and Patients By Age in the FDA Meta-analysis	
Characteristic	N
<i>Number of Trials</i>	110
<i>Number of Patients</i>	
<i>Total</i>	60,954
<i>By LABA Treatment</i>	
Received a LABA	30,148
Did not receive a LABA	30,806
<i>By Trial Study Drug</i>	
Serevent Trials	43,824
Advair Trials	13,212
Foradil Trials	3,765
Symbicort Trials	1,270
<i>By Age (years)</i>	
4-11	3,415
12-17	6,392
18-64	46,878
≥65	4,214

Key results of FDA meta-analysis

The key results in unadjusted and adjusted risk differences in the FDA meta-analysis are presented below.

Unadjusted risk differences between LABA subjects and non-LABA subjects

- Overall, there were 20 asthma-related deaths. Sixteen of the deaths were in the LABA group (all associated with Serevent). Four deaths were in the non-LABA group.

- The overall unadjusted risk difference for death associated with asthma was 0.4 per 1000 subjects.
- The unadjusted asthma composite risk difference was 2.8 per 1000 subjects. (Note that the asthma composite endpoint is driven by the asthma hospitalization component).
- There was a difference overall in unadjusted risk difference comparing LABAs in the context of ICS use and LABAs as single entity products. The unadjusted asthma composite risk difference between LABA without ICS and non-LABA control was 4.3 per 1000 subjects versus 0.4 per 1000 subjects when LABA with ICS use was compared with ICS use.

Adjusted risk differences between LABA subjects and non-LABA subjects

- The results are similar to the unadjusted risk differences.
- The individual drug subset analysis showed that there was no risk difference between Advair and fluticasone, while there were large risk differences between Serevent and non-LABA control, between Foradil and non-LABA control, and between Symbicort and budesonide control (Table 6), with risk being greater for the LABA recipients in each analysis. Of note, the upper bound of the 95% confidence interval could not exclude a potential risk difference of 1 per 180 for Serevent, 1 per 61 for Foradil, and 1 per 106 for Symbicort.
- The Advair risk difference drives the overall risk difference between LABAs with ICS and non-LABA controls with ICS. Advair patients made up a large proportion of the ICS+LABA patients (Table 6).
- Note that only for Serevent was the sample size large. The sample size for Advair was somewhat low, and for Foradil and Symbicort, extremely small, resulting in wide confidence intervals (Tables 6 and 7).
- The age subset analysis showed a strong age effect across drugs with the youngest patients showing the highest risk difference. Notably, this pattern among the age groups existed for each drug except for Advair.
- In the case of Advair, the ≥ 65 year old age group, though small, had a highly positive risk difference 10.80 with a lower bound that exceeded 0 (1.16-20.44) (Table 7).

Table 6. Adjusted Risk Differences in Long-Acting B Agonists versus Comparator for the Asthma Composite Endpoint					
LABA	Number events/exposed persons	Comparator	Number events/exposed persons	Risk Difference per 1000	Confidence Interval per 1000
All LABAs	381/30,148	nonLABA control	304/30,806	2.80	1.11-4.49
LABAs no ICS	350/22,286	nonLABA control	279/24,474	3.63	1.51-5.75
LABAs with ICS	31/7,862	nonLABA control with ICS	26/7,330	0.25	-1.69-2.18
Advair	21/6,648	Fluticasone	20/6,564	-0.15	-2.01-1.70
Serevent	336/21,108	nonLABA control	270/22,716	3.49	1.27-5.71
Symbicort	6/766	Budesonide	1/504	7.49	-1.47-16.44
Foradil	18/1,626	nonLABA control	14/2,139	3.80	-1.80-9.40

Table 7. Adjusted Risk Differences in Long-Acting B Agonists, by drug and by age.			
LABAs overall	Risk Difference per 1000	Confidence Interval per 1000	N LABA; N comparator
4 to 11 years	14.83	3.24-26.43	1,626;1,789
12-17 years	5.57	-0.21-10.92	3,103;3,289
18-64 years	2.13	0.34-3.91	23,274;23,604
≥65 years	-3.58	-19.47-3.32	2,117;2,097
Advair			
4 to 11 years	ND	ND	409;401
12-17 years	-0.53	-4.52-3.46	627;682
18-64 years	-0.98	-3.22-1.25	5,189;5,043
≥65 years	10.80	1.16-20.44	422;433
Serevent			
4 to 11 years	16.97	-1.94-35.88	899;1,085
12-17 years	5.88	-1.07-12.83	2,205;2,411
18-64 years	3.27	0.94-5.6	16,492;17,696
≥65 years	-6.38	-15.38-2.63	1,485;1,502
Symbicort			
4 to 11 years	ND	ND	0;0
12-17 years	23.36	-2.53-49.25	155;120
18-64 years	3.55	-6.34-13.44	566;356
≥65 years	ND	ND	45;28
Foradil			
4 to 11 years	27.50	5.6-49.41	318;303
12-17 years	12.75	-16.68-42.18	116;174
18-64 years	-1.53	-5.16-2.09	1,027;1,457
≥65 years	-11.91	-32.44-8.61	165;205

B. Summary of results and concepts stemming from review of pivotal trials leading to drug approval

There are five marketed LABAs approved for the asthma indication in the U.S.: Serevent Diskus, Advair Diskus, Advair HFA, and Foradil Aerolizer. Foradil Certihaler and Serevent MDI are approved but not marketed. The FDA review packages for pivotal trials in the approval of the LABA products marketed in the US for the asthma indication were reviewed looking for measures of benefit for each of the drugs and that were common to the four drugs. For this purpose we relied on the FDA reviews, without re-evaluating the primary data as submitted by the sponsors; such review would have been beyond the scope of this project.

1. Summary tables of results from pivotal trials

The following tables summarize efficacy results for each of the 4 drugs, separating the data for adolescent and adult versus pediatric patients followed by bullet points summarizing the findings for that drug. The efficacy data in these tables is intended to show the net benefit over the comparator, by subtracting the comparator values from the LABA values. Finally, there is a summary of the points common to all 4 drugs. Statistical significance is only mentioned for the primary endpoints, for which the studies were powered. See Appendix for the scoring systems for some of the secondary endpoints in the tables below.

Foradil (Aerolizer and Certihaler)

Table 8. Pivotal controlled trials of Formoterol versus Albuterol in patients age 13 years or older.				
	Formoterol 12 µg bid (Aerolizer)		Formoterol 10 µg bid (MDDPI Certihaler)	
Study	040	041	2302	2303
Comparator	Albuterol qid	Albuterol qid	Albuterol qid	Albuterol qid
N exposed to F	136	139	86	80
1° efficacy				
Δ 12° FEV ₁ ¹	0.3	0.3		
Δ 12° AUC FEV ₁ ² (L/hr)			1.49	1.57
2° efficacy				
Δ nocturnal asthma score ³	-0.3	0	-0.06	No diff
Δ combined asthma score ⁴	-0.2	-0.1		
Δ % nights Awakened ⁵	-15	-13		
Δ % nights using rescue meds ⁶	-12	-8		
Δ rescue med use ⁷ (puffs/d)			-0.27	0.25
Δ asthma QOL ⁸			-0.01	

¹ Difference in Forced Expiratory Volume-1 (FEV-1) between patients taking Formoterol versus patients taking Albuterol at 12 hours after the first dose.

² Difference in area under the curve of Forced Expiratory Volume-1 (FEV-1) comparing patients receiving Formoterol and those receiving Albuterol between 0 and 12 hours after the first dose.

³ A negative number would be in the direction of less severe asthma symptoms in Foradil treated patients, with a total of a 5 point scale Appendix.

⁴ A negative number would be in the direction of less severe asthma symptoms in Foradil treated patients.

⁵ A decrease in this measure would be in the direction of less severe asthma symptomatology in Foradil treated patients.

⁶ Decrease in this number would be in the direction of less need for rescue medication in Foradil treated patients.

⁷A decrease in puffs per day of rescue medication would be in the direction of greater symptomatic improvement in Foradil treated patients.

⁸Standardized validated questionnaire Appendix. A decrease on this questionnaire would be in the direction of more severe symptomatology from asthma in Foradil treated patients.

- Review of the pivotal trials for the Foradil products in patients >12 years of age showed that the two FEV₁ endpoints were met. FEV₁ was significantly greater in patients receiving Foradil compared with Albuterol.
- The secondary endpoints of % nights awakened and % nights using rescue medication were both lower in Foradil treated patients than Albuterol-treated patients, though that decrease was <20%.
- All other secondary endpoints had very small changes in the Foradil recipients compared to Albuterol.

Table 9. Pivotal controlled trials of Formoterol versus Albuterol, or Formoterol versus placebo in patients age 5-12 years.			
	Formoterol 12 µg bid (Aerolizer)		Formoterol 10 µg bid (MDDPI Certihaler)
Study	049	DP/PD2	604
Comparator	Albuterol qid	Albuterol qid	Placebo
N exposed to F	171	77	127
1° efficacy			
Δ 12° AUC FEV ₁ ¹ (L/hr)	0.08		0.95
Δ PEF ² (L/min)		13.4	
2° efficacy			
Δ AM PEF ³ (L/min)	-0.25		
Δ AM asthma score ⁴ (0-3)	-0.07	-0.12	
Δ PM asthma score ⁵ (0-4)	-0.09	-0.07	-0.05
Δ sleep disturbance Score ⁶		-0.01	
Δ AM rescue med use ⁷ (puffs/d)	-0.06	-0.14	
Δ PM rescue med use ⁸ (puffs/night)	-0.09	-0.08	
Δ % using no rescue ⁹		5	
Δ rescue med use ¹⁰ (puffs/24 hr)			-0.16
Δ % with exacerbation ¹¹	1.8		

¹Difference in area under the curve of Forced Expiratory Volume-1 (FEV-1) comparing patients taking Formoterol and patients taking Albuterol between 0 and 12 hours after the first dose.

²Difference in peak flow rate in individuals receiving Formoterol versus comparator.

³Change in morning peak flow rate in patients receiving Formoterol versus comparator.

⁴ A negative number would be in the direction of less severe asthma symptoms in Foradil treated patients, with a total of a 4 point scale Appendix.

⁵A negative number would be in the direction of less severe asthma symptoms in Foradil treated patients, with a 5 point scale.

⁶A negative number would be in the direction of less severe asthma symptoms in Foradil treated patients.

⁷⁻⁸A decrease in puffs per day of rescue medication would be in the direction of less severe asthma symptoms in Foradil treated patients.

⁹Increase in this number would be in the direction of less severe asthma symptomatology in Foradil treated patients.

¹⁰A decrease in puffs per day of rescue medication would be in the direction of less severe asthma symptomatology in Foradil treated patients.

¹¹Increase in percent with asthma exacerbation would be in the direction of more severe asthma symptomatology in Foradil treated patients.

- When Formoterol was compared to Albuterol or placebo in patients 5-12 years of age, the two spirometric primary endpoints were met.
- None of the secondary endpoints showed much change in the Formoterol group compared with either Albuterol or, where relevant, placebo.

Advair Diskus and Advair HFA

Table 10. Pivotal controlled trials comparing Salmeterol/Fluticasone versus Fluticasone in patients age 12 years or older.					
	Advair Diskus		Advair HFA		
Study	3002	3003	30001	30002	30003
Dose Salmeterol Fluticasone	50 µg bid 100 µg bid	50 µg bid 100 µg bid	88 µg bid 176 µg bid	88 µg bid 176 µg bid	42 µg bid 220 µg bid
N exposed	92	84	95	92	94
1° efficacy					
Δ AM FEV ₁ ¹ (L)	0.22	0.25	0.18	0.22	0.22
Δ 12° AUC FEV ₁ @ 1 wk ² (L-hr)	4.68	4.87			
Δ 12° AUC FEV ₁ @ 12 wk ³ (L- hr)			3.4	3.4	3.4
2° efficacy					
Δ rescue med use ⁴ (puffs/d)			-0.6	-1.7	
Δ asthma QOLQ ⁵ (1-7)	0.43	0.45		-0.7	0.5
Δ % symptom- free days ⁶	18	16			
Δ % days without rescue med use ⁷	20.7	21.7			
Δ % nights with no awakenings ⁸	2.5	4.0			

¹Difference in Forced Expiratory Volume-1 (FEV-1) between patients taking Salmeterol/Fluticasone versus patients taking Fluticasone at 12 hours after the first dose.

²Difference in area under the curve of Forced Expiratory Volume-1 (FEV-1) comparing patients taking Salmeterol/Fluticasone and patients taking Fluticasone between 0 and 12 hours after the first dose one week after initiation of therapy.

³Difference in area under the curve of Forced Expiratory Volume-1 (FEV-1) comparing patients taking Salmeterol/Fluticasone and patients taking Fluticasone between 0 and 12 hours after the first dose 12 weeks after initiation of therapy.

⁴ A decrease in puffs per day of rescue medication would be in the direction of less asthma symptomatology in Advair treated patients.

⁵ Standardized validated questionnaire Appendix. A decrease on the scoring of this questionnaire would be in the direction of greater symptomatology from asthma in Advair treated patients.

⁶ A negative number would be in the direction of less asthma symptoms in Advair treated patients, with a total of a 4 point scale Appendix.

⁷ An increase in symptom-free days would be in the direction of less asthma symptomatology in Advair treated patients.

⁸ An increase in percent nights with no awakenings would be in the direction of less asthma symptomatology in Advair treated patients.

- In patients over 11 years of age, comparing Advair with Fluticasone, all 3 primary spirometric endpoints were met.
- Notably, the Δ 12° AUC FEV₁ was higher at 1 week than at 12 weeks.
- Notably, for the secondary endpoints, both Δ % symptom-free days and Δ % days without rescue medicine use showed approximately 20% increase.
- There were no efficacy trials for Advair in children.

Serevent MDPI and Serevent MDI

Table 11. Pivotal controlled trials comparing Salmeterol versus Albuterol in patients age 12 years and older.

	Serevent MDPI		Serevent MDI	
Study	SLD-311	SLD-312	SLG-311	SLG-312
Dose	50 µg bid	50 µg bid	42 µg bid	42 µg bid
N exposed	79	69	78	???
1° efficacy				
Δ % FEV ₁ increase Overall @ 4 wks ¹	-3.6 7.9	-0.2 7.7		
Δ FEV ₁ (L) Overall @ 4 wks ²			-0.12 0.24	
2° efficacy				
Δ rescue med use ³ (puffs/d)	-0.7	-0.5	-0.7	-0.7
Δ % nights with no Symptoms ⁴	19	---	---	14
Δ % days with no Symptoms ⁵	---	10	---	14
Δ asthma symptom Score ⁶ (0-3) Overall			-0.2	
Chest tightness	-0.1 -0.3		-0.4 -0.2	
SOB	-0.1		0	
Wheezing	-0.2		-0.2	
Coughing				
Δ % with asthma Exacerbations ⁷			-15	-9

¹Change in percent increase in Forced Expiratory Volume-1 (FEV-1) between patients taking Salmeterol versus patients taking Albuterol at 12 hours after the first dose four weeks after initiating therapy.

²Difference in Forced Expiratory Volume-1 (FEV-1) at 4 weeks after initiating therapy comparing patients taking Salmeterol and patients taking Albuterol.

³A decrease in puffs per day of rescue medication would be in the direction of less asthma symptomatology in Salmeterol treated patients.

⁴⁻⁵An increase in percent nights or days with no symptoms would be in the direction of less asthma symptoms in Salmeterol treated patients.

⁶ A negative number would be in the direction of less asthma symptomatology in Salmeterol treated patient, with a total of a 4 point scale Appendix.

⁷ Decrease in percent with asthma exacerbation would be in the direction of less asthma symptomatology in Salmeterol treated patients.

- In patients >11 years of age comparing Salmeterol with Albuterol, the primary spirometric endpoints were met.
- The Δ % nights with no symptoms and Δ % days with no symptoms favored Salmeterol (by 10-20%), but all other symptoms measured in the secondary endpoints showed little difference between Salmeterol and Albuterol or favored Albuterol (Δ % with asthma exacerbations).

Table 12. Pivotal trial of Salmeterol versus placebo in patients age 4-11 years.	
Study	SLD-390
Dose	50 μ g bid
N exposed	102
1° efficacy	
Δ % FEV ₁ increase ¹	3.4
Δ % PEF increase ²	6.2
2° efficacy	
Δ asthma symptom score ³ (0-3)	-0.2
Δ % with exacerbation ⁴	8
Δ AM PEF @ 9-12 wks ⁵ (L/min)	9.9
Δ PM PEF @ 9-12 wks ⁶ (L/min)	8.8

¹ Difference in Forced Expiratory Volume-1 (FEV-1) increase comparing patients taking Salmeterol and patients taking placebo.

² Difference in peak expiratory flow (PEF) increase in individuals receiving Salmeterol versus placebo.

³ A negative number would be in the direction of less asthma symptoms in Salmeterol treated patients, with a total of a 4 point scale Appendix.

⁴ Increase in percent with asthma exacerbation would be in the direction of greater asthma symptomatology in Salmeterol treated patients.

⁵⁻⁶Difference in morning or evening peak expiratory flow (PEF) at 9 to 12 weeks after initiation of therapy in individuals receiving Salmeterol versus placebo. An increase in PEF would be in the direction of less asthma symptomatology in Salmeterol treated patients.

- In patients 4-11 years of age receiving Salmeterol compared to placebo, the primary spirometric endpoints were met.
- There was little change in the asthma symptom score, but the other secondary endpoints measured showed slightly less asthma symptomatology in Salmeterol treated patients.

Symbicort

Table 12. Pivotal controlled trials comparing formoterol/budesonide vs. budesonide in patients age 12 years and older.		
Study	716	717
Formoterol dose	9 mg bid	9 mg bid
Budesonide dose	160 mg bid	320 mg bid
N exposed	123	124
1° efficacy		
Δ % 12° FEV ₁ ¹ (L)	0.18	0.20
Δ % pre-dose FEV ₁ ² (L)	0.14	0.12
2° efficacy		
Δ % nocturnal awakening ³	-3.0	-8.0
Δ % rescue med use ⁴	-2.2	-1.0
Δ % with exacerbations ⁵	-2.2	1.0

¹Difference in percent Forced Expiratory Volume-1 (FEV-1) between patients taking Symbicort versus patients taking Budesonide at 12 hours after therapy.

²Difference in percent pre-dose Forced Expiratory Volume-1 (FEV-1) between patients taking Symbicort versus patients taking Budesonide.

³Decrease in the percent nocturnal awakening would be in the direction of less asthma symptomatology in Symbicort treated patients.

⁴A decrease in percent rescue medication use would be in the direction of less asthma symptomatology in Symbicort treated patients.

⁵Decrease in percent with asthma exacerbations would be in the direction of less asthma symptomatology in Symbicort treated patients.

- In the pivotal trials comparing Symbicort with Budesonide in patients >11 years of age, the primary spirometric endpoints were met.

- There was very little, if any, difference between Symbicort and Budesonide in the secondary endpoints including Δ % nocturnal awakening, Δ % rescue medication use, and Δ % with exacerbations.

2. Overall comments on summary of pivotal trials

Several overall comments can be distilled from the above tables summarizing the pivotal trials for the 4 LABAs.

- Some measure of Forced Expiratory Volume-1 (FEV-1) was the primary endpoint in all the US studies.
- In all of the studies reviewed, there was a statistically significant increase in some spirometric measure compared to either placebo or albuterol or individual component products.
- It should be noted that in all the pivotal trials for all 4 drugs, some degree of response to a short-acting beta agonist was required for enrollment.
- Secondary endpoints varied among the drugs and across age groups. Two types of measures that were used relatively consistently in the adult studies were:
 - a. Number of puffs of rescue medication per given time period or percent change in this with LABA versus comparator, or percent change in this parameter compared to baseline data across treatment groups.
 - b. Number or percent of nighttime awakenings or symptom-free days with LABA versus comparator.
- Since comparators sometimes were short-acting beta agonists, sometimes were LABA components, and sometimes were placebo, it would not be meaningful to give summary results for these measures.
- The largest clinical differences between LABA and comparator were approximately 1.5 less puff(s) of rescue medicine per day or 15-20% more symptom-free days in the LABA versus comparator group.
- Although the pediatric studies met the spirometric endpoints, there was little in the way of improvement over comparator in the secondary endpoints for children <12 years of age.
- Adolescents were not assessed separately, thus an analysis of this group of patients with respect to LABA efficacy is not possible.

III. Discussion

Risks of LABAs

FDA meta-analysis findings

The FDA meta-analysis estimated that overall there were 2.8 more serious asthma events per 1,000 patients taking LABAs than a nonLABA comparator. Demographic factors had an impact on this finding. In young children, driven by the data for Serevent and Formoterol, the estimated risk difference increased to almost 15 more serious asthma

events per 1,000 patients or an excess of 1.5 serious asthma events for every 100 patients treated with LABAs compared to nonLABA asthma therapy. The age effect was not only marked in the youngest patients, but also gradually decreased with each age bracket, suggesting this to be a robust finding (Table 7). Notably, the subset analysis of Advair use in the elderly showed a markedly increased risk compared to the Fluticasone control, though the other age subsets, in the case of Advair, showed no increased risk. The possibility of an increased risk of LABA use in African Americans is in the current labeling from findings in the SMART study (2). In the current meta-analysis, African Americans had an estimated 8 more serious asthma events per 1,000 subjects in the LABA group than in the nonLABA comparator group compared to 2 per 1,000 in Caucasians, though it should be mentioned that, at least in the SMART study, African Americans had a higher baseline risk of serious asthma-related outcomes (2). Since previously the race affect on LABA risk had been described only in the SMART study, it is of interest that this finding was replicated in trials excluding the SMART study itself.

Another subset analysis was that of the drug-specific findings. All of the drugs analyzed had a greater estimated risk than the nonLABA comparators except Advair. Advair had an estimated risk difference of essentially zero. Although an argument could be made that this was due to the impact of ICS, the data from the FDA meta-analysis may not support that point of view. Symbicort, which also is constituted in part by an ICS, shows an estimate of 7.49 excess asthma-related serious events per 1,000 subjects receiving Symbicort compared to a nonLABA asthma therapy, despite the difference not being statistically significant. Of note, Formoterol (which is composed of the same LABA as that in Symbicort) also has an estimated 4 more asthma-related serious events per 1,000 subjects than nonLABA comparator, though this finding is not statistically significant. Therefore, these data do not enable inference as to the cause of the LABA-associated risk. However, this meta-analysis does substantiate and quantify the data on overall LABA-associated risk.

Cochrane meta-analyses

It should be highlighted that there are meta-analyses of LABA safety and efficacy outcomes in asthmatic patients that have shown, with respect to asthma-related hospitalization, either no risk of the LABA or a protective effect of the LABA on asthma-related hospitalization (21). Table 4 stratifies select recent meta-analyses related to LABA safety into those that specify a central tendency of trial duration, and those that do not. Notably, the meta-analyses considered here that noted the mean or median trial duration, with one exception (Bateman et al (10)) found a significantly elevated Odds Ratio for serious asthma-related adverse events after LABA use. Bateman et al (10) found no increased risk of hospitalization for asthma exacerbation when considering the Salmeterol+Fluticasone combination in adults compared to Fluticasone alone. Is the presence or absence of baseline steroid use the reason for mitigation of adverse effects of LABAs in some studies? (21). This review does not reject this possibility. Indeed, Advair, which has as one of its components an ICS, shows in the FDA meta-analysis a risk difference near zero. It is possible that the sample size of the population that received Symbicort, which also is a combination product including an ICS, is too small to see this

effect (or lack of effect). However, given the limited data on Symbicort, and that the data in the FDA meta-analysis show an elevated risk difference for this drug, it is impossible to be certain that LABA+ICS combinations are in every case either beneficial or indifferent to the asthmatic patient.

Age Effect

It should also be highlighted that the risk of LABA use in younger individuals is evident from several sources of information. The FDA meta-analysis shows an age effect driven by Serevent and Formoterol, but also evident in a small number of adolescents using Symbicort (see Table 7 below). The younger patients show a higher risk difference which in these 3 drugs, decreases with age, though the age differences are not statistically significant. These observations, combined with those in Table 4 (see below), while not giving statistical proof of younger patients being at greater risk than older ones with LABA use, suggest that LABA use in children <18 years of age may not be even as safe as it is in adult asthmatic patients. Examination of Table 4 shows that in every case, except one (9) (in which the endpoint was “nonfatal serious adverse events” rather than asthma-related outcomes), the Odds Ratio of serious asthma exacerbation was greater in children compared to the overall nonsubsetted population. With a number of sources of information showing a “signal” regarding LABA safety in children this “signal”, now reinforced by the FDA meta-analysis, must be addressed.

Note that Advair does not show the same age effect (with younger aged being at greater risk than older aged individuals). In fact, Advair, on the contrary, shows a higher risk in the elderly (individuals >65 years of age) in the FDA meta-analysis, though this age subset is small, and the “signal” in the elderly is not known to this reviewer from other sources of information.

Benefits in the context of LABA-associated risks

Overall population

As stated in the Results section, the primary endpoint for all of the LABA studies reviewed was based on spirometric measurement. A consistent and significant increase in some FEV-1 measure shows that the LABAs are effective bronchodilators. Because the short-acting beta agonists are also effective bronchodilators, it is important, especially in light of the significant and well documented risks of LABAs, to show what the long-acting drugs offer above what is offered by the short-acting beta agonists.

Because secondary endpoints in the efficacy pivotal studies vary and because the studies were not powered to measure the differences between treatment and control group with respect to these measures, it is difficult to meaningfully summarize the data with respect to these measures across studies and across the 4 drugs. But one way of looking at this would be to ask the question:

- “What is the largest measured clinical impact differentiating long- versus short-acting beta agonists?”

- In trials where a long-acting was compared with a short-acting beta agonist, there was a 0.4-0.7 puff/day difference between LABA and comparator. In percent nights with awakenings there was an 8 to 15% decrease in LABA-treated patients compared to Albuterol treated patients or a 19% increase in nights with no symptoms.

LABA use in children

Given the concerns about the safety of LABA use in the pediatric population, a relevant question is whether the benefit or efficacy data suggests that the benefits outweigh the risks in this subpopulation. Two of the four drugs, Salmeterol and Formoterol, had independent data on children in the pivotal studies for approval (Tables 8 and 11).

- As is true in adults, the primary efficacy endpoints were spirometric, and were met.
- There were very few if any secondary endpoints in the pivotal pediatric studies of LABAs that demonstrated a clinical difference between children receiving LABA and comparator.
- The question could be asked, given what appears to be an increased risk in children, in comparison to adults, “Do the benefits of LABAs outweigh the risks in children and adolescents?”

It is important to bring out that further subgroup analysis of the benefits of LABAs (in light of a potential increased risk), are not possible due to lack of subgroup data, as outlined below. Included in this list of potentially important subgroups are:

1. Children 12-17 years of age. There are little data separately analyzing efficacy data in this group and the existing data have low power due to small sample size.
2. Racial differences. Although there was an increased risk of LABA use documented in African Americans compared to Caucasians, there was no race-specific efficacy data presented.

IV. Conclusion

The subject of the risks of LABA use in patients with asthma is a longstanding public debate. This review highlights the findings of the large safety trials which show an imbalance in asthma-related serious events in the LABA-treated group. The more recent meta-analyses show mixed results. The meta-analysis described herein (Appendix I) shows no protective affect of the LABAs against asthma-related hospitalization and other asthma-related serious outcomes, but documents very clearly the risk difference in LABA treatment arms compared to non-LABA treatment arms. Notably, Advair, which is a combination product of salmeterol and ICS, showed no risk difference between the treatment arm and the ICS comparator. Although it may be tempting to interpret this as an effect of concomitant steroid use, the other LABA/ICS combination product, Symbicort (formoterol + budesonide), did not show this lack of risk. From this, the

conclusion is these data do not suggest an etiology of the overall risk difference or the risk differences of the subsets. However, these data do substantiate and quantify an increased risk overall in serious asthma-related events with the use of LABAs.

Additionally, the FDA meta-analysis shows that there appear to be subsets of the population that are at greater risk of the adverse effects of LABAs. The increased risk in African Americans is already mentioned in the LABA labels, though changes in specificity and quantification of risk could be made. The FDA meta-analysis shows that the race-specific finding is maintained outside the SMART study, though data on baseline risk for racial sub-groupings was not available in this analysis. A compelling and significant subgroup analysis is the age effect noted with Symbicort, Serevent, and Foradil, which shows a gradual decrease in the point estimates of risk difference, with the 4-11 year age group showing a 1.5 in 100 subjects increased risk of asthma-related hospitalization or serious events compared to the non-LABA treatment group. The efficacy data presented in the pivotal trials for this age group do not show clear “added value” in terms of health benefits for this age group compared to short-acting beta agonists. The most pressing questions are:

- Should salmeterol continue to be indicated for the treatment of asthma, including the possible effects of concomitant controller therapy, e.g. inhaled corticosteroids?
 - in adults [≥ 18 years of age]
 - in adolescents [12-17 years of age]
 - in children [4-11 years of age]
- Should formoterol continue to be indicated for the treatment of asthma, including the possible effects of concomitant controller therapy, e.g. inhaled corticosteroids?
 - in adults [≥ 18 years of age]
 - in adolescents [12-17 years of age]
 - in children [5-11 years of age]
- Are there further risk mitigation strategies for LABAs that would be advisable?

IV. Recommendations

There are a range of possible recommendations that might address the benefit risk questions outlined above.

1. Continue to market LABAs with no changes to the labeling or indications.
 - i. This action would have to be justified in light of the newly acquired data.
2. Change the labeling on all LABAs to reflect not only the risk of serious asthma-related adverse effects which are already in the black boxed warning, but also populations now known to be at the highest risk for these effects:
 - i. African Americans (strengthen the language in the labels)
 - ii, Children <18 years of age (clarify the paucity of data on benefit

specific to these patients, and clarify the increased age-specific risk)
iii. This recommendation should be considered separately for Salmeterol-containing products and Formoterol-containing products, considering the possible effects of controller therapy

3. Withdraw the asthma indication as follows:
 - i. Withdraw the asthma indication and contraindicate the use of all LABAs in patients <18 years of age (Serevent, Foradil, Advair, Symbicort).
 - ii. Withdraw the asthma indication for Serevent and Foradil for adults (≥ 18 years of age).
 - iii. Obtain a post-marketing commitment for the the 2 ICS-containing products (Symbicort and Advair) for asthma treatment in adults.
4. Withdraw the asthma indication, or withdraw from the market as follows, with the exception of Advair:
 - i. Withdraw the asthma indication for Foradil and Serevent.
 - ii. Withdraw Symbicort from the market.
 - iii. Continue to indicate Advair for asthma in adults.
5. Withdraw the asthma indication, or withdraw from the market as follows:
 - i. Withdraw the asthma indication for Foradil, Serevent, and Advair.
 - ii. Withdraw Symbicort from the market.

The LABA review team in the Office of Surveillance and Epidemiology has shared views on the FDA meta-analysis and much of the large body of data in the public domain on LABA safety. The matters of agreement are that:

- There is a signal for asthma-associated morbidity and mortality in adults for at least some of the LABA products, most particularly for Serevent, which is a single entity LABA and is the LABA for which there are the most data.
- It is unclear what role inhaled corticosteroids play in mitigating LABA-associated risk.
- There is an age effect, such that the risk of LABA-attributable asthma-associated hospitalization is increased in children.
- The extent of increased risk of LABA use for other demographic subsets among adults is less clear than the risk of LABA use for the youngest age demographic.
- Therefore, the team unanimously recommends:
 - Withdrawing the asthma indication from all LABAs for individuals <18 years of age.
 - Removing the asthma indication and contraindicating the use of the single entity LABAs (Serevent and Foradil) for all ages.

However, the OSE LABA team did not reach consensus on recommendations for Symbicort and Advair use for the asthma indication in adults. The opinions varied:

- Two reviewers (AWM and SB) recommend a post-marketing commitment for Sponsors to perform large safety studies of Advair and Symbicort in adults, with a short-acting beta agonist + ICS as one of the control arms, and ICS as one of the control arms. This would be the next step towards addressing two of the large remaining questions: 1. how the safety and efficacy of short-acting beta agonists + ICS compare with the safety and efficacy of LABAs + ICS, and 2. whether concomitant ICS use mitigates LABA-associated risk in asthmatic patients.
- One reviewer (ADM) feels that it would be prudent to withdraw the asthma indications for Advair and Symbicort in adults as well, for the following reasons.
 1. Salmeterol increased asthma mortality in large controlled studies (i.e., the SMART and SNS trials).
 2. For formoterol, comparable data from large controlled trials are lacking, but it would not be prudent to assume formoterol is free from a similar risk.
 3. The data establishing that concomitant ICS fully protects against LABA-related asthma mortality are not robust.
 - a. Although salmeterol-related asthma mortality in SMART was more frequent among subjects who did not use ICS at baseline, this observation can provide only limited reassurance, because it relies on a post-hoc analysis of a small numbers of deaths, and requires extrapolating concomitant ICS from baseline ICS use.
 - b. In FDA's meta-analysis and one published meta-analysis, Advair appeared to have a neutral effect on the risk of asthma hospitalizations. However, in both SMART and SNS, the relative risk of asthma mortality was higher than the relative risk for asthma hospitalization, which in both trials was close to one. Accordingly, ruling out a risk of increased asthma hospitalizations may not rule out a risk of increased asthma deaths.
 - c. It could be argued that the asthma death rate with Advair in FDA's meta-analysis was lower than for salmeterol in SMART, but such cross-study comparisons must be made very cautiously.
 - d. For formoterol, FDA's meta-analysis suggests that concomitant ICS may not even prevent an increase in asthma hospitalizations.
 4. The nature and magnitude of the clinical benefits demonstrated for Advair and Symbicort in controlled trials are not judged to outweigh the aforementioned risk of increased mortality in asthma patients.
 5. Finally, from a public health policy standpoint, it would seem undesirable to continue to expose roughly three million asthma patients yearly to the LABA-ICS combination products, until there is more robust evidence that concomitant ICS ameliorates the increase in asthma mortality that would be expected from the LABA component.
- One reviewer (DJG) further recommends that the use of Symbicort be contraindicated in adults with asthma.
 1. Symbicort does not appear to confer a meaningful or substantial health benefit. From Table 12, we see that there was virtually no difference

between Symbicort and budesonide with respect to rescue medication use, asthma exacerbations, or nocturnal awakenings.

2. From Table 6, Symbicort conferred a net absolute risk increase of 7.5 per 1000 (~1 per 133) for the composite outcome of asthma hospitalization, intubation, or death, compared with budesonide.
3. Although the 95% confidence interval included 0, the importance and statistical probability that the risk is increased is far more likely than not. In matters where the risks are serious or potentially life-threatening, and the benefit is not life-saving, a demand for definitive proof of harm in the form of conventional statistical significance is not reasonable and undoubtedly injures more patients than it helps.
 - a. First, it rewards companies that perform small, statistically under-powered studies, as is the case here. Such studies are almost guaranteed to have wide confidence intervals, assuring the sponsor of a “negative” study.
 - b. Additionally, although the lower 95% bound on the interval was -1.47, the upper bound reached 16.44, which translates to an absolute risk of 1 per 61 patients. Statistically speaking, the value of 7.5 is the maximum likelihood, the most likely value describing the extent of risk. The minimal to non-existent health benefits documented in the pivotal trials for Symbicort do not justify a risk of hospitalization, intubation, or death of 1 per 133 or 1 per 61.

The situation with Advair is more complicated. If the risk of asthma hospitalization was increased by 1 per 284 per year or the risk of asthma death was increased by 1 per 900 per year with Advair use, would the modest health benefits observed justify continued use for asthma? These levels of risk with Advair are possible given the current data. Or, would it be more prudent to remove the indication for treatment of asthma in adults until better quality data become available to reduce the level of uncertainty? This is the dilemma we are faced with. Given that there are no data that suggest a protective effect for mortality with Advair, I’m inclined to recommend prudence and the withdrawal of the Advair indication for asthma in adults.

- Advair use was associated with an increase in the proportion of days without asthma symptoms and the proportion of days without rescue therapy use, when compared to fluticasone use (Table 10). Changes in the asthma quality of life score were modest at best and somewhat inconsistent across trials.
- Of the four LABA products evaluated, Advair was the only drug that did not appear to increase the absolute risk of asthma hospitalization, intubation, and death (Table 6). On the other hand, it did not reduce this risk either.
- The five pivotal trials conducted for the two formulations of Advair included fewer than 500 Advair-exposed patients total, a number far too small to exclude a risk of asthma death of greater than 1 per 200.

Basing an approval on such small numbers seems surprising given what was known about salmeterol and its risks from SNS at the time of approval of Advair Diskus in 2000, and from SNS and SMART at the time of approval of Advair HFA in 2006.

- Based on the total number of Advair-exposed patients included in the FDA meta-analysis (n=6648), and a mean duration of exposure of about 6 months, there was sufficient statistical power to exclude a risk of asthma death greater than about 1 per 900 person-years. This rate is not far-removed from that observed for Serevent in SNS and SMART (~1 per 700 person-years). For asthma hospitalization, an upper 95% bound of 1.70 per 1000 translates to an excess incidence of 1 per 284 person-years.

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Appendix

Scoring systems for select asthma outcome secondary endpoints.

Nocturnal asthma symptom score

5-point scale

- 0: Did not awaken due to breathing symptoms
- 1: Awakened at least once by breathing symptoms but did not use relief medication
- 2: Awakened once by breathing symptoms that were controlled by relief medication
- 3: Awakened more than once by breathing symptoms that were controlled by relief medications
- 4: Difficulty sleeping due to breathing symptoms despite relief medication use

Daytime asthma score

Scoring based on composite scoring of 4 symptoms: SOB, cough, chest tightness, wheezing

4-point scale

- 0: no symptoms
- 1: mild symptoms
- 2: moderate symptoms
- 3: severe symptoms

Quality of life scale (Juniper et al. Eur Resp J 1999; 14(1):32-38)

Validated 15-item self-administered questionnaire covering 4 domains:

- Symptoms (SOB; chest tightness; wheezing; cough; nocturnal awakening)
- Activity limitations (strenuous; moderate; social; work-related)
- Emotional functioning (frustration; concern ~ asthma; afraid of not having medication)
- Environmental stimuli (dust; cigarette smoke; weather/air pollution)

7-point scale

- 1: all the time
- 2: most of the time
- 3: a good bit of the time
- 4: some of the time
- 5: a little of the time
- 6: hardly any time
- 7: none of the time

Scores for all 15 items are combined to produce a composite score ranging from 1 (low QOL) TO 7 (QOL not impaired by asthma)

Long-Acting Beta-Agonists and Adverse Asthma Events Meta-Analysis

Statistical Briefing Package for

Joint Meeting of the Pulmonary-Allergy Drugs Advisory Committee, Drug Safety and Risk Management Advisory Committee and Pediatric Advisory Committee on
December 10-11, 2008

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1 EXECUTIVE SUMMARY

1.1 *Background*

This draft review presents a meta-analysis that explores possible associations of four long-acting beta agonists (LABAs) currently marketed in the United States with asthma-related hospitalization, asthma-related intubation, and asthma-related death in asthmatic patients. This meta-analysis was in response to the recommendations from the November 28, 2007 Pediatric Advisory Committee meeting to continue to assess the risks and benefits of the LABAs. The meta-analysis was not intended to be or capable of being definitive. Statistical significance was evaluated and confidence intervals are provided on major findings. Comparisons among drugs and subgroups do not involve statistical testing and are exploratory in nature. The major findings and the comparisons among drugs and subgroups, although not definitive, are intended to contribute to the information on the safety of these drugs for regulatory purposes.

The meta-analysis was based on patient-level data from randomized parallel controlled clinical trials available to the sponsors of LABAs. Although some of these drugs are marketed for other indications besides the treatment of asthma, only data from trials that studied the treatment of asthma were included. FDA provided instructions to the sponsors on the post-hoc adjudication of outcomes and the structure of data to be submitted. FDA prespecified the process for the statistical analysis including the overall review objectives; the definitions of the endpoints, study population, and selected subgroups; and the statistical methods. Revisions to certain definitions were necessary because of limitations in the data and are noted.

1.2 *Findings*

The meta-analysis considered four products that contain a LABA and are approved in the United States for the treatment of asthma: Advair (salmeterol, fluticasone), Foradil (formoterol), Serevent (salmeterol), and Symbicort (formoterol, budesonide). Two of these products, Advair and Symbicort, are combination products each containing a LABA and an inhaled corticosteroid (ICS). The study used data from 110 trials and 60,954 subjects that met the inclusion criteria for the analysis. The amount of data available varied for the products. The majority of subjects (43,824) were from Serevent trials. Advair trials accounted for 13,212 subjects, Foradil trials accounted for 3,765 subjects, and Symbicort trials accounted for 1,270 subjects. Note that some trials involved both Advair and Serevent subjects. The Serevent trial—Salmeterol Multicenter Asthma Research Trial (SMART) (Nelson et al. 2006)—provided a substantial percentage (43%) of the total subjects.

For the overall analysis set, 77% of subjects were between 18 and 64 years old, 11% between 12 and 17, 7% 65 and over, and 6% between 4 and 11. The majority of subjects were white/Caucasian (72%), female (57%), from United States centers (69%), and from trials with nominal treatment durations of 12 weeks or more (94%). The median actual treatment duration was 169 days. For age, gender, race, location, and trial duration, there were no notable differences between the treatment groups. Among subjects with available information, 55% of subjects used an ICS at baseline (based on N=55,062) and 65% used an ICS during the trial (based on N=55,611), including assigned treatment or concomitant

therapy. For both baseline ICS use and trial ICS use, there were no notable differences between treatment groups.

Overall, the meta-analysis showed that LABAs were associated with an increased risk of asthma-related events relative to non-LABA treatment as measured by the asthma composite endpoint consisting of asthma-related death, asthma-related intubation, and asthma-related hospitalization. Non-LABA treatment included ICSs, short-acting beta-agonists, other non-LABA treatments, placebo, or a combination of treatments. The risk difference estimate for the asthma composite endpoint of the LABA rate minus the non-LABA rate was 2.80 (95% CI: 1.11, 4.49) per 1000 subjects. This overall finding for the asthma composite endpoint was supported by both the asthma-related hospitalization and the asthma-related death components. However, findings for individual drugs and subgroups were driven by the asthma-related hospitalization component.

Three of the four drugs (Foradil, Serevent, Symbicort) had positive risk difference estimates for the asthma composite endpoint; however, only Serevent had a statistically significant estimate. The risk difference estimates for the asthma composite endpoint were positive both when (1) LABA without assigned ICS was compared to non-LABA treatment and (2) LABA with assigned ICS was compared to assigned ICS treatment. However, only comparison (1) was statistically significant [3.63 (95% CI: 1.51 – 5.75) per 1000 subjects], and comparison (2) had a small risk difference estimate [0.25 (95% CI: -1.69 – 2.18) per 1000 subjects].

There were 20 asthma-related deaths, 16 of which were in the LABA group and 4 of which were in the non-LABA group. All the asthma-related deaths were among Serevent-treated subjects.

There was a general trend among the age groups for the asthma composite endpoint, with higher risk difference estimates among the younger age groups. The 4 – 11 age group had a risk difference estimate of 14.83 (95% CI: 3.24, 26.43) per 1000 subjects. The risk difference estimates for all the age groups except for the ≥ 65 age group were positive and statistically significant. The trend among the age groups for the asthma composite endpoint was observed for each drug except for Advair.

All the race subgroups had positive risk difference estimates for the asthma composite endpoint. The black/African American subgroup had the highest risk difference estimate: 8.13 (95%CI: 1.88, 14.38) per 1000 subjects. Differences among race subgroups for the individual drugs were not apparent. The risk difference estimate for the asthma composite endpoint for females was somewhat larger than that for males. This difference between genders existed for individual drugs. There were no clear patterns among the other subgroups considered, which include subgroups based on center location, nominal trial duration, baseline ICS use, and trial ICS use.

From an examination of the Kaplan-Meier cumulative incidence curves for the asthma composite endpoint, it appeared that the increased hazard of events for the LABA treatment relative to the non-LABA treatment existed over the period of at least one year. The effect was driven by asthma-related hospitalizations.

Several sensitivity analyses were performed to examine the robustness of the primary findings to the inclusion of large trials and to statistical methods. The exclusion of the large trial SMART did not reduce the overall estimate for the asthma composite endpoint. The inclusion of the large trial Serevent Nationwide Surveillance (SNS) (Castle et al. 1993), which was not part of the primary analysis because of data availability, did not qualitatively affect the results. Various statistical methods did not reveal any notable deficiency in the primary method. However, there appeared to be some heterogeneity among the trials of the LABA effect. A statistical method that accounts for the heterogeneity produced qualitatively similar results as the primary method.

1.3 Limitations

The study had several limitations. (1) The trials included in the study were generally not designed to collect the endpoints considered in the analysis. (2) Information on dropout from the trials was not obtained. Differential dropout patterns may introduce bias. However, information on treatment duration was obtained and found to be similar between the comparison groups. (3) Information on individual subject and trial characteristics were limited. Potential unobserved differences in study populations among the drugs and subgroups may have been associated with the observed effects. This included concomitant ICS use and adverse event information ascertainment. (4) The study was designed with knowledge of the findings from SMART, which was included in the present study. Addressing this limitation, sensitivity analysis excluding SMART did not result in notable changes in the results based on the asthma composite endpoint. However, SMART was responsible for the majority of asthma-related deaths.

1.4 Conclusions

Based on the findings from this meta-analysis, LABAs as a group were associated with an increased risk of an asthma composite endpoint consisting of asthma-related hospitalization, asthma-related intubation, and asthma-related death among asthmatic subjects. This overall finding for the asthma composite endpoint was supported both by asthma-related hospitalization and the asthma-related death components. However, findings for individual drugs and subgroups were driven by the asthma-related hospitalization component.

The increased risk was seen in three of the four drugs studied, Foradil, Serevent, and Symbicort, but was not apparent in Advair. The increased risk was not apparent when the LABA was used in conjunction with an ICS.

Youths (age 4 – 11 years) appeared to be at the greatest risk among age groups. Blacks/ African Americans had observed elevated risks relative to other race subgroups. Females had observed elevated risks relative to males.

Differences in observed risk among the four drugs and in the use of ICS may be an artifact of differences among trials included in the meta-analysis and limitations on the information available for the meta-analysis.

2 INTRODUCTION

2.1 Background

This draft review presents a meta-analysis that explores possible associations of four long-acting beta agonists (LABAs) currently marketed in the United States with asthma-related hospitalization, asthma-related intubation, and asthma-related death in asthmatic patients. This meta-analysis was in response to the recommendations from the November 28, 2007 Pediatric Advisory Committee meeting to continue to assess the risks and benefits of the LABAs.

The labeling for these drugs currently contains a boxed warning that warns of asthma-related deaths associated with LABAs and specifies that these drugs should only be used for patients not adequately controlled on other asthma-controller medications or whose severity clearly warrants initiation of treatment with two maintenance therapies.

The boxed warnings were first applied to salmeterol containing products based on the Salmeterol Multicenter Asthma Research Trial (SMART) (Nelson et al. 2006). It was later extended to all LABAs. The SMART trial was a large simple randomized controlled safety trial (26,355 subjects, 28 week duration), which compared salmeterol plus usual care to placebo plus usual care. The primary hypothesis concerned respiratory death and life-threatening experiences. The secondary hypothesis concerned asthma-related deaths. The trial was stopped early due to safety concerns and subject recruitment issues. The salmeterol group had a worse outcome for asthma-related death. The adverse finding was differentially worse in the African American subgroup.

There are currently six LABA-containing products approved in the United States. Some of these LABAs have multiple approved delivery devices. Table 1 lists these products and a summary of their indications. The products Brovana and Perforomist are approved in the United States for only chronic obstructive pulmonary disease (COPD) and only a small number of asthma trials are available for these drugs. These two drugs were not considered in the review, because of the limited data and the lack of corresponding benefit information for asthmatic patients.

Table 1: LABA Containing Products Approved in the United States and their Indications.

Brand Name	Sponsor	Active Ingredient(s)	Indication Summary
Advair	GSK	salmeterol, fluticasone	asthma, age ≥ 4 years; COPD
Brovana	Sepracor	arformoterol	COPD
Foradil	Novartis	formoterol	asthma, age ≥ 5 years; COPD, age ≥ 5
Perforomist	Dey	formoterol	COPD
Serevent	GSK	salmeterol	asthma, age ≥ 4 years; COPD
Symbicort	AstraZeneca	formoterol, budesonide	asthma, age ≥ 12 years

2.2 Review Objectives

1. Examine if LABAs are associated with increased risks of the serious asthma related events: asthma-related death, asthma-related intubation, and asthma-related hospitalizations.
2. Examine the risk in subgroups defined by
 - a. inhaled corticosteroid (ICS) use
 - b. demographics, with special interest to age, sex, and race
 - c. baseline asthma severity
 - d. baseline asthma control

The factors baseline asthma severity and asthma-control status could not be considered because insufficient information was available.

3 DATA SOURCES

3.1 Data Requests

On January 9, February 13, March 6, April 21, and May 7, 2008, FDA sent letters to the sponsors of LABAs requesting trial-level and patient-level data for asthma trials. These letters specified the inclusion criteria for trials, the adjudication of asthma-related events, the format and variables of the data to be submitted to FDA, and quality assurance procedures to be performed by the sponsors.

3.1.1 Trial Inclusion Criteria

The patient-level request specified the following inclusion and exclusion criteria:

- Include all blinded, parallel-arm, randomized, controlled trials conducted with LABAs in the treatment of asthma.
- Include trials in which the compound was administered as randomized treatment, either with or without a concomitant inhaled corticosteroid (ICS) or other adjunctive therapy.
- Include placebo- and/or active-controlled trials.

- Include trials in which there was a randomized blinded phase followed by an open-label extension phase.
- Include randomized, double-blind crossover design trials. However, include only the first cross-over period of the trial.
- Do not include trials in indications other than asthma, uncontrolled trials, or trials designed primarily to obtain clinical pharmacology data (e.g., Phase I trials).
- Include only trials in which unblinded and locked data were available as of January 1, 2008.

3.1.2 Identification and Adjudication of Events

The request called for the search and identification of the following events:

- (1) All-cause death
- (2) Asthma-related death
- (3) Asthma-related intubation
- (4) Asthma-related hospitalization.

A patient may have more than one of these events related to a single experience. For example, a patient who had an asthma-related hospitalization, followed by an asthma-related intubation and died of an asthma-related cause was to be considered as having each of the four events. All four events were to be reported not just the most critical.

The request stated all serious adverse events reported in the trials should be reviewed, in a manner blinded to treatment, to determine whether the event involved death, hospitalization, or intubation and whether the event occurred in the setting of an acute asthma exacerbation or was otherwise asthma-related. The determination of asthma-relatedness was to be based on the clinical judgment of at least one physician blinded to treatment. The search was not to be based on medical dictionary coded terms alone.

The patient-level request specified the search period:

- For parallel-arm trials without an open-label extension, the search period was from the beginning of treatment to the end of follow-up. The complete follow-up period included the entire period of observation and was not taken to mean the last date on study drug for subjects who discontinued prior to the end of the study.
- For parallel-arm trials with an open-label extension, the search period was from the beginning of treatment to the last day of blinded treatment.
- For crossover design trials, the search period was from the beginning of treatment to the last day of blinded treatment in the first cross-over period.

3.1.3 Dataset Definition

The patient-level request called for a patient-level dataset and an auxiliary trial-level dataset. The patient-level dataset was to contain one record for each event or for each patient for patients without events. The patient-level dataset included variables for trial identification, patient identification, age, sex, race, treatment assignment, ICS use at baseline and during trial, rescue medicine episodes, dosages, event type and relative day, location of center (United States v. Non- United States), baseline smoker status, baseline COPD comorbidity, and baseline and end-of-therapy forced expiratory volume in one second (FEV1) measurements.

The auxiliary trial-level datasets was to contain trial identification, studied indication, nominal treatment duration, nominal follow-up duration, ICS-use inclusion and exclusion criteria, age inclusion and exclusion criteria, trial design characteristics, trial dosages, and subject counts.

4 METHODS

The meta-analysis was not intended to be or capable of being definitive. Statistical significance was evaluated and confidence intervals are provided on major findings. Comparisons among drugs and subgroups do not involve statistical testing and are exploratory in nature. The major findings and the comparisons among drugs and subgroups, although not definitive, are intended to contribute to the information on the safety of these drugs for regulatory purposes.

The process of exploration was pre-specified. This included the review objectives; the proposed definitions of the endpoints, study population, and selected subgroups; and the statistical methods. Some of these proposals were modified, chiefly because of data limitations. These modifications are highlighted below. Members of the review team participated in the development of the proposed analysis plan.

4.1 Endpoints

The original intention was to consider each of the three asthma-related events (asthma-related death, asthma-related intubation, and asthma-related hospitalization) separately and jointly as a composite endpoint. However, because of limitation of the data, the asthma-related intubation endpoint could not be considered separately.

As noted above, a subject may have experienced more than one of these events. Only events that occurred during blinded treatment are considered. The endpoints are:

1. Asthma-related death (asthma death)
2. Asthma-related death and/or intubation (asthma death/intubation)
3. Asthma-related hospitalization (asthma hospitalization)
4. Asthma-related death, intubation, or hospitalization (asthma composite)

In addition to the above endpoints, death of any cause endpoint was considered. This endpoint includes all deaths during blinded treatment.

4.2 Analysis Set

The overall analysis set consisted of all subjects in trials that met the trial inclusion and exclusion criteria specified in the requests to the sponsors and the following additional exclusion criteria:

- Exclude trials if the nominal blinded-treatment duration was less than 7 days
- Exclude trials if there were fewer than 20 subjects in any comparison group
- Exclude subjects with assigned doses not approved for the treatment of asthma.
- Exclude subjects whose age is not in the approved age range for the (see Table 1).

Although only subjects with approved dosage treatments were included, the specific delivery device was not part of the inclusion/exclusion criteria. For each drug, data from multiple delivery devices were included. For Symbicort, both Symbicort pMDI and Symbicort TBH were included. Symbicort TBH is not approved in the United States.

4.3 Comparisons

Subjects randomized to treatment with a LABA were compared to subjects randomized to non-LABA treatment. Non-LABA treatment refers to ICSs, short-acting beta-agonists, other non-LABA treatments, placebo, or a combination of treatments. For each trial, the LABA group may have had therapy (assigned therapy or “usual” therapy) in addition to the LABA if the comparison group had the same therapy, including dosing.

In addition to the overall comparison, two additional comparisons were considered. Each of these comparisons is a subset of the overall comparison.

4.3.1 LABA without Randomized ICS versus No LABA, (LABA wo/R ICS v. No LABA)

Subjects randomized to a LABA but not randomized to an ICS were compared to subjects randomized to non-LABA treatments. This comparison is referred to as LABA wo/R ICS v. No LABA. Note that the combination products Advair and Symbicort cannot be part of this comparison.

4.3.2 LABA with Randomized ICS versus Randomized ICS, (LABA w/R ICS v. R ICS)

Subjects randomized to treatment with a LABA and an ICS were compared to subjects randomized to ICS and any non-LABA treatment. The specific ICS must have been the same for both treatment groups within each trial, including dosing. This comparison is referred to as LABA w/R ICS v. R ICS.

4.4 Subgroups

The following subgroups were analyzed for the overall analysis set and for each LABA separately if the necessary data were available.

4.4.1 Nominal Trial Duration

- Trials with less than 12 weeks of blinded treatment
- Trials with 12 or more weeks of blinded treatment

4.4.2 Baseline Asthma Severity

- Mild: Predicted FEV1 \geq 80%
- Moderate: $60\% \leq$ Predicted FEV1 $< 80\%$
- Severe: Predicted FEV1 $< 60\%$

Insufficient data were obtained from the sponsors on baseline asthma severity and the subgroup is not analyzed.

4.4.3 Baseline Asthma Control

Note: There was no direct measure of baseline asthma control.

4.4.4 Baseline ICS Use

- ICS use at baseline
- No ICS use at baseline

4.4.5 ICS Trial Use

- ICS use during trial (including assigned therapy and concomitant use)

- No ICS use during trial

4.4.6 *Demographics*

1. Age
 - 4-11
 - 12-17
 - 18-64
 - ≥ 65
2. Race
 - White/Caucasian
 - Black/African American
 - Asian
 - Other
3. Gender
 - Male
 - Female
4. Location
 - United States
 - Other

4.5 ***Statistical Methods***

4.5.1 *Primary Method*

The primary analysis method was the Mantel-Haenszel risk difference and associated confidence interval (Greenland, Robins 1985). This method makes use of trials with no events. The unit of analysis was the subject and the stratification factor was the trial.

4.5.2 *Sensitivity Analyses*

Several sensitivity analyses were employed to examine the robustness of the primary method. The sensitivity analyses were performed with the asthma composite endpoint.

The first sensitivity analysis examined the effect of the small numbers of events. The exact method for a stratified odds ratio and associated 95% confidence interval (Agresti 1992) was used for this purpose. The unit of analysis was the subject and the stratification factor was the trial.

The second sensitivity analysis examined between-trial heterogeneity of the effect measure and its consequences on the overall estimate. Zelen's test (Agresti 1992), an exact test, was used to test the hypothesis of a common odds ratio. However, because of the small number of events, there was expected to be little power to detect heterogeneity of the odds ratio across trials. The result of the test was intended for qualitative purposes. A generalized linear mixed model (GLMM) (McCulloch, Searle 2001) was used to estimate the overall odds ratio in the presence of trial heterogeneity of the odds ratio. The model used the binomial error distribution and logit link function. The model included fixed effects for the trial and treatment effects and a random effect on the trial-level for the treatment-trial interaction. The estimate and the 95% confidence interval of the treatment effect were qualitatively compared to those from the exact odds ratio method to

examine the effect of trial heterogeneity. The confidence interval of the variance component of the random effect was examined to evaluate trial heterogeneity.

The influence of two large trials was examined. These trials were SMART and Serevent Nationwide Surveillance (SNS) (Castle et al. 1993). Patient-level data were available for SMART and the trial is included in the primary analysis. Only trial-level summary data for asthma hospitalization and asthma death were available for SNS and the trial is not included in the primary analysis. One sensitivity analysis examined the overall results with the exclusion of SMART. A second sensitivity analysis examined the overall results with the inclusion of SNS.

4.5.3 Exploratory

Kaplan-Meier survival curves were used to examine the time-pattern (hazard function) of the asthma composite endpoint.

4.5.4 Missing values

For each analysis, all subjects with the necessary information for the specific analysis were used. No imputation was used.

4.5.5 Multiplicity

Because the analysis was exploratory in nature, no adjustments for multiplicity will be made unless otherwise noted.

4.5.6 Statistical Significance

Statistical significance refers to a two-sided type 1 error of 0.05.

5 PATIENT SUMMARY

Table 2 gives the number of trials and subjects by treatment group for the overall analysis set, the “LABA w/R ICS v. No LABA” comparison, the “LABA w/R ICS v. R ICS” comparison, and for each drug. Overall, there were 110 trials that met the analysis inclusion criteria consisting of 60,954 subjects. There were roughly equal numbers of LABA subjects (30,148) and No LABA subjects (30,806). There were appreciably more subjects (46,760) from trials in which the LABA treatment group did not include assigned ICS (LABA w/R ICS v. No LABA” comparison) than subjects (15,192) from trials in which the LABA treatment group included assigned ICS (“LABA w/R ICS v. R ICS” comparison).

The majority of subjects (43,824) were from Serevent trials. Of these subjects, 26,355 subjects were from SMART. There were 13,212 subjects from Advair trials, 3,765 subjects from Foradil trials, and 1,270 subjects from Symbicort trials.

Table 2: Trial and Subject Counts by Comparison Group and Drug.

	Trials		Subjects	
	N=110 n (n/N%)	No LABA N=30806 n (n/N%)	LABA N=30148 n (n/N%)	Total N=60954 n (n/N%)
LABA wo/ R ICS v. No LABA	77 (70)	24474 (79)	22286 (74)	46760 (77)
LABA w/R ICS v. R ICS	43 (39)	7330 (24)	7862 (26)	15192 (25)
Advair				
Total	36 (33)	6564 (21)	6648 (22)	13212 (22)
LABA wo/ R ICS v. No LABA	-	-	-	-
LABA w/R ICS v. R ICS	36 (33)	6564 (21)	6648 (22)	13212 (22)
Serevent				
Total	66 (60)	22716 (74)	21108 (70)	43824 (72)
LABA wo/ R ICS v. No LABA	63 (57)	22335 (73)	20660 (69)	42995 (71)
LABA w/R ICS v. R ICS	4 (4)	427 (1)	448 (1)	875 (1)
Foradil				
Total	14 (13)	2139 (7)	1626 (5)	3765 (6)
LABA wo/ R ICS v. No LABA	14 (13)	2139 (7)	1626 (5)	3765 (6)
LABA w/R ICS v. R ICS	-	-	-	-
Symbicort				
Total	4 (4)	504 (2)	766 (3)	1270 (2)
LABA wo/ R ICS v. No LABA	-	-	-	-
LABA w/R ICS v. R ICS	4 (4)	504 (2)	766 (3)	1270 (2)

Notes:

11 trials and 1163 “No LABA” subjects appear in more than one category. Specifically,

- 1 trial appears in both the Advair and Serevent analysis sets and only in the “LABA w/R ICS v. R ICS comparison”. 165 “No LABA” subjects from this trial appear in both the Advair and Serevent analysis sets.
- 9 trials appear in both the Advair and Serevent analysis sets in which all the Advair subjects appear in the “LABA w/R ICS v. R ICS” comparison and all the Serevent subjects appear in the “LABA wo/R ICS v. No LABA” comparison. 952 “No LABA” subjects from these trials appear in both the “LABA wo/R ICS v. No LABA”, and “LABA w/R ICS v. R ICS” comparisons.
- 1 trial appears in both the “LABA wo/R ICS v. No LABA” and the “LABA w/R ICS v. R ICS” comparisons and only in the Serevent analysis set. 46 “No LABA” subjects from this trial appear in both the “LABA wo/R ICS v. No LABA” and the “LABA w/R ICS v. RICS” comparisons.

Tables 3 and 4 give the subject characteristics and asthma characteristics for the overall analysis set. The Appendix provides these summaries for the each comparison and for each drug.

For the overall analysis set, 77% of subjects were between 18 and 64 years old, 11% between 12 and 17, 7% 65 and over, and 6% between 4 and 11. There were 3,415 subjects between age 4 and 11. For race, 72% were white/Caucasian, 14% were other or unknown, 11% were black/African American, and 4% were Asian. There were 6,852 black/African American subjects. The majority of subjects were female (57%), from United States centers (69%), and from trials with nominal treatment durations of 12 weeks or more (94%). For age, gender, race, location, and nominal trial duration, there were no notable differences between the treatment groups and the percentages of missing values were small. The median treatment duration was 169 days in both the LABA and non-LABA group.

There were large numbers of missing values for baseline predicted FEV1. This characteristic was not analyzed. Among subjects with available information, 55% of subjects used ICS at baseline and 65% used ICS during the trial, including assigned treatment or concomitant therapy. For both baseline ICS use and trial ICS use, there were no notable differences between treatment groups.

The “LABA wo/R ICS v. No LABA” comparison had similar characteristics as the overall analysis set (see Table 7) but had higher percentages of subjects with United-States Centers. The “LABA w/R ICS v. RICS” comparison also had similar characteristics (see Table 8) but with a majority of subjects in non-United States centers. This comparison also had shorter median treatment durations than the overall groups 91 versus 169 days.

Table 3: Subject Characteristics.

Characteristic		No LABA N=30806 n (n/N%)	LABA N=30148 n (n/N%)	Total N=60954 n (n/N%)
Age (Years)	4-11	1789 (6)	1626 (6)	3415 (6)
	12-17	3289 (11)	3103 (11)	6392 (11)
	18-64	23604 (77)	23274 (77)	46878 (77)
	≥ 65	2097 (7)	2117 (7)	4214 (7)
	Missing	27 (0)	28 (0)	55 (0)
	Median (Min - Max)	36 (4 – 93)	37 (4 – 100)	37 (4 – 100)
Gender	Female	17528 (57)	17177 (57)	34705 (57)
	Male	13121 (43)	12830 (43)	25951 (43)
	Missing	157 (1)	141 (0)	298 (0)
Race	Asian	1029 (3)	1116 (4)	2145 (4)
	Black/African American	3428 (11)	3424 (11)	6852 (11)
	White/Caucasian	22150 (72)	21558 (72)	43708 (72)
	Other/Unknown	4199 (14)	4050 (13)	8249 (14)
Location	United States	21478 (70)	20497 (68)	41975 (69)
	Other	8339 (27)	8959 (30)	17298 (28)
	Missing	989 (3)	692 (2)	1681 (3)
Nominal Trial Duration (weeks)	< 12	1663 (5)	1733 (6)	3396 (6)
	≥ 12	29143 (95)	28415 (94)	57558 (94)
Treatment Duration (days)	Median (Min - Max)	169 (1 – 506)	169 (1 – 506)	169 (1 – 506)
	Missing	620	573	1193

Table 4: Subject Asthma Characteristics.

Characteristic		No LABA N=30806 n (n/N%)	LABA N=30148 n (n/N%)	Total N=60954 n (n/N%)
Baseline Predicted FEV1 (%)	< 60	3905 (13)	3791 (13)	7696 (13)
	60 – 80	7194 (23)	7005 (23)	14199 (23)
	≥ 80	3460 (11)	3273 (11)	6733 (11)
	Missing	16247 (53)	16079 (53)	32326 (53)
Baseline ICS Use	No	12763 (41)	11905 (39)	24668 (41)
	Yes	14956 (49)	15438 (51)	30394 (50)
	Missing	3087 (10)	2805 (9)	5892 (10)
ICS Use During Trial	No	9723 (32)	9678 (32)	19401 (32)
	Yes	18312 (59)	17898 (59)	36210 (59)
	Missing	2771 (9)	2572 (9)	5343 (9)

6 OVERALL FINDINGS

Of the 110 trials, 77 had at least one asthma composite event. Table 5 gives the number of events for each endpoint by treatment group and for the two additional comparisons. Table 6 gives the number of events for each endpoint by treatment group for each drug. For the overall analysis set, there were 20 Asthma deaths with 16 occurring in the LABA group and 4 occurring in the No LABA group. There were 71 Asthma Death/Intubation events, with 44 occurring in the LABA group and 27 occurring in the No LABA group. There were 668 Asthma Hospitalization events, with 369 occurring in the LABA group and 299 occurring in the No LABA group. For the overall analysis set, for each endpoint, the percentage of subjects with an event was higher in the LABA groups than in the No LABA group.

All the asthma-related deaths and intubations were from Serevent subjects. Conversely, for the drugs Advair, Foradil, and Symbicort, the only adverse asthma-related events were asthma-related hospitalization. For each drug, for the asthma-related hospitalization endpoint, the percentage of subjects with an event was higher in the LABA groups than in the No LABA group. However, the difference for Advair was lower than for the other drugs.

Table 5: Event Counts by Comparison Group.

	No LABA	LABA	Total
	N=30806	N=30148	N=60954
Overall	n (n/N%)	n (n/N%)	n (n/N%)
Asthma Death	4 (.01)	16 (.05)	20 (.03)
Asthma Death/Intubation	27 (.09)	44 (.15)	71 (.12)
Asthma Hospitalization	299 (.97)	369 (1.22)	668 (1.10)
Asthma Composite	304 (.99)	381 (1.26)	685 (1.12)
All Cause Death	40 (.13)	51 (.17)	91 (.15)
	N=24474	N=22286	N=46760
LABA wo/ RICS v. No LABA	n (n/N%)	n (n/N%)	n (n/N%)
Asthma Death	4 (.02)	15 (.07)	19 (.04)
Asthma Death/Intubation	27 (.11)	43 (.19)	70 (.15)
Asthma Hospitalization	274 (1.12)	338 (1.52)	612 (1.31)
Asthma Composite	279 (1.14)	350 (1.57)	629 (1.35)
All Cause Death	36 (.15)	47 (.21)	83 (.18)
	N=7330	N=7862	N=15192
LABA w/R ICS v. R ICS	n (n/N%)	n (n/N%)	n (n/N%)
Asthma Death	0 (.00)	1 (.01)	1 (.01)
Asthma Death/Intubation	0 (.00)	1 (.01)	1 (.01)
Asthma Hospitalization	26 (.35)	31 (.39)	57 (.38)
Asthma Composite	26 (.35)	31 (.39)	57 (.38)
All Cause Death	4 (.05)	4 (.05)	8 (.05)

1 “No LABA” subject with an asthma hospitalization appears in the summaries for the endpoints asthma hospitalization and asthma composite in both the “LABA wo/R ICS v. No LABA” and “LABA w/R ICS v. R ICS” comparisons.

Table 6: Event Counts by Drug.

	No LABA	LABA	Total
Advair	N=6564 n (n/N%)	N=6648 n (n/N%)	N=13212 n (n/N%)
Asthma Death	0 (0)	0 (0)	0 (0)
Asthma Death/Intubation	0 (0)	0 (0)	0 (0)
Asthma Hospitalization	20 (.30)	21 (.32)	41 (.31)
Asthma Composite	20 (.30)	21 (.32)	41 (.31)
All Cause Death	4 (.06)	3 (.05)	7 (.05)
Serevent	N=22716 n (n/N%)	N=21108 n (n/N%)	N=43824 n (n/N%)
Asthma Death	4 (.02)	16 (.08)	20 (.05)
Asthma Death/Intubation	27 (.12)	44 (.21)	71 (.16)
Asthma Hospitalization	265 (1.17)	324 (1.53)	589 (1.34)
Asthma Composite	270 (1.19)	336 (1.59)	606 (1.38)
All Cause Death	35 (.15)	48 (.23)	83 (.19)
Foradil	N=2139 n (n/N%)	N=1626 n (n/N%)	N=3765 n (n/N%)
Asthma Death	0 (0)	0 (0)	0 (0)
Asthma Death/Intubation	0 (0)	0 (0)	0 (0)
Asthma Hospitalization	14 (.65)	18 (1.11)	32 (.85)
Asthma Composite	14 (.65)	18 (1.11)	32 (.85)
All Cause Death	1 (.05)	0 (.00)	1 (.03)
Symbicort	N=504 n (n/N%)	N=766 n (n/N%)	N=1270 n (n/N%)
Asthma Death	0 (0)	0 (0)	0 (0)
Asthma Death/Intubation	0 (0)	0 (0)	0 (0)
Asthma Hospitalization	1 (.20)	6 (.78)	7 (.55)
Asthma Composite	1 (.20)	6 (.78)	7 (.55)
All Cause Death	0 (0)	0 (0)	0 (0)

1 “No LABA” subject with an asthma hospitalization appears in the summaries for the endpoints “asthma hospitalization” and “asthma composite” in both Advair and Serevent.

Figure 1 shows the estimated risk differences and 95% confidence intervals for the four asthma endpoints for the overall analysis set. A positive risk difference implies that the LABA group was associated with a higher rate of the endpoint than the No LABA group. Note that a positive risk difference estimate does not imply that the true risk difference was positive. A confidence interval that does not contain the value of 0 implies that the risk difference was statistically significant.

The risk difference estimate for each endpoint was positive and statistically significant. The risk difference estimated for the asthma composite endpoint was 2.80 (95% CI: 1.11 – 4.49) per 1000 subjects. The discussion in this section focuses on the asthma composite endpoint. This endpoint was driven by asthma-related hospitalization. The Appendix provides tables of all risk difference estimates and associated confidence intervals for all endpoints, comparisons, and subgroups. Discussion for the other endpoints and the individual drugs are based on the Appendix tables.

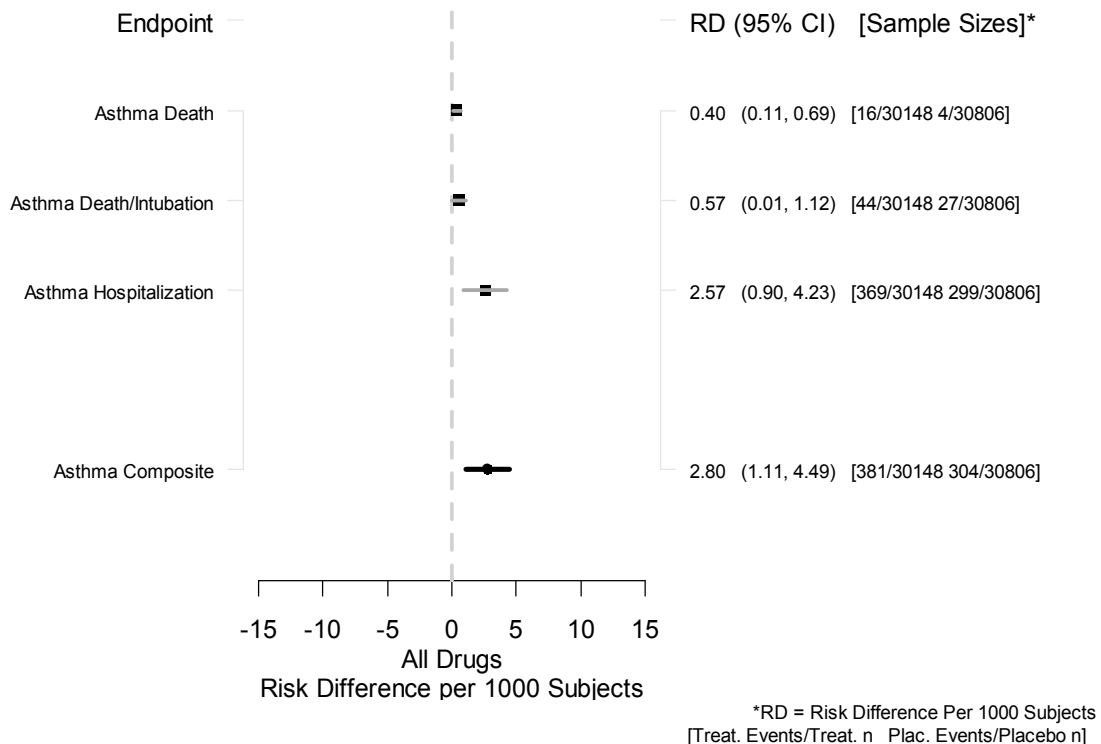


Figure 1: Risk Difference Estimates: Asthma Endpoints.

Figure 2 shows the results for the asthma composite endpoint for the overall analysis set and for the “LABA wo/R ICS v. No LABA” and “LABA w/R ICS v. R ICS” comparisons. For the “LABA wo/R ICS v. No LABA” comparison, the risk difference estimate was 3.63 (95% CI: 1.51 – 5.75) per 1000 subjects, which was statistically significant. For the “LABA w/R ICS v. R ICS” comparison, the risk difference estimate was 0.25 (95% CI: -1.69 – 2.18) per 1000 subjects, which was not statistically significant.

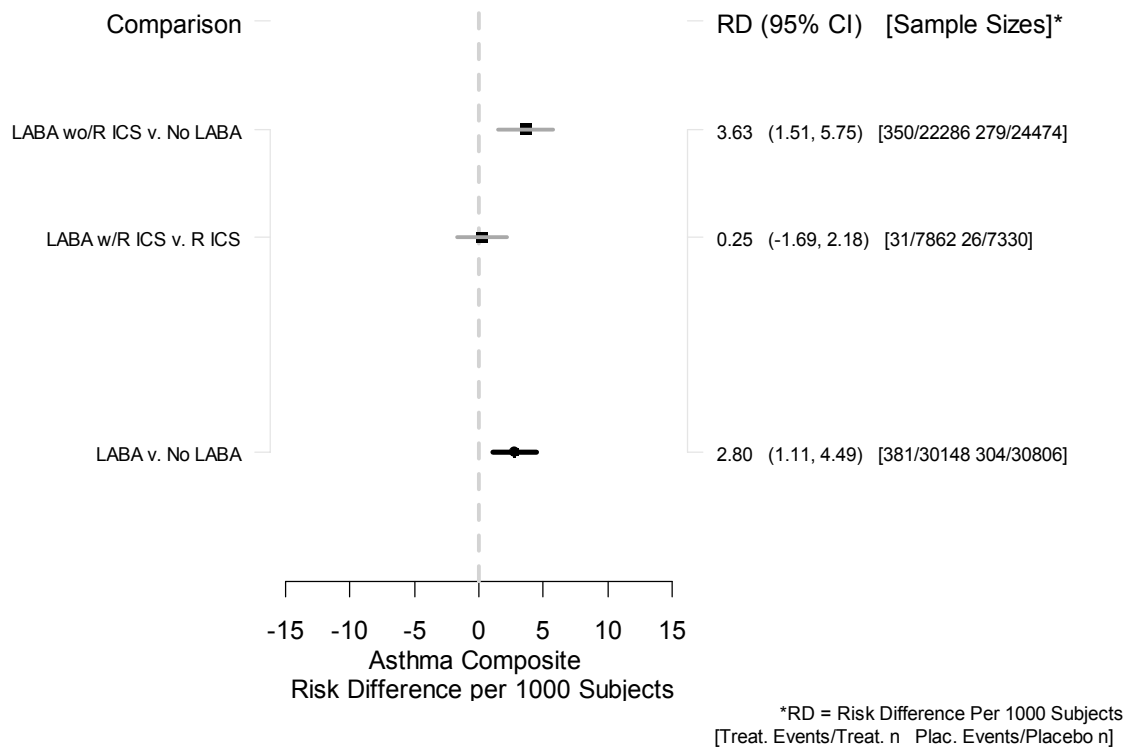


Figure 2: Risk Difference Estimates: Asthma Composite by Comparison.

Figure 3 shows the results for the asthma composite endpoint for the individual drugs. Three of the four drugs, Serevent, Foradil, and Symbicort had positive risk difference estimates for the asthma composite endpoint. Only Serevent had statistically significant risk difference estimate. The risk difference estimate for Advair was negative and not statistically significant. The risk difference estimate for Advair was negative and not statistically significant.

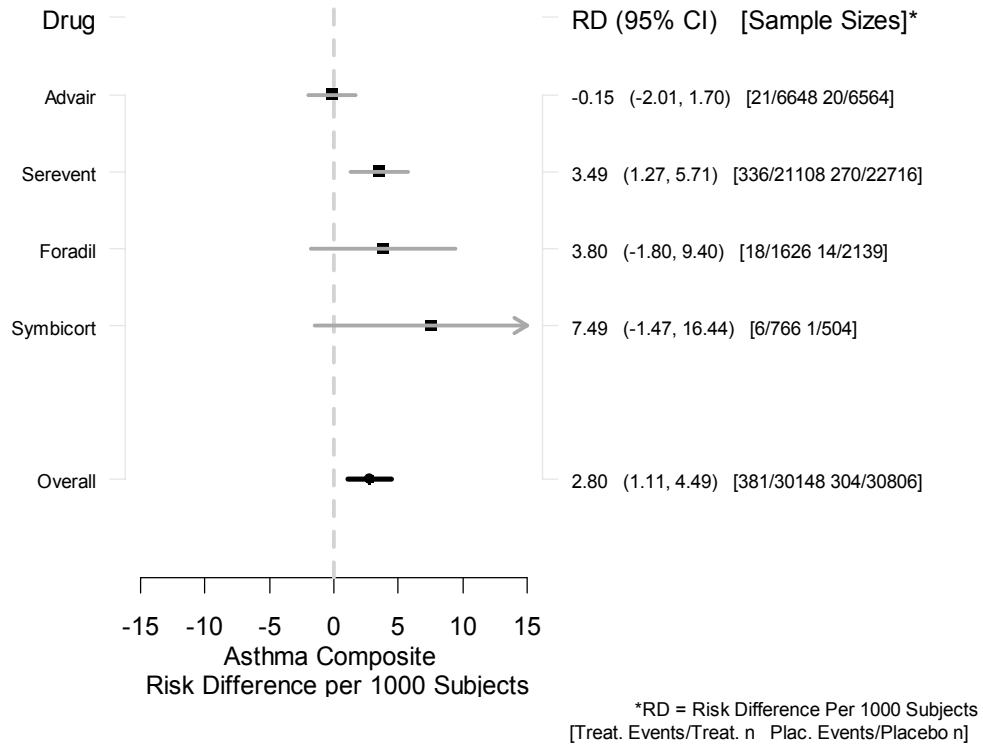


Figure 3: Risk Difference Estimates: Asthma Composite by Drug.

6.1.1 Age

Figure 4 shows the results for the asthma composite endpoint for the overall analysis set by the age subgroups. There was a general trend among the age groups, with higher risk difference estimates among the younger age groups. The 4 -11 age group had a risk difference estimate of 14.83 (95% CI: 3.24, 26.43) per 1000 subjects. The risk difference estimates for all the age groups but the ≥ 65 age group were positive and statistically significant. Based on the review of the results of the individual endpoints given in the Appendix, the results and trend among the age groups were driven by the asthma hospitalization component of the asthma composite endpoint. This trend among the age groups for the asthma composite endpoint was apparent when each drug is considered individually, except in the case of Advair (see Appendix).

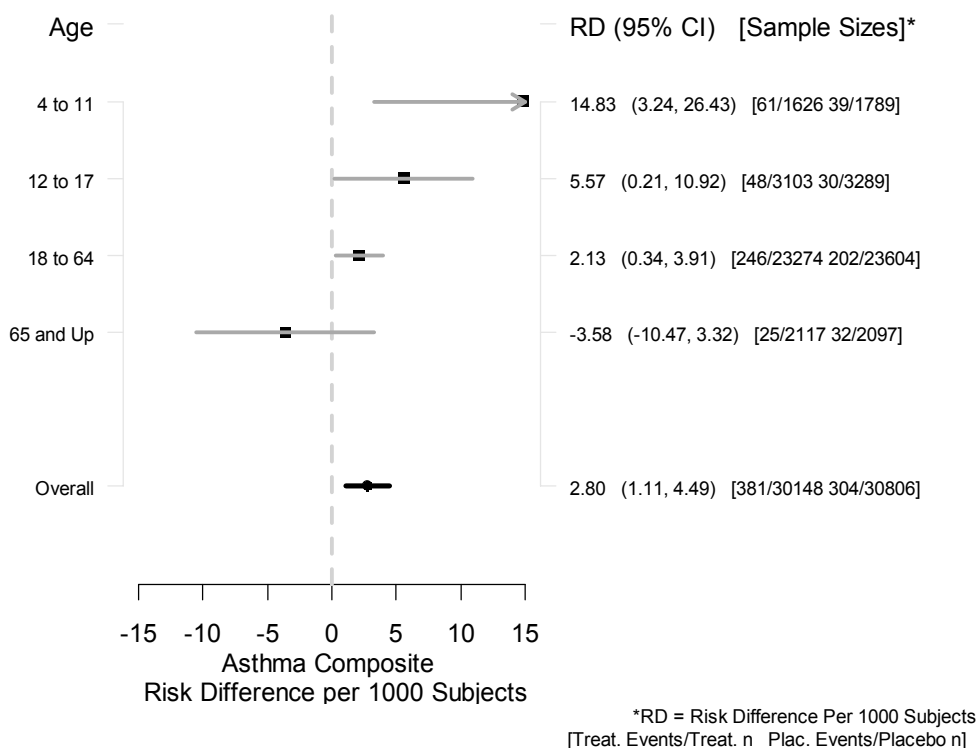


Figure 4: Risk Difference Estimates: Asthma Composite by Age Subgroups.

6.1.2 Race

Figure 5 shows the results for the asthma composite endpoint for the overall analysis set by the race subgroups. All the race subgroups had positive risk difference estimates. The risk differences estimate for black/African American and white subgroups were statistically significant. The black/African Americans subgroup had the highest risk difference estimate 8.13 (95% CI: 1.88, 14.38) per 1000 subjects. The white subgroup had the largest number of subjects resulting in the narrowest confidence interval. Differences among race subgroups for the individual drugs were not apparent (see Appendix).

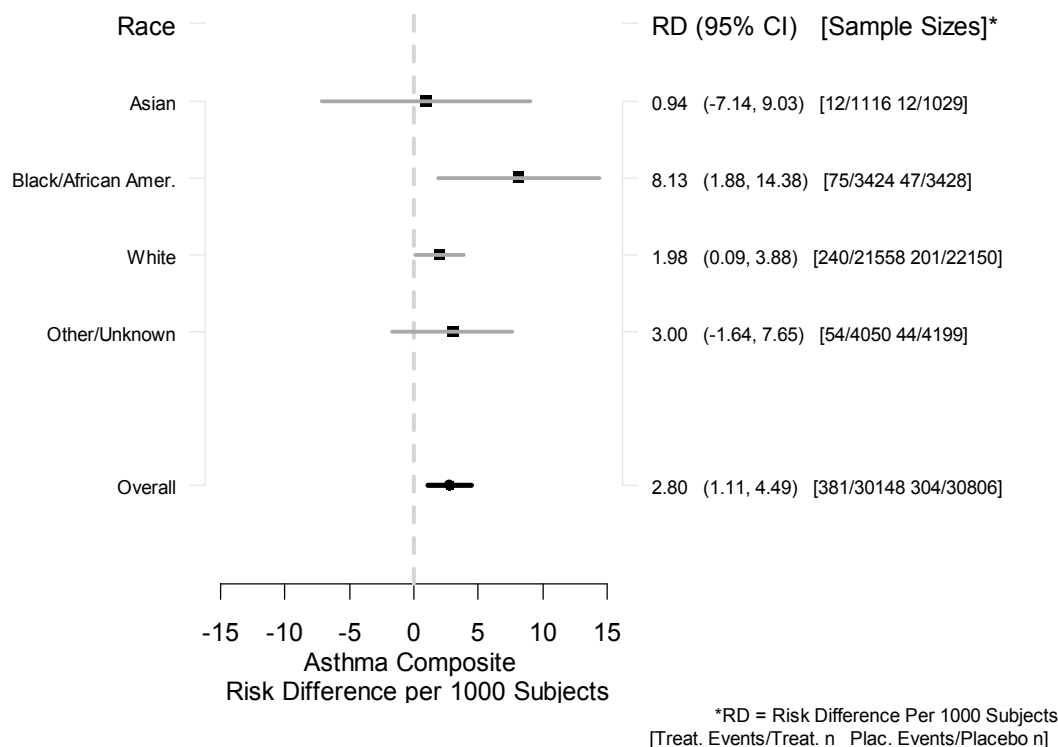


Figure 5: Risk Difference Estimates: Asthma Composite by Race Subgroups.

6.1.3 Gender

Figure 6 shows the results for the asthma composite endpoint for the overall analysis set by the gender subgroups. The risk difference estimate for females was notably larger than that for males. This difference between genders existed for individual drugs (see Appendix)

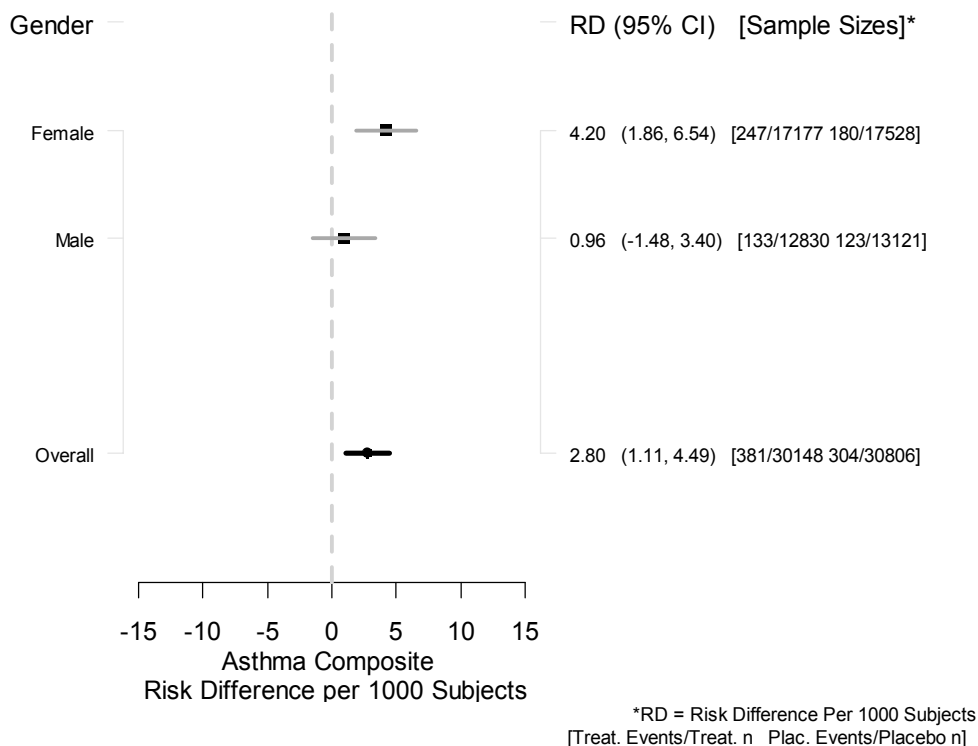


Figure 6: Risk Difference Estimates: Asthma Composite by Gender Subgroups.

6.1.4 Location

Figure 7 shows the results for the asthma composite endpoint for the overall analysis set by the location subgroups. The results for the United States and Non-United States subgroups were not statistically different.

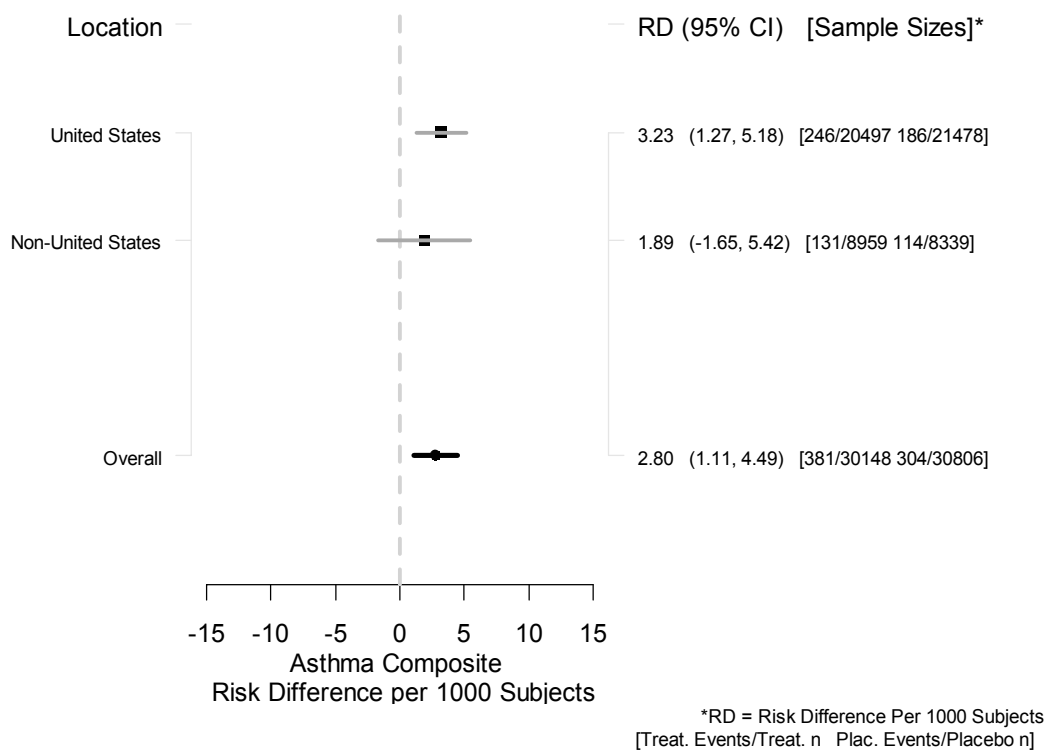


Figure 7: Risk Difference Estimates: Asthma Composite by Location Subgroups.

6.1.5 Nominal Trial Duration

Figure 8 shows the results for the asthma composite endpoint for the overall analysis set by the trial duration subgroups. The results for trials with less than 12 weeks treatment duration and for trials with 12 or more weeks of treatment duration were not statistically different.

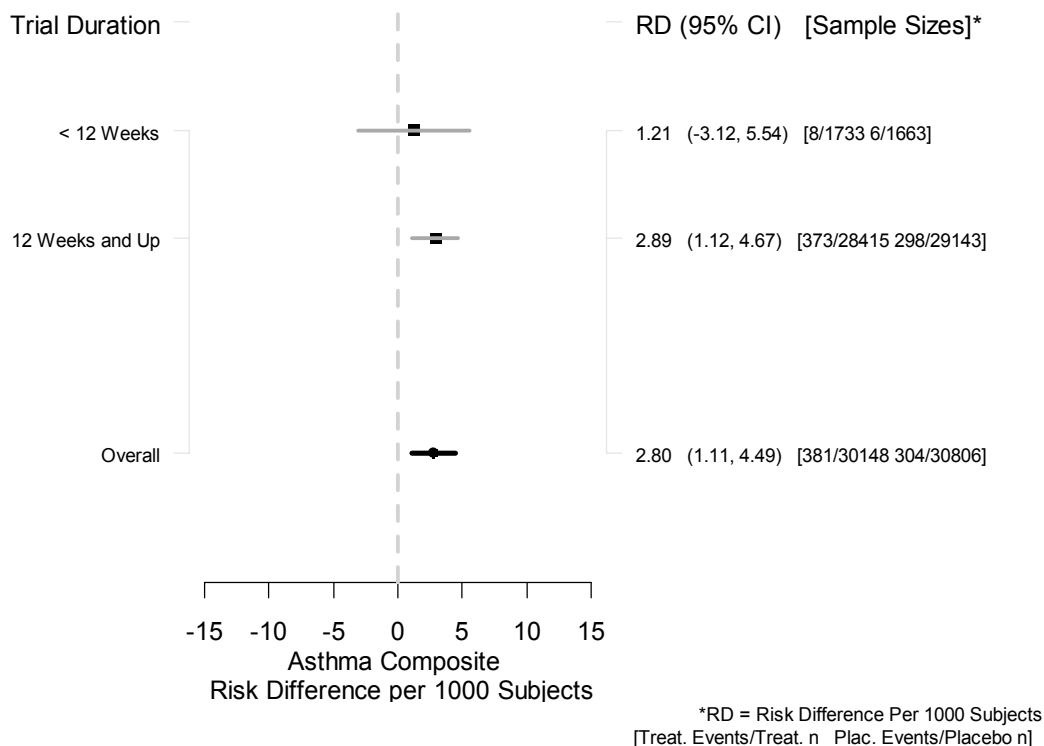


Figure 8: Risk Difference Estimates: Asthma Composite by Trial Duration Subgroups.

6.1.6 Baseline ICS Use

Figure 9 shows the results for the asthma composite endpoint for the overall analysis set by ICS baseline use subgroups. The results for subjects who received ICS at baseline and those who did not received ICS at baseline were not statistically different.

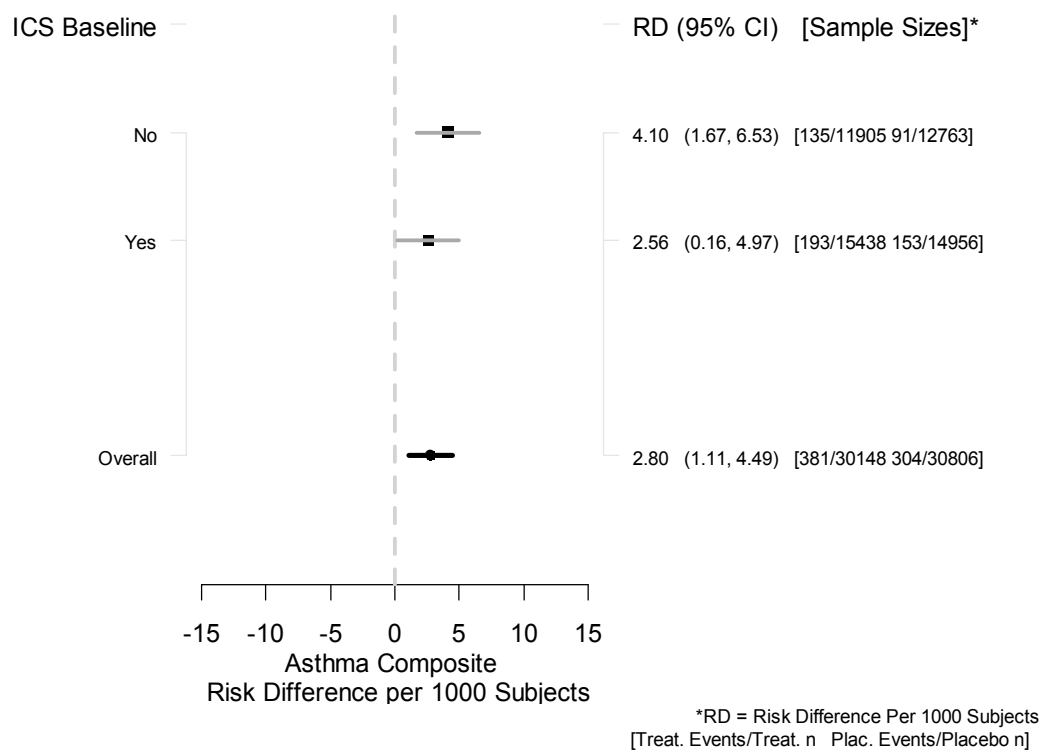


Figure 9: Risk Difference Estimates: Asthma Composite by ICS Baseline Subgroups.

6.1.7 ICS Use During Trial

Figure 10 shows the results for the asthma composite endpoint for the overall analysis set by ICS during trial. This treatment includes assigned ICS and concomitant ICS use. The results for subjects who received ICS during treatment and those who did not received ICS during treatment were not statistically different. It should be noted that specifics of the concomitant ICS use was not known.

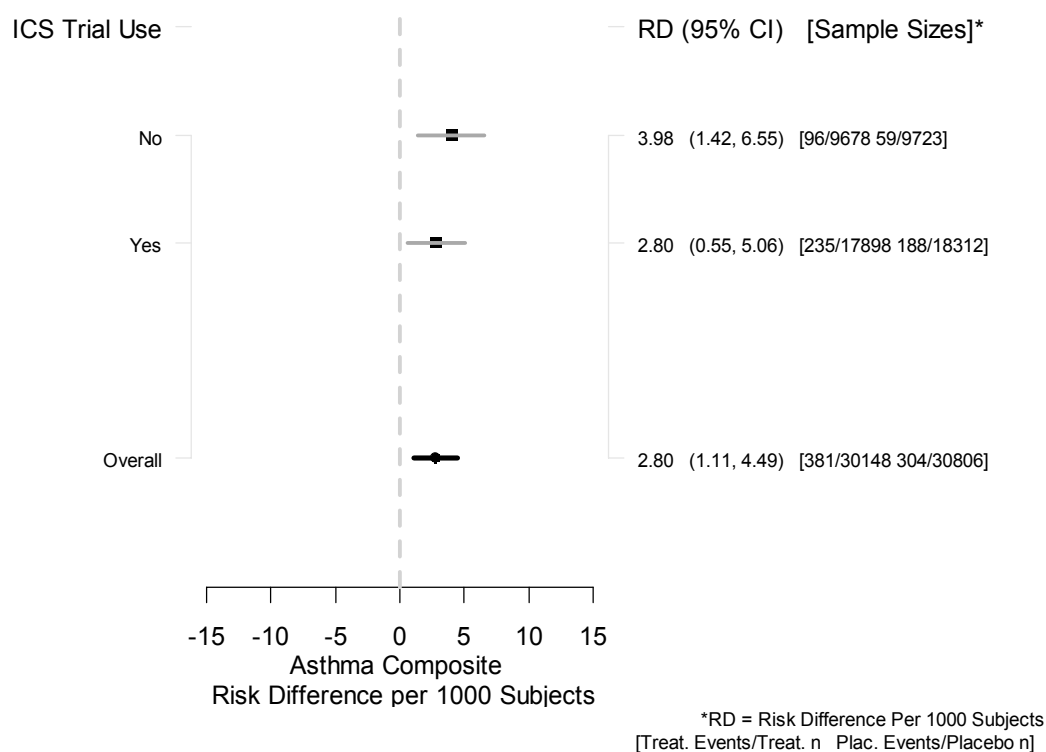


Figure 10: Risk Difference Estimates: Asthma Composite by ICS Trial Use Subgroups.

6.1.8 Hazard Pattern

Figure 11 shows the Kaplan-Meier cumulative incidence curves for the asthma composite endpoint for the overall analysis set. The last observed event was at 366 days. The estimate incidence at one year for the LABA group was 25 per 1000 subjects and for the non-LABA group was 20 per 1000 subjects.

From a visual inspection of the curves, it appeared that the incidence curves for the LABA and No LABA groups diverge over the range of the data, which is 1 year. It thus appeared that the increased hazard of events for the LABA group relative to the No LABA group existed over a period of 1 year at least. Figure 12 shows the Kaplan-Meier cumulative incidence curves for the asthma hospitalization endpoint for the overall analysis set, which appeared similar to that of the asthma composite endpoint.

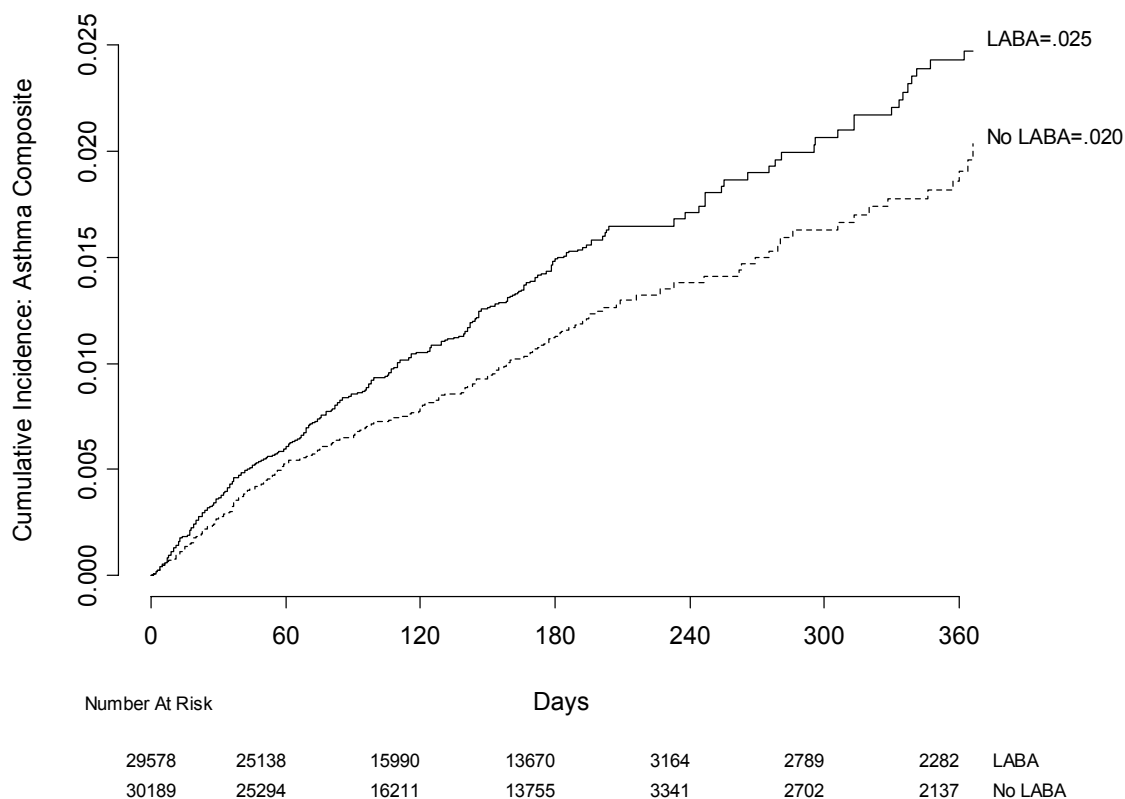


Figure 11: Kaplan -Meier Cumulative Incidence Curves: Asthma Composite.

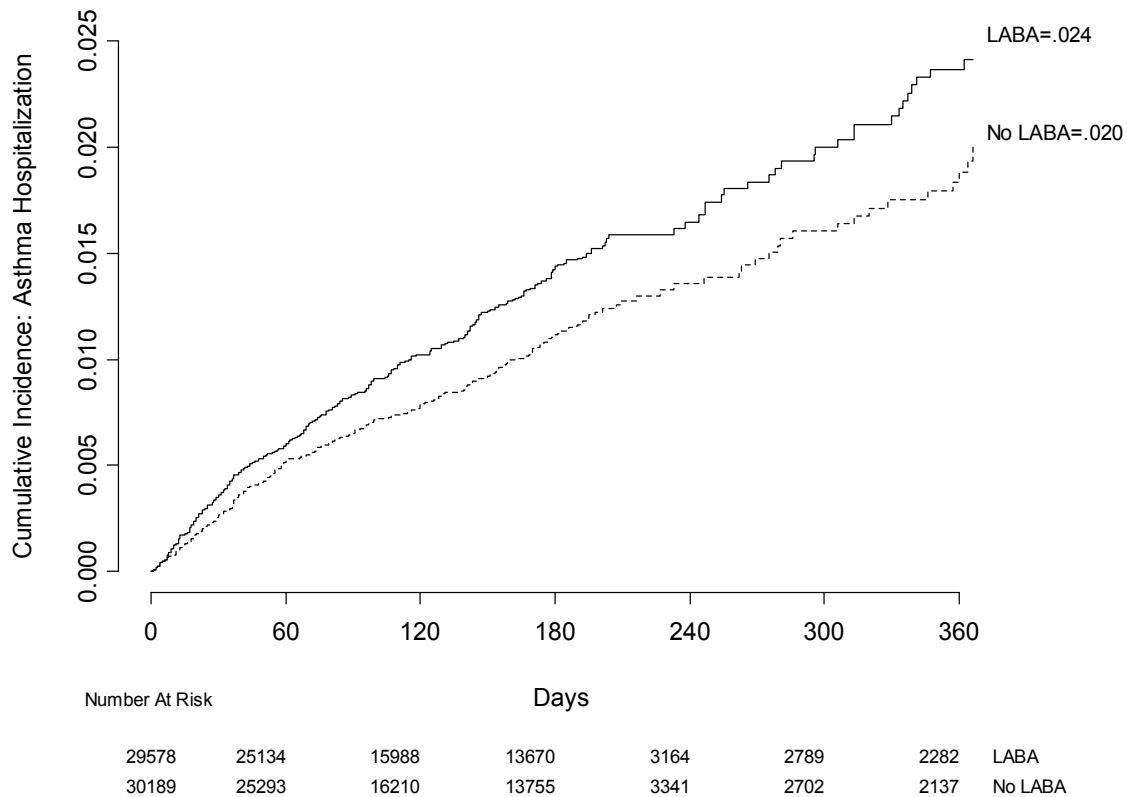


Figure 12: Kaplan -Meier Cumulative Incidence Curves: Asthma Hospitalization.

7 SENSITIVITY ANALYSIS

7.1 SMART Exclusion and SNS Inclusion

This section addresses the sensitivity of the overall results to (1) the exclusion of SMART and (2) inclusion of SNS. Table 7 gives the number of events for each endpoint overall and by treatment group for Serevent, SMART, Serevent without SMART, and SNS. SMART accounted for 16 of the 20 deaths observed for Serevent. However, the difference in crude hospitalization percentages between treatment groups was lower for SMART (.18%) than for Serevent without SMART (.70%).

Table 7: Event Counts Serevent With and Without SMART and SNS.

	No LABA	LABA	Total
	N=22716 n (n/N%)	N=21108 n (n/N%)	N=43824 n (n/N%)
Serevent			
Asthma Death	4 (.02)	16 (.08)	20 (.05)
Asthma Death/Intubation	27 (.12)	44 (.21)	71 (.16)
Asthma Hospitalization	265 (1.17)	324 (1.53)	589 (1.34)
Asthma Composite	270 (1.19)	336 (1.59)	606 (1.38)
All Cause Death	35 (.15)	48 (.23)	83 (.19)
	N=13179 n (n/N%)	N=13176 n (n/N%)	N=26355 n (n/N%)
SMART			
Asthma Death	3 (.02)	13 (.10)	16 (.06)
Asthma Death/Intubation	22 (.17)	37 (.28)	59 (.22)
Asthma Hospitalization	153 (1.16)	176 (1.34)	329 (1.25)
Asthma Composite	157 (1.19)	188 (1.43)	345 (1.31)
All Cause Death	32 (.24)	42 (.32)	74 (.28)
	N=9537 n (n/N%)	N=7932 n (n/N%)	N=17469 n (n/N%)
Serevent without SMART			
Asthma Death	1 (.01)	3 (.04)	4 (.02)
Asthma Death/Intubation	5 (.05)	7 (.09)	12 (.07)
Asthma Hospitalization	112 (1.17)	148 (1.87)	260 (1.49)
Asthma Composite	113 (1.18)	148 (1.87)	261 (1.49)
All Cause Death	3 (.03)	6 (.08)	9 (.05)
	N=8393 n (n/N%)	N=16787 n (n/N%)	N=25180 n (n/N%)
SNS			
Asthma Death	2 (.02)	12 (.07)	14 (.06)
Asthma Death/Intubation			
Asthma Hospitalization	102 (1.22)	196 (1.17)	298 (1.18)
Asthma Composite			
All Cause Death	20 (.24)	54 (.32)	74 (.29)

7.1.1 SMART Exclusion

With the exclusion of SMART from the analysis, the overall risk difference estimate for the asthma composite endpoint was 3.15 (95% CI: 1.04 – 5.26) per 1000 subjects, which was statistically significant. Note that this estimate was greater than the comparable estimate that included SMART, which was 2.80 (95%CI: 1.11 – 4.49)

The exclusion of SMART only affects Serevent among the four drugs. The risk difference estimate without SMART for Serevent for the asthma composite endpoint for the overall analysis set was 5.27 (95% CI: 1.52 – 9.01) per 1000 subjects. This estimate

was greater than the comparable estimate that included SMART, which is 3.49 (95% CI: 1.27 – 5.71) per 1000 subjects.

7.1.2 SNS Inclusion

Trial-level information for SNS was available only for the asthma death and asthma hospitalization endpoints. For the asthma death endpoint and the overall analysis set with the inclusion of SNS, the risk difference estimate was 0.42 (95% CI: 0.17 – 0.68) per 1000 subjects, which was statistically significant. Note that this estimate was very similar to the comparable estimate that did not include SNS, which was 0.40 (95% CI: 0.11 – 0.69) per 1000 subjects (see Appendix Table 12).

For the asthma hospitalization endpoint with the inclusion of SNS, the risk difference estimate was 1.74 (95% CI: 0.30 – 3.18) per 1000 subjects. This estimate was lower than the comparable estimate that did not include SNS, which was 2.57 (95% CI: 0.90 – 4.23) per 1000 subjects (see Appendix Table 14).

7.2 Method Sensitivity

Several alternative methods were employed to test the sensitivity of the primary statistical method, the Mantel-Haenszel risk difference. The exact method for an odds ratio was used to examine the consequences of low event rates. Figure 13 shows the odds ratio results for the asthma composite endpoint for the individual drugs. Note that the scale for the odds ratio is different than that of the risk difference. An odds ratio greater than 1 implies that the LABA group was associated with a higher rate of the endpoint than the non-LABA group. A confidence interval that does not contain the value of 1 implies that the risk difference was statistically significant. The odds ratio estimates followed a similar pattern as the risk difference estimates (see Figure 3). As in the case of the risk difference estimate, the overall odds ratio estimate was statistically significant, 1.29 (95% CI: 1.11 – 1.50). Likewise, the same three drugs with positive risk differences estimates had odds ratios estimates greater than 1. Serevent had statistically significant odds estimate as was the case for the risk difference estimate.

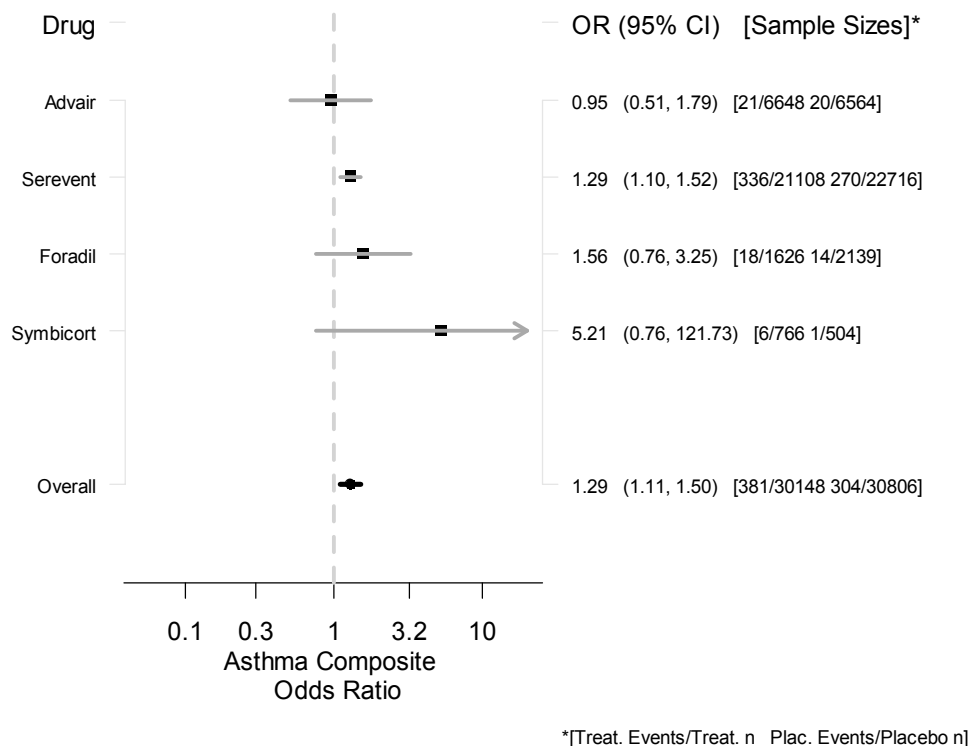


Figure 13: Odds Ratio Estimates: Asthma Composite by Drug.

The generalized linear mixed model (GLMM) was used to examine the consequences of the possibility of heterogeneity of the LABA effect among trials. The odds ratio estimate for the asthma composite endpoint from the GLMM was 1.53 (95% CI: 1.15 – 2.02). The result was qualitatively similar to the overall odds ratio estimate from the exact method. The variance component estimate for the trial heterogeneity effect was 0.33 with a standard error of 0.24. The scale of the component is complex. However, the fact the estimate was greater than its standard error suggests some trial heterogeneity. The p-value for Zelen’s test of the homogeneity of the odds ratio was 0.018.

8 LIMITATIONS

The study had several limitations.

The trials included in the study were generally not designed to address the present research objectives. In particular, the trials did not generally collect the endpoints considered in the analysis. Post-hoc identification and adjudication of events were based on existing adverse event reports.

Information on dropout from the trials was not obtained. Differential dropout patterns may introduce bias. For example, some dropouts may have experienced an adverse outcome after dropout possibly related to treatment. However, information on treatment duration was obtained and found to be similar between the comparison groups.

Information on individual subject and trial characteristics was limited. Potential differences in study populations among the drugs and subgroups may be associated with the observed effects. For example, trials may have differed in baseline asthma control. To the extent that baseline asthma control was associated with adverse effects of therapy relative to control, differences in findings among trials and drugs may have been observed.

Additionally, it was not known whether individual trials were Phase II or III trials. Adverse event information may have been more complete in Phase III trials. However, 96% of the trials were greater than 12 weeks and were likely Phase III trials.

Concomitant ICS use information was limited to whether subjects received concomitant ICS or not. Patients without assigned ICS but with concomitant ICS use may have had varying concomitant use. To the extent that ICS use affected the LABA effect, differences in findings among trials and drugs may have been observed based on unobserved differences in ICS use.

The study was designed with knowledge of the findings from SMART, which was one of the trials included in the present study. SMART contributed a large percentage of the subjects in the study. Findings from SMART can thus be expected to have a large influence in the present study. Addressing this limitation, sensitivity analysis excluding SMART did not result in notable changes in the results based on the asthma composite endpoint. However, SMART was responsible for the majority of asthma-related deaths.

9 SUMMARY AND CONCLUSIONS

9.1 Review Summary

This review examines the association of long-acting beta agonists with asthma-related hospitalization, asthma-related intubation, and asthma-related death in asthmatic patients through a retrospective meta-analysis. The meta-analysis was based on patient-level data from randomized controlled clinical trials available to the sponsors of LABAs. FDA provided instructions to the sponsors on the post-hoc adjudication of outcomes and the structure of data to be submitted.

The meta-analysis considered four products that contain a LABA and are approved in the United States for the treatment of asthma: Advair (salmeterol, fluticasone), Foradil (formoterol), Serevent (salmeterol), and Symbicort (formoterol, budesonide). Two of these products, Advair and Symbicort, are combination products each containing a LABA and an ICS. The study used data from 110 trials and 60,954 subjects that met the inclusion criteria for the analysis. There were roughly equal numbers of subjects assigned to LABA treatment and assigned to treatment other than LABA. The majority of subjects (43,824) were from Serevent trials. Advair trials accounted for 13,212 subjects, Foradil trials accounted for 3,765 subjects, and Symbicort trials accounted for 1,270 subjects. The Serevent trial SMART accounted for a substantial fraction (43%) of total subjects. Note that some trials involved both Advair and Serevent patients.

For the overall analysis set, the majority of subjects were between 18 and 64 years old (77%), white/Caucasian (72%), female (57%), from United States centers (69%), and

from trials with nominal treatment durations of 12 weeks or more (94%). There were 3,415 (6%) subjects between age 4 and 11 and 6,852 (11%) black/African American subjects. The median treatment duration was 169 days with a range from 1 day to 506 days. For age, gender, race, location, and treatment duration, there were no notable differences between the treatment groups, and the percentages of missing values were small. Among subjects with available information, 55% of subjects used an ICS at baseline (based on N=55,062) and 65% used an ICS during the trial (based on N=55,611), including assigned treatment or concomitant therapy. For both baseline ICS use and trial ICS use, there were no notable differences between treatment groups.

The study showed that overall LABAs were associated with an increased risk of asthma events as measured by the asthma composite endpoint consisting of asthma-related death, asthma-related intubation, and asthma-related hospitalization. The risk difference estimate for the composite endpoint of the LABA rate minus the non-LABA rate was 2.80 (95% CI: 1.11, 4.49) per 1000 subjects.

This overall finding for the asthma composite endpoint was supported by both the asthma-related hospitalization and the asthma-related death components. However, findings for individual drugs and subgroups were driven by the asthma-related hospitalization component.

Three of the four drugs (Foradil, Serevent, Symbicort) had positive risk difference estimates for the asthma composite endpoint; however, only Serevent had a statistically significant risk difference estimate. The risk difference estimates for the asthma composite endpoint were positive both when (1) LABA without assigned ICS was compared to non-LABA treatment and (2) LABA with assigned ICS was compared to assigned ICS treatment. However, only comparison (1) was statistically significant [3.63 (95% CI: 1.51 – 5.75) per 1000 subjects] and comparison (2) had a small risk difference estimate [0.25 (95% CI: -1.69 – 2.18) per 1000 subjects].

There were 20 asthma-related deaths, 16 of which were in the LABA group and 4 of which were in the non-LABA group. All the asthma-related deaths were among Serevent-treated subjects.

There was a general trend among the age groups for the asthma composite endpoint, with higher risk difference estimates among the younger age groups. The 4 – 11 age group had a risk difference estimate of 14.83 (95% CI: 3.24, 26.43) per 1000 subjects. The risk difference estimates for all the age groups but the ≥ 65 age group were positive and statistically significant. The results and trend among the age groups were driven by the asthma-related hospitalization component of the asthma composite endpoint. The trend among the age groups for the asthma composite endpoint was observed for each drug except for Advair.

All the race subgroups had positive risk difference estimates for the asthma composite endpoint. The risk differences estimate for the black/African American and white subgroups were statistically significant. The black/African Americans subgroup had the highest risk difference estimate 8.13 (95%CI: 1.88, 14.38) per 1000 subjects. Differences among race subgroups for the individual drugs were not clear. The risk difference estimate for the asthma composite endpoint for females was somewhat larger than that

for males. This difference between genders existed for individual drugs. There were no clear patterns among the other subgroups considered, which include subgroups based on center location, nominal trial duration, baseline ICS use, and trial ICS use.

From an examination of the Kaplan-Meier cumulative incidence curves for the asthma composite endpoint, it appeared that the increased hazard of events for the LABA treatment relative to the non-LABA treatment existed over the period of at least one year. The effect was driven by asthma-related hospitalizations.

Several sensitivity analyses were performed to examine the robustness of the primary results to the inclusion of large trials and to statistical methods. The exclusion of the large trial SMART did not reduce the overall estimate for the asthma composite endpoint, although SMART accounted for the majority of asthma-related deaths. The inclusion of the large trial SNS, which was not part of the primary analysis because of data availability, did not qualitatively affect the results. Various statistical methods did not reveal any notable deficiency in the primary method. However, there appeared to be some heterogeneity among the trials of the LABA effect. A statistical method that accounts for the heterogeneity produced qualitatively similar results as the primary method.

The study had several limitations. (1) The trials included in the study were generally not designed to collect the endpoints considered in the analysis. (2) Information on dropout from the trials was not obtained. Differential dropout patterns may introduce bias. However, information on treatment duration was obtained and found to be similar between the comparison groups. (3) Information on individual subject and trial characteristics were limited. Potential unobserved differences in study populations among the drugs and subgroups may have been associated with the observed effects. This included concomitant ICS use and adverse event information ascertainment. (4) The study was designed with knowledge of the findings from SMART, which was included in the present study. Addressing this limitation, sensitivity analysis excluding SMART did not result in notable changes in the results based on the asthma composite endpoint. However, SMART was responsible for the majority of asthma-related deaths.

10 APPENDIX

This appendix provides the numerical result summaries for all analyses that are not provided in body of the report. This includes the following:

- Subject and asthma characteristics for the “LABA wo/R ICS v. No LABA” comparison
- Subject and asthma characteristics for the “LABA w/R ICS v. R ICS” comparison
- Risk difference estimates for overall analysis set for each endpoint
- Subject and asthma characteristics and risk difference estimates for the asthma composite endpoint for each drug.

**10.1 “LABA Wo/R ICS v. No LABA” and “LABA w/R ICS v. R ICS”
Comparisons Subject and Asthma Characteristics**

Table 8: Subject Characteristics: “LABA Wo/R ICS v. No LABA” Comparison.

Characteristic		No LABA N=24474 n (n/N%)	LABA N=22286 n (n/N%)	Total N=46760 n (n/N%)
Age (Years)	4-11	1352 (6)	1177 (5)	2529 (5)
	12-17	2562 (10)	2293 (10)	4855 (10)
	18-64	18885 (77)	17186 (77)	36071 (77)
	≥ 65	1653 (7)	1603 (7)	3256 (7)
	Missing	22 (0)	27 (0)	49 (0)
	Median (Min - Max)	36 (4 – 93)	37 (4 – 100)	36 (4 – 100)
Gender	Female	13944 (57)	12803 (57)	26747 (57)
	Male	10373 (42)	9342 (42)	19715 (42)
	Missing	157 (1)	141 (1)	298 (1)
Race	Asian	303 (1)	295 (1)	598 (1)
	Black/African American	2910 (12)	2835 (13)	5745 (12)
	White/Caucasian	17687 (72)	15902 (71)	33589 (72)
	Other/Unknown	3574 (15)	3254 (15)	6828 (15)
Location	United States	20234 (83)	18398 (83)	38632 (83)
	Other	3959 (16)	3694 (17)	7653 (16)
	Missing	281 (1)	194 (1)	475 (1)
Nominal Trial Duration (weeks)				
	< 12	1019 (4)	1031 (5)	2050 (4)
	≥ 12	23455 (96)	21255 (95)	44710 (96)
Treatment Duration (days)	Median (Min - Max)	170 (1 – 408)	187 (1 – 408)	177 (1 – 408)
	Missing	589	533	1122

Table 9: Subject Characteristics: “LABA W/R ICS v. R ICS” Comparison.

Characteristic		No LABA N=7330 n (n/N%)	LABA N=7862 n (n/N%)	Total N=15192 n (n/N%)
Age (Years)	4-11	437 (6)	449 (6)	886 (6)
	12-17	828 (11)	810 (10)	1638 (11)
	18-64	5577 (76)	6088 (77)	11665 (77)
	≥ 65	483 (7)	514 (7)	997 (7)
	Missing	5 (0)	1 (0)	6 (0)
	Median (Min - Max)	37 (4 – 83)	38 (4 – 88)	37 (4 – 88)
Gender	Female	4118 (56)	4374 (56)	8492 (56)
	Male	3212 (44)	3488 (44)	6700 (44)
	Missing	4118 (56)	4374 (56)	8492 (56)
Race	Asian	743 (10)	821 (10)	1564 (10)
	Black/African American	603 (8)	589 (7)	1192 (8)
	White/Caucasian	5232 (71)	5656 (72)	10888 (72)
	Other/Unknown	752 (10)	796 (10)	1548 (10)
Location	United States	2061 (28)	2099 (27)	4160 (27)
	Other	4472 (61)	5265 (67)	9737 (64)
	Missing	797 (11)	498 (6)	1295 (9)
Nominal Trial Duration (weeks)				
	< 12	690 (9)	702 (9)	1392 (9)
	≥ 12	6640 (91)	7160 (91)	13800 (91)
Treatment Duration (days)	Median (Min - Max)	94 (1 – 506)	89 (1 – 506)	91 (1 – 506)
	Missing	35	40	75

Table 10: Asthma Characteristics: “LABA Wo/R ICS v. No LABA” Comparison.

Characteristic		No LABA N=24474 n (n/N%)	LABA N=22286 n (n/N%)	Total N=46760 n (n/N%)
Baseline Predicted FEV1 (%)	< 60	2693 (11)	2084 (9)	4777 (10)
	60 – 80	4198 (17)	3326 (15)	7524 (16)
	≥ 80	1832 (7)	1294 (6)	3126 (7)
	Missing	15751 (64)	15582 (70)	31333 (67)
Baseline ICS Use	No	11249 (46)	10255 (46)	21504 (46)
	Yes	10209 (42)	9395 (42)	19604 (42)
	Missing	3016 (12)	2636 (12)	5652 (12)
ICS Use During Trial	No	9723 (40)	9678 (43)	19401 (41)
	Yes	11980 (49)	10036 (45)	22016 (47)
	Missing	2771 (11)	2572 (12)	5343 (11)

Table 11: Asthma Characteristics: “LABA W/R ICS v. R ICS” Comparison.

Characteristic		No LABA N=7330 n (n/N%)	LABA N=7862 n (n/N%)	Total N=15192 n (n/N%)
Baseline Predicted FEV1 (%)	< 60	1503 (21)	1707 (22)	3210 (21)
	60 – 80	3460 (47)	3679 (47)	7139 (47)
	≥ 80	1870 (26)	1979 (25)	3849 (25)
	Missing	497 (7)	497 (6)	994 (7)
Baseline ICS Use	No	1830 (25)	1650 (21)	3480 (23)
	Yes	5337 (73)	6043 (77)	11380 (75)
	Missing	163 (2)	169 (2)	332 (2)
ICS Use During Trial	No	0 (0)	0 (0)	0 (0)
	Yes	7330 (100)	7862 (100)	15192 (100)
	Missing	0 (0)	0 (0)	0 (0)

10.2 Overall Analysis Set, Endpoint Results

10.2.1 Asthma Death

Table 12: Adjusted Risk Difference Estimates: Asthma Death.

Subgroup	Risk Difference Per 1000 Subjects		Events/n	
	Estimate	(95% CI)	LABA	No LABA
LABA v. No LABA	0.40	(0.11,0.69)	16/30148	4/30806
LABA wo/R ICS v. No LABA	0.48	(0.11,0.85)	15/22286	4/24474
LABA w/R ICS v. R ICS	0.13	(-0.12,0.39)	1/7862	0/7330
Trial Duration: <12 Weeks	0.61	(-0.58,1.8)	1/1733	0/1663
Trial Duration: ≥12 Weeks	0.39	(0.09,0.69)	15/28415	4/29143
ICS Baseline Use: No	0.83	(0.32,1.34)	10/11905	0/12763
ICS Baseline Use: Yes	0.13	(-0.24,0.5)	5/15438	3/14956
ICS Trial Use: No	0.85	(0.26,1.44)	9/9678	0/9723
ICS Trial Use: Yes	0.17	(-0.16,0.5)	6/17898	3/18312
Age :4 - 11	-0.63	(-1.86,0.6)	0/1626	1/1789
Age: 12 - 17	0.32	(-0.31,0.95)	1/3103	0/3289
Age: 18 - 64	0.52	(0.18,0.87)	14/23274	2/23604
Age: 65 and Up	-0.01	(-1.36,1.33)	1/2117	1/2097
Race: Asian	ND.	ND.	0/1116	0/1029
Race: Black/African Amer.	2.05	(0.32,3.78)	8/3424	1/3428
Race: White	0.23	(-0.04,0.51)	7/21558	2/22150
Race: Other/Unknown	-0.01	(-0.69,0.67)	1/4050	1/4199
Gender: Female	0.24	(-0.09,0.56)	6/17177	2/17528
Gender: Male	0.64	(0.1,1.17)	10/12830	2/13121
Location: United States	0.48	(0.1,0.86)	13/20497	3/21478
Location: Other	0.24	(-0.23,0.7)	3/8959	1/8339
Advair	ND.	ND.	0/6648	0/6564
Serevent	0.56	(0.15,0.96)	16/21108	4/22716
Foradil	ND.	ND.	0/1626	0/2139
Symbicort	ND.	ND.	0/766	0/504

10.2.2 Asthma Death/Intubation

Table 13: Adjusted Risk Difference Estimates: Asthma Death/Intubation.

Subgroup	Risk Difference Per 1000 Subjects		Events/n	
	Estimate	(95% CI)	LABA	No LABA
LABA v. No LABA	0.57	(0.01,1.12)	44/30148	27/30806
LABA wo/R ICS v. No LABA	0.70	(-0.02,1.41)	43/22286	27/24474
LABA w/R ICS v. R ICS	0.13	(-0.12,0.39)	1/7862	0/7330
Trial Duration: <12 Weeks	0.61	(-0.58,1.8)	1/1733	0/1663
Trial Duration: ≥12 Weeks	0.56	(-0.02,1.15)	43/28415	27/29143
ICS Baseline Use: No	1.16	(0.21,2.11)	24/11905	10/12763
ICS Baseline Use: Yes	0.27	(-0.5,1.03)	19/15438	15/14956
ICS Trial Use: No	1.05	(-0.05,2.16)	20/9678	9/9723
ICS Trial Use: Yes	0.41	(-0.29,1.1)	23/17898	16/18312
Age :4 - 11	-1.25	(-2.97,0.47)	0/1626	2/1789
Age: 12 - 17	-0.02	(-1.28,1.25)	2/3103	2/3289
Age: 18 - 64	0.88	(0.24,1.52)	38/23274	18/23604
Age: 65 and Up	-0.56	(-3.42,2.3)	4/2117	5/2097
Race: Asian	ND.	ND.	0/1116	0/1029
Race: Black/African Amer.	4.68	(1.86,7.5)	20/3424	4/3428
Race: White	0.04	(-0.56,0.65)	22/21558	21/22150
Race: Other/Unknown	-0.01	(-0.98,0.96)	2/4050	2/4199
Gender: Female	0.41	(-0.28,1.09)	21/17177	14/17528
Gender: Male	0.80	(-0.13,1.72)	23/12830	13/13121
Location: United States	0.82	(0.06,1.59)	41/20497	24/21478
Location: Other	0.00	(-0.58,0.57)	3/8959	3/8339
Advair	ND.	ND.	0/6648	0/6564
Serevent	0.79	(0.02,1.55)	44/21108	27/22716
Foradil	ND.	ND.	0/1626	0/2139
Symbicort	ND.	ND.	0/766	0/504

10.2.3 Asthma Hospitalization

Table 14: Adjusted Risk Difference Estimates: Asthma Hospitalization.

Subgroup	Risk Difference Per 1000 Subjects		Events/n	
	Estimate	(95% CI)	LABA	No LABA
LABA v. No LABA	2.57	(0.9,4.23)	369/30148	299/30806
LABA wo/R ICS v. No LABA	3.33	(1.24,5.42)	338/22286	274/24474
LABA w/R ICS v. R ICS	0.25	(-1.69,2.18)	31/7862	26/7330
Trial Duration: <12 Weeks	1.21	(-3.12,5.54)	8/1733	6/1663
Trial Duration: ≥12 Weeks	2.65	(0.9,4.4)	361/28415	293/29143
ICS Baseline Use: No	3.35	(0.97,5.74)	126/11905	91/12763
ICS Baseline Use: Yes	2.63	(0.25,5.01)	190/15438	149/14956
ICS Trial Use: No	3.13	(0.64,5.63)	88/9678	59/9723
ICS Trial Use: Yes	2.80	(0.57,5.03)	231/17898	184/18312
Age :4 - 11	15.46	(3.92,27.01)	61/1626	38/1789
Age: 12 - 17	5.25	(-0.07,10.57)	47/3103	30/3289
Age: 18 - 64	1.86	(0.1,3.63)	237/23274	199/23604
Age: 65 and Up	-4.04	(-10.74,2.66)	23/2117	31/2097
Race: Asian	0.94	(-7.14,9.03)	12/1116	12/1029
Race: Black/African Amer.	6.96	(0.87,13.05)	70/3424	46/3428
Race: White	1.79	(-0.08,3.67)	233/21558	198/22150
Race: Other/Unknown	3.25	(-1.36,7.87)	54/4050	43/4199
Gender: Female	4.08	(1.76,6.4)	242/17177	177/17528
Gender: Male	0.57	(-1.83,2.96)	126/12830	121/13121
Location: United States	2.84	(0.92,4.76)	234/20497	182/21478
Location: Other	2.01	(-1.52,5.54)	131/8959	113/8339
Advair	-0.15	(-2.01,1.7)	21/6648	20/6564
Serevent	3.16	(0.97,5.35)	324/21108	265/22716
Foradil	3.80	(-1.8,9.4)	18/1626	14/2139
Symbicort	7.49	(-1.47,16.44)	6/766	1/504

10.2.4 Asthma Composite

Table 15: Adjusted Risk Difference Estimates: Asthma Composite.

Subgroup	Risk Difference Per 1000 Subjects		Events/n	
	Estimate	(95% CI)	LABA	No LABA
LABA v. No LABA	2.80	(1.11,4.49)	381/30148	304/30806
LABA wo/R ICS v. No LABA	3.63	(1.51,5.75)	350/22286	279/24474
LABA w/R ICS v. R ICS	0.25	(-1.69,2.18)	31/7862	26/7330
Trial Duration: <12 Weeks	1.21	(-3.12,5.54)	8/1733	6/1663
Trial Duration: ≥12 Weeks	2.89	(1.12,4.67)	373/28415	298/29143
ICS Baseline Use: No	4.10	(1.67,6.53)	135/11905	91/12763
ICS Baseline Use: Yes	2.56	(0.16,4.97)	193/15438	153/14956
ICS Trial Use: No	3.98	(1.42,6.55)	96/9678	59/9723
ICS Trial Use: Yes	2.80	(0.55,5.06)	235/17898	188/18312
Age :4 - 11	14.83	(3.24,26.43)	61/1626	39/1789
Age: 12 - 17	5.57	(0.21,10.92)	48/3103	30/3289
Age: 18 - 64	2.13	(0.34,3.91)	246/23274	202/23604
Age: 65 and Up	-3.58	(-10.47,3.32)	25/2117	32/2097
Race: Asian	0.94	(-7.14,9.03)	12/1116	12/1029
Race: Black/African Amer.	8.13	(1.88,14.38)	75/3424	47/3428
Race: White	1.98	(0.09,3.88)	240/21558	201/22150
Race: Other/Unknown	3.00	(-1.64,7.65)	54/4050	44/4199
Gender: Female	4.20	(1.86,6.54)	247/17177	180/17528
Gender: Male	0.96	(-1.48,3.4)	133/12830	123/13121
Location: United States	3.23	(1.27,5.18)	246/20497	186/21478
Location: Other	1.89	(-1.65,5.42)	131/8959	114/8339
Advair	-0.15	(-2.01,1.7)	21/6648	20/6564
Serevent	3.49	(1.27,5.71)	336/21108	270/22716
Foradil	3.80	(-1.8,9.4)	18/1626	14/2139
Symbicort	7.49	(-1.47,16.44)	6/766	1/504

10.2.5 All Death

Table 16: Adjusted Risk Difference Estimates: All Death.

Subgroup	Risk Difference Per 1000 Subjects		Events/n	
	Estimate	(95% CI)	LABA	No LABA
LABA v. No LABA	0.38	(-0.24,1)	51/30148	40/30806
LABA wo/R ICS v. No LABA	0.50	(-0.28,1.27)	47/22286	36/24474
LABA w/R ICS v. R ICS	-0.01	(-0.75,0.74)	4/7862	4/7330
Trial Duration: <12 Weeks	0.61	(-0.58,1.8)	1/1733	0/1663
Trial Duration: ≥12 Weeks	0.36	(-0.29,1.02)	50/28415	40/29143
ICS Baseline Use: No	0.28	(-0.85,1.41)	26/11905	23/12763
ICS Baseline Use: Yes	0.60	(-0.19,1.4)	23/15438	14/14956
ICS Trial Use: No	0.22	(-1.18,1.63)	25/9678	22/9723
ICS Trial Use: Yes	0.46	(-0.24,1.17)	24/17898	16/18312
Age :4 - 11	-0.63	(-1.86,0.6)	0/1626	1/1789
Age: 12 - 17	0.32	(-0.31,0.95)	1/3103	0/3289
Age: 18 - 64	0.67	(0.07,1.28)	33/23274	18/23604
Age: 65 and Up	-2.26	(-8.07,3.55)	17/2117	21/2097
Race: Asian	ND.	ND.	0/1116	0/1029
Race: Black/African Amer.	1.72	(-0.87,4.31)	13/3424	7/3428
Race: White	0.40	(-0.32,1.12)	35/21558	27/22150
Race: Other/Unknown	-0.76	(-2.22,0.7)	3/4050	6/4199
Gender: Female	0.61	(-0.18,1.4)	29/17177	19/17528
Gender: Male	0.08	(-0.93,1.09)	22/12830	21/13121
Location: United States	0.45	(-0.36,1.27)	42/20497	33/21478
Location: Other	0.23	(-0.7,1.16)	9/8959	7/8339
Advair	-0.16	(-0.95,0.64)	3/6648	4/6564
Serevent	0.60	(-0.22,1.43)	48/21108	35/22716
Foradil	-0.38	(-1.12,0.36)	0/1626	1/2139
Symbicort	ND.	ND.	0/766	0/504

10.3 Individual Drug Results

10.3.1 Advair

Table 17: Subject Characteristics: Advair.

Characteristic		No LABA N=6564 n (n/N%)	LABA N=6648 n (n/N%)	Total N=13212 n (n/N%)
Age (Years)	4-11	401 (6)	409 (6)	810 (6)
	12-17	682 (10)	627 (9)	1309 (10)
	18-64	5043 (77)	5189 (78)	10232 (77)
	≥ 65	433 (7)	422 (6)	855 (6)
	Missing	5 (0)	1 (0)	6 (0)
Median (Min - Max)		37 (4 – 83)	37 (4 – 88)	37 (4 – 88)
Gender	Female	3684 (56)	3684 (55)	7368 (56)
	Male	2880 (44)	2964 (45)	5844 (44)
	Missing	0 (0)	0 (0)	0 (0)
Race	Asian	691 (11)	720 (11)	1411 (11)
	Black/African American	568 (9)	548 (8)	1116 (8)
	White/Caucasian	4755 (72)	4833 (73)	9588 (73)
	Other/Unknown	550 (8)	547 (8)	1097 (8)
Location	United States	1785 (27)	1806 (27)	3591 (27)
	Other	3982 (61)	4344 (65)	8326 (63)
	Missing	797 (12)	498 (7)	1295 (10)
Nominal Trial Duration (weeks)				
	< 12	644 (10)	656 (10)	1300 (10)
	≥ 12	5920 (90)	5992 (90)	11912 (90)
Treatment Duration (days)	Median (Min - Max)	112 (1 – 506)	95 (1 – 506)	104 (1 – 506)
	Missing	33	38	71

Table 18: Subject Asthma Characteristics: Advair.

Characteristic		No LABA N=6564 n (n/N%)	LABA N=6648 n (n/N%)	Total N=13212 n (n/N%)
Baseline Predicted FEV1 (%)	< 60	1337 (20)	1416 (21)	2753 (21)
	60 – 80	3066 (47)	3083 (46)	6149 (47)
	≥ 80	1667 (25)	1660 (25)	3327 (25)
	Missing	494 (8)	489 (7)	983 (7)
Baseline ICS Use	No	1693 (26)	1511 (23)	3204 (24)
	Yes	4708 (72)	4968 (75)	9676 (73)
	Missing	163 (2)	169 (3)	332 (3)
ICS Use During Trial	No	0 (0)	0 (0)	0 (0)
	Yes	6564 (100)	6648 (100)	13212 (100)
	Missing	0 (0)	0 (0)	0 (0)

Table 19: Asthma Composite Adjusted Risk Difference Estimates: Advair.

Subgroup	Risk Difference Per 1000 Subjects		Events/n	
	Estimate	(95% CI)	LABA	No LABA
Trial Duration: <12 Weeks	ND.	ND.	0/656	0/644
Trial Duration: ≥12 Weeks	-0.17	(-2.23,1.89)	21/5992	20/5920
ICS Baseline Use: No	-2.55	(-5.61,0.51)	1/1511	5/1693
ICS Baseline Use: Yes	0.61	(-1.71,2.93)	20/4968	15/4708
Age :4 - 11	ND.	ND.	0/409	0/401
Age: 12 - 17	-0.53	(-4.52,3.46)	1/627	1/682
Age: 18 - 64	-0.98	(-3.22,1.25)	15/5189	19/5043
Age: 65 and Up	10.80	(1.16,20.44)	5/422	0/433
Race: Asian	-2.00	(-10.15,6.14)	4/720	6/691
Race: Black/African Amer.	0.83	(-10.12,11.78)	4/548	4/568
Race: White	0.09	(-1.74,1.92)	12/4833	10/4755
Race: Other/Unknown	1.08	(-0.93,3.08)	1/547	0/550
Gender: Female	1.10	(-1.77,3.97)	18/3684	13/3684
Gender: Male	-1.69	(-3.88,0.5)	3/2964	7/2880
Location: United States	-1.13	(-4.2,1.95)	3/1806	5/1785
Location: Other	0.25	(-2.24,2.75)	17/4344	13/3982

10.3.2 Serevent

Table 20: Subject Characteristics: Serevent.

Characteristic		No LABA N=22716 n (n/N%)	LABA N=21108 n (n/N%)	Total N=43824 n (n/N%)
Age (Years)	4-11	1085 (5)	899 (4)	1984 (5)
	12-17	2411 (11)	2205 (10)	4616 (11)
	18-64	17696 (78)	16492 (78)	34188 (78)
	≥ 65	1502 (7)	1485 (7)	2987 (7)
	Missing	22 (0)	27 (0)	49 (0)
	Median (Min - Max)	36 (4 – 93)	37 (4 – 100)	37 (4 – 100)
Gender	Female	12999 (57)	12265 (58)	25264 (58)
	Male	9560 (42)	8702 (41)	18262 (42)
	Missing	157 (1)	141 (1)	298 (1)
Race	Asian	297 (1)	290 (1)	587 (1)
	Black/African American	2810 (12)	2756 (13)	5566 (13)
	White/Caucasian	16799 (74)	15372 (73)	32171 (73)
	Other/Unknown	2810 (12)	2690 (13)	5500 (13)
Location	United States	19117 (84)	17768 (84)	36885 (84)
	Other	3318 (15)	3146 (15)	6464 (15)
	Missing	281 (1)	194 (1)	475 (1)
Nominal Trial Duration (weeks)				
	< 12	980 (4)	1036 (5)	2016 (5)
	≥ 12	21736 (96)	20072 (95)	41808 (95)
Treatment Duration (days)	Median (Min - Max)	183 (1 – 408)	197 (1 – 408)	193 (1 – 408)
	Missing	592	535	1127

Table 21: Subject Asthma Characteristics: Serevent.

Characteristic		No LABA N=22716 n (n/N%)	LABA N=21108 n (n/N%)	Total N=43824 n (n/N%)
Baseline Predicted FEV1 (%)	< 60	2207 (10)	1761 (8)	3968 (9)
	60 – 80	3267 (14)	2697 (13)	5964 (14)
	≥ 80	1500 (7)	1076 (5)	2576 (6)
	Missing	15742 (69)	15574 (74)	31316 (71)
Baseline ICS Use	No	10670 (47)	9884 (47)	20554 (47)
	Yes	10510 (46)	9745 (46)	20255 (46)
	Missing	1536 (7)	1479 (7)	3015 (7)
ICS Use During Trial	No	9145 (40)	9270 (44)	18415 (42)
	Yes	12182 (54)	10359 (49)	22541 (51)
	Missing	1389 (6)	1479 (7)	2868 (7)

Table 22: Asthma Composite Adjusted Risk Difference Estimates: Serevent.

Subgroup	Risk Difference Per 1000 Subjects		Events/n	
	Estimate	(95% CI)	LABA	No LABA
Trial Duration: <12 Weeks	1.07	(-6.01,8.15)	7/1036	6/980
Trial Duration: ≥12 Weeks	3.60	(1.3,5.91)	329/20072	264/21736
ICS Baseline Use: No	5.20	(2.37,8.03)	130/9884	83/10670
ICS Baseline Use: Yes	3.39	(-0.01,6.8)	166/9745	135/10510
ICS Trial Use: No	4.07	(1.42,6.72)	93/9270	57/9145
ICS Trial Use: Yes	4.53	(1.02,8.04)	203/10359	161/12182
Age :4 - 11	16.97	(-1.94,35.88)	50/899	37/1085
Age: 12 - 17	5.88	(-1.07,12.83)	41/2205	27/2411
Age: 18 - 64	3.27	(0.94,5.6)	225/16492	177/17696
Age: 65 and Up	-6.38	(-15.38,2.63)	19/1485	28/1502
Race: Asian	8.80	(-13.75,31.34)	8/290	6/297
Race: Black/African Amer.	9.98	(2.59,17.36)	70/2756	43/2810
Race: White	2.03	(-0.43,4.5)	213/15372	186/16799
Race: Other/Unknown	4.25	(-2.09,10.59)	45/2690	35/2810
Gender: Female	4.74	(1.72,7.77)	215/12265	161/12999
Gender: Male	1.77	(-1.51,5.05)	120/8702	108/9560
Location: United States	3.55	(1.36,5.73)	234/17768	177/19117
Location: Other	3.06	(-5.22,11.35)	99/3146	91/3318

10.3.3 Foradil

Table 23: Subject Characteristics: Foradil.

Characteristic		No LABA N=2139 n (n/N%)	LABA N=1626 n (n/N%)	Total N=3765 n (n/N%)
Age (Years)	4-11	303 (14)	318 (20)	621 (16)
	12-17	174 (8)	116 (7)	290 (8)
	18-64	1457 (68)	1027 (63)	2484 (66)
	≥ 65	205 (10)	165 (10)	370 (10)
	Missing	303 (14)	318 (20)	621 (16)
	Median (Min - Max)	36 (5 – 85)	35 (5 – 82)	35 (5 – 85)
Gender	Female	1123 (53)	766 (47)	1889 (50)
	Male	1016 (47)	860 (53)	1876 (50)
	Missing	1123 (53)	766 (47)	1889 (50)
Race	Asian	13 (1)	10 (1)	23 (1)
	Black/African American	103 (5)	87 (5)	190 (5)
	White/Caucasian	1097 (51)	791 (49)	1888 (50)
	Other/Unknown	926 (43)	738 (45)	1664 (44)
Location	United States	1117 (52)	676 (42)	1793 (48)
	Other	1022 (48)	950 (58)	1972 (52)
	Missing	1117 (52)	676 (42)	1793 (48)
Nominal Trial Duration (weeks)				
	< 12	39 (2)	41 (3)	80 (2)
	≥ 12	2100 (98)	1585 (97)	3685 (98)
Treatment Duration (days)	Median (Min - Max)	85 (1 – 395)	85 (1 – 386)	85 (1 – 395)
	Missing	0	0	0

Table 24: Subject Asthma Characteristics: Foradil.

Characteristic		No LABA N=2139 n (n/N%)	LABA N=1626 n (n/N%)	Total N=3765 n (n/N%)
Baseline Predicted FEV1 (%)	< 60	620 (29)	474 (29)	1094 (29)
	60 – 80	1099 (51)	836 (51)	1935 (51)
	≥ 80	409 (19)	307 (19)	716 (19)
	Missing	11 (1)	9 (1)	20 (1)
Baseline ICS Use	No	583 (27)	421 (26)	1004 (27)
	Yes	76 (4)	48 (3)	124 (3)
	Missing	1480 (69)	1157 (71)	2637 (70)
ICS Use During Trial	No	578 (27)	408 (25)	986 (26)
	Yes	179 (8)	125 (8)	304 (8)
	Missing	1382 (65)	1093 (67)	2475 (66)

Table 25: Asthma Composite Adjusted Risk Difference Estimates: Foradil.

Subgroup	Risk Difference Per 1000 Subjects		Events/n	
	Estimate	(95% CI)	LABA	No LABA
Trial Duration: <12 Weeks	24.39	(-22.83,71.61)	1/41	0/39
Trial Duration: ≥12 Weeks	3.32	(-2.3,8.94)	17/1585	14/2100
ICS Baseline Use: No	0.53	(-9.54,10.59)	3/421	3/583
ICS Baseline Use: Yes	-8.25	(-72.54,56.03)	2/48	3/76
ICS Trial Use: No	2.35	(-7.23,11.93)	3/408	2/578
ICS Trial Use: Yes	-8.47	(-47.41,30.47)	5/125	7/179
Age :4 - 11	27.50	(5.6,49.41)	11/318	2/303
Age: 12 - 17	12.75	(-16.68,42.18)	3/116	2/174
Age: 18 - 64	-1.53	(-5.16,2.09)	3/1027	6/1457
Age: 65 and Up	-11.91	(-32.44,8.61)	1/165	4/205
Race: Asian	ND.	ND.	0/10	0/13
Race: Black/African Amer.	6.44	(-4.85,17.74)	1/87	0/103
Race: White	7.21	(-0.66,15.07)	9/791	5/1097
Race: Other/Unknown	-0.07	(-8.95,8.82)	8/738	9/926
Gender: Female	6.34	(-1.54,14.22)	9/766	6/1123
Gender: Male	1.42	(-6.9,9.73)	9/860	8/1016
Location: United States	2.40	(-4.28,9.09)	5/676	5/1117
Location: Other	5.08	(-3.66,13.81)	13/950	9/1022

10.3.4 Symbicort

Table 26: Subject Characteristics: Symbicort.

Characteristic		No LABA N=504 n (n/N%)	LABA N=766 n (n/N%)	Total N=1270 n (n/N%)
Age (Years)	4-11	0 (0)	0 (0)	0 (0)
	12-17	120 (24)	155 (20)	275 (22)
	18-64	356 (71)	566 (74)	922 (73)
	≥ 65	28 (6)	45 (6)	73 (6)
	Missing	0 (0)	0 (0)	0 (0)
	Median (Min - Max)	37 (12 – 80)	37 (12 – 78)	37 (12 – 80)
Gender	Female	318 (63)	462 (60)	780 (61)
	Male	186 (37)	304 (40)	490 (39)
	Missing	0 (0)	0 (0)	0 (0)
Race	Asian	48 (10)	96 (13)	144 (11)
	Black/African American	33 (7)	33 (4)	66 (5)
	White/Caucasian	383 (76)	562 (73)	945 (74)
	Other/Unknown	40 (8)	75 (10)	115 (9)
Location	United States	230 (46)	247 (32)	477 (38)
	Other	274 (54)	519 (68)	793 (62)
	Missing	0 (0)	0 (0)	0 (0)
Nominal Trial Duration (weeks)				
	< 12	0 (0)	0 (0)	0 (0)
	≥ 12	504 (100)	766 (100)	1270 (100)
Treatment Duration (days)	Median (Min - Max)	85 (1 – 120)	85 (1 – 109)	85 (1 – 120)
	Missing	0	0	0

Table 27: Subject Asthma Characteristics: Symbicort.

Characteristic		No LABA N=504 n (n/N%)	LABA N=766 n (n/N%)	Total N=1270 n (n/N%)
Baseline Predicted FEV1 (%)	< 60	75 (15)	140 (18)	215 (17)
	60 – 80	272 (54)	389 (51)	661 (52)
	≥ 80	156 (31)	230 (30)	386 (30)
	Missing	1 (0)	7 (1)	8 (1)
Baseline ICS Use	No	91 (18)	89 (12)	180 (14)
	Yes	413 (82)	677 (88)	1090 (86)
	Missing	0 (0)	0 (0)	0 (0)
ICS Use During Trial	No	0 (0)	0 (0)	0 (0)
	Yes	504 (100)	766 (100)	1270 (100)
	Missing	0 (0)	0 (0)	0 (0)

Table 28: Asthma Composite Adjusted Risk Difference Estimates: Symbicort.

Subgroup	Risk Difference Per 1000 Subjects		Events/n	
	Estimate	(95% CI)	LABA	No LABA
Trial Duration: ≥12 Weeks	7.49	(-1.47,16.44)	6/766	1/504
ICS Baseline Use: No	11.24	(-10.66,33.13)	1/89	0/91
ICS Baseline Use: Yes	6.85	(-2.99,16.7)	5/677	1/413
Age: 12 - 17	23.36	(-2.53,49.25)	3/155	0/120
Age: 18 - 64	3.55	(-6.34,13.44)	3/566	1/356
Age: 65 and Up	ND.	ND.	0/45	0/28
Race: Asian	ND.	ND.	0/96	0/48
Race: Black/African Amer.	ND.	ND.	0/33	0/33
Race: White	9.84	(-1.97,21.65)	6/562	1/383
Race: Other/Unknown	ND.	ND.	0/75	0/40
Gender: Female	9.41	(-3.65,22.47)	5/462	1/318
Gender: Male	4.23	(-3.97,12.42)	1/304	0/186
Location: United States	15.96	(0.47,31.45)	4/247	0/230
Location: Other	1.77	(-8.98,12.51)	2/519	1/274

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ADVAIR DISKUS safely and effectively. See full prescribing information for ADVAIR DISKUS.

ADVAIR DISKUS® 100/50 (fluticasone propionate 100 mcg and salmeterol 50 mcg inhalation powder)

ADVAIR DISKUS® 250/50 (fluticasone propionate 250 mcg and salmeterol 50 mcg inhalation powder)

ADVAIR DISKUS® 500/50 (fluticasone propionate 500 mcg and salmeterol 50 mcg inhalation powder)

FOR ORAL INHALATION

Initial U.S. Approval: 2000

WARNING: RISK OF ASTHMA-RELATED DEATH

See full prescribing information for complete boxed warning.

- Long-acting beta₂-adrenergic agonists, such as salmeterol, one of the active ingredients in ADVAIR DISKUS, may increase the risk of asthma-related death. A US study showed an increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176 patients treated for 28 weeks on salmeterol versus 3 out of 13,179 patients on placebo). (5.1)
- When treating patients with asthma, only prescribe ADVAIR DISKUS for patients not adequately controlled on other asthma-controller medications or whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies. (1.1, 5.1)

RECENT MAJOR CHANGES

Indications and Usage, Maintenance Treatment of Chronic Obstructive Pulmonary Disease (1.2)	April 2008
Dosage and Administration, Chronic Obstructive Pulmonary Disease, (2.2)	April 2008
Warnings and Precautions, Pneumonia (5.5)	April 2008
Drug Interactions, Inhibitors of Cytochrome P450 3A4 (7.1)	April 2008

INDICATIONS AND USAGE

ADVAIR DISKUS is a combination product containing a corticosteroid and a long-acting beta₂-adrenergic agonist indicated for:

- Maintenance treatment of asthma in patients 4 years of age and older. (1.1)
- Maintenance treatment of airflow obstruction and reducing exacerbations in patients with chronic obstructive pulmonary disease (COPD). (1.2)

Important limitations:

- Not indicated for patients whose asthma can be managed by inhaled corticosteroids with occasional use of inhaled short-acting beta₂-agonists. (1.1)
- Not indicated for the relief of acute bronchospasm. (1.1, 1.2)

DOSAGE AND ADMINISTRATION

For oral inhalation only.

- Maintenance treatment of asthma in patients ≥12 years: 1 inhalation of ADVAIR DISKUS 100/50, 250/50, or 500/50 twice daily. Starting dosage is based on asthma severity. (2.1)
- Maintenance treatment of asthma in patients 4 to 11 years: 1 inhalation of ADVAIR DISKUS 100/50 twice daily. (2.1)
- Maintenance treatment of COPD: 1 inhalation of ADVAIR DISKUS 250/50 twice daily. (2.2)

DOSAGE FORMS AND STRENGTHS

DISKUS® device containing a combination of fluticasone propionate (100, 250, or 500 mcg) and salmeterol (50 mcg) as an oral inhalation powder. (3)

CONTRAINDICATIONS

- Primary treatment of status asthmaticus or acute episodes of asthma or COPD requiring intensive measures. (4)
- Severe hypersensitivity to milk proteins. (4)

WARNINGS AND PRECAUTIONS

- Asthma-related death: Long-acting beta₂-adrenergic agonists may increase the risk. Prescribe only for recommended patient populations. (5.1)
- Deterioration of disease and acute episodes: Do not initiate in acutely deteriorating asthma or to treat acute symptoms. (5.2)

- Use with additional long-acting beta₂-agonist: Do not use in combination because of risk of overdose. (5.3)
- Localized infections: *Candida albicans* infection of the mouth and throat may occur. Monitor patients periodically for signs of adverse effects on the oral cavity. Advise patients to rinse the mouth following inhalation. (5.4)
- Pneumonia: Increased risk in patients with COPD. Monitor patients for signs and symptoms of pneumonia. (5.5)
- Immunosuppression: Potential worsening of infections (e.g., existing tuberculosis, fungal, bacterial, viral, or parasitic infection; or ocular herpes simplex). Use with caution in patients with these infections. More serious or even fatal course of chickenpox or measles can occur in susceptible patients. (5.6)
- Transferring patients from systemic corticosteroids: Risk of impaired adrenal function when transferring from oral steroids. Taper patients slowly from systemic corticosteroids if transferring to ADVAIR DISKUS. (5.7)
- Hypercorticism and adrenal suppression: May occur with very high dosages or at the regular dosage in susceptible individuals. If such changes occur, discontinue ADVAIR DISKUS slowly. (5.8)
- Strong cytochrome P450 3A4 inhibitors (e.g., ritonavir): Risk of increased systemic corticosteroid and cardiovascular effects. Use not recommended with ADVAIR DISKUS. (5.9)
- Paradoxical bronchospasm: Discontinue ADVAIR DISKUS and institute alternative therapy if paradoxical bronchospasm occurs. (5.10)
- Patients with cardiovascular or central nervous system disorders: Use with caution because of beta-adrenergic stimulation. (5.12)
- Decreases in bone mineral density: Assess bone mineral density initially and periodically thereafter. (5.13)
- Effects on growth: Monitor growth of pediatric patients. (5.14)
- Glaucoma and cataracts: Close monitoring is warranted. (5.15)
- Metabolic effects: Be alert to eosinophilic conditions, hypokalemia, and hyperglycemia. (5.16, 5.18)
- Coexisting conditions: Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis. (5.17)

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥3%) are:

- Asthma: upper respiratory tract infection or inflammation, pharyngitis, dysphonia, oral candidiasis, bronchitis, cough, headaches, nausea and vomiting. (6.1)
- COPD: pneumonia, oral candidiasis, throat irritation, dysphonia, viral respiratory infections, headaches, musculoskeletal pain. (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Strong cytochrome P450 3A4 inhibitors (e.g., ritonavir): Use not recommended. May cause systemic corticosteroid and cardiovascular effects. (7.1)
- Monoamine oxidase inhibitors and tricyclic antidepressants: Use with extreme caution. May potentiate effect of salmeterol on vascular system. (7.2)
- Beta-blockers: Use with caution. May block bronchodilatory effects of beta-agonists and produce severe bronchospasm. (7.3)
- Diuretics: Use with caution. Electrocardiographic changes and/or hypokalemia associated with nonpotassium-sparing diuretics may worsen with concomitant beta-agonists. (7.4)

USE IN SPECIFIC POPULATIONS

Hepatic impairment: Monitor patients for signs of increased drug exposure. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and MEDICATION GUIDE.

Revised: April 2008
ADD:3PI

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FULL PRESCRIBING INFORMATION

WARNING: RISK OF ASTHMA-RELATED DEATH

Long-acting beta₂-adrenergic agonists, such as salmeterol, one of the active ingredients in ADVAIR DISKUS, may increase the risk of asthma-related death. Therefore, when treating patients with asthma, physicians should only prescribe ADVAIR DISKUS 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 2 maintenance therapies. Data from a large placebo-controlled US study that compared the safety of salmeterol (SEREVENT[®] Inhalation Aerosol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176 patients treated for 28 weeks on salmeterol versus 3 deaths out of 13,179 patients on placebo) [*see Warnings and Precautions (5.1)*].

1 INDICATIONS AND USAGE

1.1 Maintenance Treatment of Asthma

ADVAIR DISKUS is indicated for the long-term, twice-daily, maintenance treatment of asthma in patients 4 years of age and older.

Long-acting beta₂-adrenergic agonists, such as salmeterol, one of the active ingredients in ADVAIR DISKUS, may increase the risk of asthma-related death [*see Warnings and Precautions (5.1)*]. Therefore, when treating patients with asthma, physicians should only prescribe ADVAIR DISKUS 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 2 maintenance therapies.

Important Limitations of Use:

- ADVAIR DISKUS is NOT indicated for the relief of acute bronchospasm.
- ADVAIR DISKUS is not indicated in patients whose asthma can be successfully managed by inhaled corticosteroids along with occasional use of inhaled, short-acting beta₂-agonists.

1.2 Maintenance Treatment of Chronic Obstructive Pulmonary Disease

ADVAIR DISKUS 250/50 is indicated for the twice-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. ADVAIR DISKUS 250/50 is also indicated to reduce exacerbations of COPD in patients with a history of exacerbations. ADVAIR DISKUS 250/50 twice daily is the only approved dosage for the treatment of COPD because an efficacy advantage of the higher strength ADVAIR DISKUS 500/50 over ADVAIR DISKUS 250/50 has not been demonstrated.

Important Limitations of Use: ADVAIR DISKUS is NOT indicated for the relief of acute bronchospasm.

2 DOSAGE AND ADMINISTRATION

ADVAIR DISKUS should be administered twice daily every day by the orally inhaled route only. After inhalation, the patient should rinse the mouth with water without swallowing [see Patient Counseling Information (17.4)].

More frequent administration or a higher number of inhalations (more than 1 inhalation twice daily) of the prescribed strength of ADVAIR DISKUS is not recommended as some patients are more likely to experience adverse effects with higher doses of salmeterol. Patients using ADVAIR DISKUS should not use additional long-acting beta₂-agonists for any reason. [See Warnings and Precautions (5.3, 5.12).]

2.1 Asthma

If asthma symptoms arise in the period between doses, an inhaled, short-acting beta₂-agonist should be taken for immediate relief.

Adult and Adolescent Patients 12 Years of Age and Older: For patients 12 years of age and older, the dosage is 1 inhalation twice daily (morning and evening, approximately 12 hours apart).

The recommended starting dosages for ADVAIR DISKUS for patients 12 years of age and older are based upon patients' asthma severity. For patients not currently on inhaled corticosteroids whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies, or patients inadequately controlled on an inhaled corticosteroid, the recommended starting dosage is ADVAIR DISKUS 100/50 or 250/50 twice daily.

The maximum recommended dosage is ADVAIR DISKUS 500/50 twice daily.

For all patients it is desirable to titrate to the lowest effective strength after adequate asthma stability is achieved.

Improvement in asthma control following inhaled administration of ADVAIR DISKUS can occur within 30 minutes of beginning treatment, although maximum benefit may not be achieved for 1 week or longer after starting treatment. Individual patients will experience a variable time to onset and degree of symptom relief.

For patients who do not respond adequately to the starting dosage after 2 weeks of therapy, replacing the current strength of ADVAIR DISKUS with a higher strength may provide additional improvement in asthma control.

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

Pediatric Patients 4 to 11 Years of Age: For patients with asthma aged 4 to 11 years who are symptomatic on an inhaled corticosteroid, the dosage is 1 inhalation of ADVAIR DISKUS 100/50 twice daily (morning and evening, approximately 12 hours apart).

2.2 Chronic Obstructive Pulmonary Disease

The recommended dosage for patients with COPD is 1 inhalation of ADVAIR DISKUS 250/50 twice daily (morning and evening, approximately 12 hours apart).

If shortness of breath occurs in the period between doses, an inhaled, short-acting beta₂-agonist should be taken for immediate relief.

3 DOSAGE FORMS AND STRENGTHS

Disposable purple device with 60 blisters containing a combination of fluticasone propionate (100, 250, or 500 mcg) and salmeterol (50 mcg) as an oral inhalation powder formulation. An institutional pack containing 28 blisters is also available.

4 CONTRAINDICATIONS

The use of ADVAIR DISKUS is contraindicated in the following conditions:

- Primary treatment of status asthmaticus or other acute episodes of asthma or COPD where intensive measures are required.
- Severe hypersensitivity to milk proteins [*see Warnings and Precautions (5.11), Description (11)*].

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Asthma-Related Death With Long-Acting Beta₂-Adrenergic Agonists

Long-acting beta₂-adrenergic agonists, such as salmeterol, one of the active ingredients in ADVAIR DISKUS, may increase the risk of asthma-related death. Therefore, when treating patients with asthma, physicians should only prescribe ADVAIR DISKUS 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 2 maintenance therapies.

A large placebo-controlled US study that compared the safety of salmeterol with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in patients receiving salmeterol. The Salmeterol Multi-center Asthma Research Trial (SMART) was a randomized, double-blind study that enrolled long-acting beta₂-agonist-naïve patients with asthma to assess the safety of salmeterol (SEREVENT Inhalation Aerosol) 42 mcg twice daily over 28 weeks compared with placebo when added to usual asthma therapy. A planned interim analysis was conducted when approximately half of the intended number of patients had been enrolled (N = 26,355), which led to premature termination of the study. The results of the interim analysis showed that patients receiving salmeterol were at increased risk for fatal asthma events (see Table 1 and Figure 1). In the total population, a higher rate of asthma-related death occurred in patients treated with salmeterol than those treated with placebo (0.10% vs. 0.02%, relative risk 4.37 [95% CI: 1.25, 15.34]).

Post-hoc subpopulation analyses were performed. In Caucasians, asthma-related death occurred at a higher rate in patients treated with salmeterol than in patients treated with placebo (0.07% vs. 0.01%, relative risk 5.82 [95% CI: 0.70, 48.37]). In African Americans also, asthma-related death occurred at a higher rate in patients treated with salmeterol than those

treated with placebo (0.31% vs. 0.04%, relative risk 7.26 [95% CI: 0.89, 58.94]). Although the relative risks of asthma-related death were similar in Caucasians and African Americans, the estimate of excess deaths in patients treated with salmeterol was greater in African Americans because there was a higher overall rate of asthma-related death in African American patients (see Table 1). Given the similar basic mechanisms of action of beta₂-agonists, it is possible that the findings seen in the SMART study represent a class effect.

The data from the SMART study are not adequate to determine whether concurrent use of inhaled corticosteroids, such as fluticasone propionate, the other active ingredient in ADVAIR DISKUS, or other asthma-controller therapy modifies the risk of asthma-related death.

Table 1. Asthma-Related Deaths in the 28-Week Salmeterol Multi-center Asthma Research Trial (SMART)

	Salmeterol n (% [*])	Placebo n (% [*])	Relative Risk [†] (95% Confidence Interval)	Excess Deaths Expressed per 10,000 Patients [‡] (95% Confidence Interval)
Total Population[§] Salmeterol: N = 13,176 Placebo: N = 13,179	13 (0.10%)	3 (0.02%)	4.37 (1.25, 15.34)	8 (3, 13)
Caucasian Salmeterol: N = 9,281 Placebo: N = 9,361	6 (0.07%)	1 (0.01%)	5.82 (0.70, 48.37)	6 (1, 10)
African American Salmeterol: N = 2,366 Placebo: N = 2,319	7 (0.31%)	1 (0.04%)	7.26 (0.89, 58.94)	27 (8, 46)

^{*} Life-table 28-week estimate, adjusted according to the patients' actual lengths of exposure to study treatment to account for early withdrawal of patients from the study.

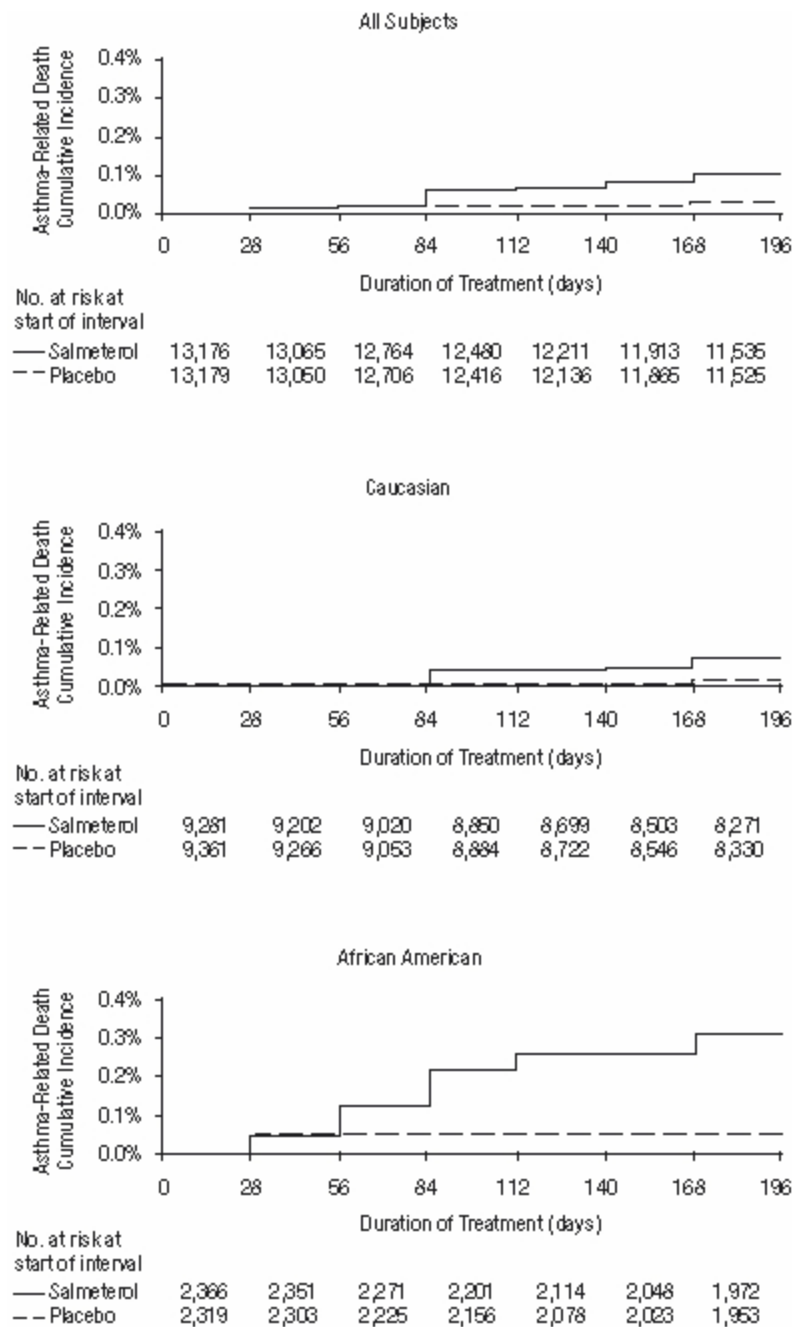
[†] Relative risk is the ratio of the rate of asthma-related death in the salmeterol group and the rate in the placebo group. The relative risk indicates how many more times likely an asthma-related death occurred in the salmeterol group than in the placebo group in a 28-week treatment period.

[‡] Estimate of the number of additional asthma-related deaths in patients treated with salmeterol in SMART, assuming 10,000 patients received salmeterol for a 28-week treatment period. Estimate calculated as the difference between the salmeterol and placebo groups in the rates of asthma-related death multiplied by 10,000.

[§] The Total Population includes the following ethnic origins listed on the case report form: Caucasian, African American, Hispanic, Asian, and "Other." In addition, the Total Population includes those patients whose ethnic origin was not reported. The results for Caucasian and African American subpopulations are shown above. No asthma-related deaths occurred in the

Hispanic (salmeterol n = 996, placebo n = 999), Asian (salmeterol n = 173, placebo n = 149), or “Other” (salmeterol n = 230, placebo n = 224) subpopulations. One asthma-related death occurred in the placebo group in the subpopulation whose ethnic origin was not reported (salmeterol n = 130, placebo n = 127).

Figure 1. Cumulative Incidence of Asthma-Related Deaths in the 28-Week Salmeterol Multi-center Asthma Research Trial (SMART), by Duration of Treatment



A 16-week clinical study performed in the United Kingdom, the Salmeterol Nationwide Surveillance (SNS) study, showed results similar to the SMART study. In the SNS study, the rate of asthma-related death was numerically, though not statistically significantly, greater in patients with asthma treated with salmeterol (42 mcg twice daily) than those treated with albuterol (180 mcg 4 times daily) added to usual asthma therapy.

The SNS and SMART studies enrolled patients with asthma. No studies have been conducted that were primarily designed to determine whether the rate of death in patients with COPD is increased by long-acting beta₂-adrenergic agonists.

5.2 Deterioration of Disease and Acute Episodes

ADVAIR DISKUS should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of asthma or COPD. ADVAIR DISKUS has not been studied in patients with acutely deteriorating asthma or COPD. The initiation of ADVAIR DISKUS in this setting is not appropriate.

Serious acute respiratory events, including fatalities, have been reported when salmeterol, a component of ADVAIR DISKUS, has been initiated in patients with significantly worsening or acutely deteriorating asthma. In most cases, these have occurred in patients with severe asthma (e.g., patients with a history of corticosteroid dependence, low pulmonary function, intubation, mechanical ventilation, frequent hospitalizations, previous life-threatening acute asthma exacerbations) and in some patients with acutely deteriorating asthma (e.g., patients with significantly increasing symptoms; increasing need for inhaled, short-acting beta₂-agonists; decreasing response to usual medications; increasing need for systemic corticosteroids; recent emergency room visits; deteriorating lung function). However, these events have occurred in a few patients with less severe asthma as well. It was not possible from these reports to determine whether salmeterol contributed to these events.

Increasing use of inhaled, short-acting beta₂-agonists is a marker of deteriorating asthma. In this situation, the patient requires immediate reevaluation with reassessment of the treatment regimen, giving special consideration to the possible need for replacing the current strength of ADVAIR DISKUS with a higher strength, adding additional inhaled corticosteroid, or initiating systemic corticosteroids. Patients should not use more than 1 inhalation twice daily (morning and evening) of ADVAIR DISKUS.

ADVAIR DISKUS should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. An inhaled, short-acting beta₂-agonist, not ADVAIR DISKUS, should be used to relieve acute symptoms such as shortness of breath. When prescribing ADVAIR DISKUS, the physician must also provide the patient with an inhaled, short-acting beta₂-agonist (e.g., albuterol) for treatment of acute symptoms, despite regular twice-daily (morning and evening) use of ADVAIR DISKUS.

When beginning treatment with ADVAIR DISKUS, 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.

5.3 Excessive Use of ADVAIR DISKUS and Use With Other Long-Acting Beta₂-Agonists

As with other inhaled drugs containing beta₂-adrenergic agents, ADVAIR DISKUS should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medications containing long-acting beta₂-agonists, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using ADVAIR DISKUS should not use an additional long-acting beta₂-agonist (e.g., salmeterol, formoterol fumarate, arformoterol tartrate) for any reason, including prevention of exercise-induced bronchospasm (EIB) or the maintenance treatment of asthma or COPD.

5.4 Local Effects

In clinical studies, the development of localized infections of the mouth and pharynx with *Candida albicans* has occurred in patients treated with ADVAIR DISKUS. When such an infection develops, it should be treated with appropriate local or systemic (i.e., oral antifungal) therapy while treatment with ADVAIR DISKUS continues, but at times therapy with ADVAIR DISKUS may need to be interrupted. Patients should rinse the mouth after inhalation of ADVAIR DISKUS.

5.5 Pneumonia

Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of pneumonia and exacerbations frequently overlap.

Lower respiratory tract infections, including pneumonia, have been reported in patients with COPD following the inhaled administration of corticosteroids, including fluticasone propionate and ADVAIR DISKUS. In 2 replicate 12-month studies of 1,579 patients with COPD, there was a higher incidence of pneumonia reported in patients receiving ADVAIR DISKUS 250/50 (7%) than in those receiving salmeterol 50 mcg (3%). The incidence of pneumonia in the patients treated with ADVAIR DISKUS was higher in patients over 65 years of age (9%) compared with the incidence in patients less than 65 years of age (4%). [*See Adverse Reactions (6.2), Use in Specific Populations (8.5).*]

In a 3-year study of 6,184 patients with COPD, there was a higher incidence of pneumonia reported in patients receiving ADVAIR DISKUS 500/50 compared with placebo (16% with ADVAIR DISKUS 500/50, 14% with fluticasone propionate 500 mcg, 11% with salmeterol 50 mcg, and 9% with placebo). Similar to what was seen in the 1-year studies with ADVAIR DISKUS 250/50, the incidence of pneumonia was higher in patients over 65 years of age (18% with ADVAIR DISKUS 500/50 vs. 10% with placebo) compared with patients less than 65 years of age (14% with ADVAIR DISKUS 500/50 vs. 8% with placebo). [*See Adverse Reactions (6.2), Use in Specific Populations (8.5).*]

5.6 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. How the dose, route, and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If a patient is exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If a patient is 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.

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

5.7 Transferring Patients From Systemic Corticosteroid Therapy

Particular care is needed for patients who have been transferred from systemically active corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function.

Patients who have been previously maintained on 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 ADVAIR DISKUS 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 warning card indicating that they may need supplementary systemic corticosteroids during periods of stress or a severe asthma attack.

Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to ADVAIR DISKUS. Prednisone reduction can be accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during therapy with ADVAIR DISKUS. Lung function (mean forced expiratory volume in 1 second [FEV₁] or morning peak expiratory flow [PEF]), beta-agonist use, and asthma symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition to monitoring asthma signs and symptoms, patients should be observed for signs and symptoms of adrenal insufficiency, such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension.

Transfer of patients from systemic corticosteroid therapy to inhaled corticosteroids or ADVAIR DISKUS may unmask conditions previously suppressed by the systemic corticosteroid therapy (e.g., rhinitis, conjunctivitis, eczema, arthritis, eosinophilic conditions). Some patients may experience symptoms of systemically active corticosteroid withdrawal (e.g., joint and/or muscular pain, lassitude, depression) despite maintenance or even improvement of respiratory function.

5.8 Hypercorticism and Adrenal Suppression

Fluticasone propionate, a component of ADVAIR DISKUS, will often help control asthma symptoms with less suppression of HPA function than therapeutically equivalent oral doses of prednisone. Since fluticasone propionate is absorbed into the circulation and can be systemically active at higher doses, the beneficial effects of ADVAIR DISKUS in minimizing HPA dysfunction may be expected only when recommended dosages are not exceeded and individual patients are titrated to the lowest effective dose. A relationship between plasma levels of fluticasone propionate and inhibitory effects on stimulated cortisol production has been shown after 4 weeks of treatment with fluticasone propionate inhalation aerosol. Since individual sensitivity to effects on cortisol production exists, physicians should consider this information when prescribing ADVAIR DISKUS.

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

It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression (including adrenal crisis) may appear in a small number of patients, particularly when fluticasone propionate is administered at higher than recommended doses over prolonged periods of time. If such effects occur, the dosage of ADVAIR DISKUS should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids and for management of asthma symptoms.

5.9 Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors

The use of strong CYP 3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, ketoconazole, telithromycin) with ADVAIR DISKUS is not recommended because increased systemic corticosteroid and increased cardiovascular adverse effects may occur [*see Drug interactions (7.1), Clinical Pharmacology (12.3)*].

5.10 Paradoxical Bronchospasm and Upper Airway Symptoms

As with other inhaled medications, ADVAIR DISKUS can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with ADVAIR DISKUS, it should be treated immediately with an inhaled, short-acting bronchodilator, ADVAIR DISKUS should be discontinued immediately, and alternative therapy should be instituted. Upper airway symptoms of laryngeal spasm, irritation, or swelling, such as

stridor and choking, have been reported in patients receiving fluticasone propionate and salmeterol.

5.11 Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions may occur after administration of ADVAIR DISKUS, as demonstrated by cases of urticaria, angioedema, rash, and bronchospasm. There have been reports of anaphylactic reactions in patients with severe milk protein allergy; therefore, patients with severe milk protein allergy should not take ADVAIR DISKUS [*see Contraindications (4)*].

5.12 Cardiovascular and Central Nervous System Effects

Excessive beta-adrenergic stimulation has been associated with seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, palpitation, nausea, dizziness, fatigue, malaise, and insomnia [*see Overdosage (10)*]. Therefore, ADVAIR DISKUS, like all products containing sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Salmeterol, a component of ADVAIR DISKUS, can 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 salmeterol at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce 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. Large doses of inhaled or oral salmeterol (12 to 20 times the recommended dose) have been associated with clinically significant prolongation of the QTc interval, which has the potential for producing ventricular arrhythmias. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

5.13 Reduction in Bone Mineral Density

Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing inhaled corticosteroids. The clinical significance of small changes in BMD with regard to long-term consequences such as fracture is unknown. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, post-menopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care. Since patients with COPD often have multiple risk factors for reduced BMD, assessment of BMD is recommended prior to initiating ADVAIR DISKUS and periodically thereafter. If significant reductions in BMD are seen and ADVAIR DISKUS is still considered medically important for that patient's COPD therapy, use of medication to treat or prevent osteoporosis should be strongly considered.

A 2-year study of 160 patients (females 18 to 40 years of age, males 18 to 50) with asthma receiving CFC-propelled fluticasone propionate inhalation aerosol 88 or 440 mcg twice

daily demonstrated no statistically significant changes in BMD at any time point (24, 52, 76, and 104 weeks of double-blind treatment) as assessed by dual-energy x-ray absorptiometry at lumbar regions L1 through L4.

Effects of treatment with ADVAIR DISKUS 500/50, fluticasone propionate 500 mcg, salmeterol 50 mcg, or placebo on BMD was evaluated in a subset of 658 patients (females and males 40 to 80 years of age) with COPD in the 3-year survival study. BMD evaluations were conducted at baseline and at 48, 108, and 158 weeks. Conclusions cannot be drawn from this study because of the large number of drop outs (>50%) before the end of the follow-up and the maldistribution of covariates among the treatment groups that can affect BMD.

Fracture risk was estimated for the entire population of patients with COPD in the survival study (N = 6,184). The probability of a fracture over 3 years was 6.3% for ADVAIR DISKUS, 5.4% for fluticasone propionate, 5.1% for salmeterol, and 5.1% for placebo.

5.14 Effect on Growth

Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to pediatric patients. Monitor the growth of pediatric patients receiving ADVAIR DISKUS routinely (e.g., via stadiometry). To minimize the systemic effects of orally inhaled corticosteroids, including ADVAIR DISKUS, titrate each patient's dose to the lowest dosage that effectively controls his/her symptoms. *[See Dosage and Administration (2.1), Use in Specific Populations (8.4).]*

5.15 Glaucoma and Cataracts

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

Effects of treatment with ADVAIR DISKUS 500/50, fluticasone propionate 500 mcg, salmeterol 50 mcg, or placebo on development of cataracts or glaucoma was evaluated in a subset of 658 patients with COPD in the 3-year survival study. Ophthalmic examinations were conducted at baseline and at 48, 108, and 158 weeks. Conclusions about cataracts cannot be drawn from this study because the high incidence of cataracts at baseline (61% to 71%) resulted in an inadequate number of patients treated with ADVAIR DISKUS 500/50 who were eligible and available for evaluation of cataracts at the end of the study (n = 53). The incidence of newly diagnosed glaucoma was 2% with ADVAIR DISKUS 500/50, 5% with fluticasone propionate, 0% with salmeterol, and 2% with placebo.

5.16 Eosinophilic Conditions and Churg-Strauss Syndrome

In rare cases, patients on inhaled fluticasone propionate may present with systemic eosinophilic conditions. Some of these patients have clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of fluticasone propionate. Cases of

serious eosinophilic conditions have also been reported with other inhaled corticosteroids in this clinical setting. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal relationship between fluticasone propionate and these underlying conditions has not been established.

5.17 Coexisting Conditions

ADVAIR DISKUS, like all medications containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the related beta₂-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

5.18 Hypokalemia and Hyperglycemia

Beta-adrenergic agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects [*see Clinical Pharmacology (12.2)*]. The decrease in serum potassium is usually transient, not requiring supplementation. Clinically significant changes in blood glucose and/or serum potassium were seen infrequently during clinical studies with ADVAIR DISKUS at recommended doses.

6 ADVERSE REACTIONS

Long-acting beta₂-adrenergic agonists, such as salmeterol, may increase the risk of asthma-related death. Data from a large, placebo-controlled US study that compared the safety of salmeterol (SEREVENT Inhalation Aerosol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol [*see Warnings and Precautions (5.1)*]. Salmeterol is a component of ADVAIR DISKUS. However, the data from this study are not adequate to determine whether concurrent use of inhaled corticosteroids, such as fluticasone propionate, the other component of ADVAIR DISKUS, or other asthma-controller therapy modifies the risk of asthma-related death.

Systemic and local corticosteroid use may result in the following:

- *Candida albicans* infection [*see Warnings and Precautions (5.4)*]
- Pneumonia in patients with COPD [*see Warnings and Precautions (5.5)*]
- Immunosuppression [*see Warnings and Precautions (5.6)*]
- Hypercorticism and adrenal suppression [*see Warnings and Precautions (5.8)*]
- Growth effects [*see Warnings and Precautions (5.14)*]
- Glaucoma and cataracts [*see Warnings and Precautions (5.15)*]

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.1 Clinical Trials Experience in Asthma

Adult and Adolescent Patients 12 Years of Age and Older: The incidence of adverse reactions associated with ADVAIR DISKUS in Table 2 is based upon 2 placebo-controlled, 12-week, US clinical studies (Studies 1 and 2). A total of 705 adolescent and adult patients (349 females and 356 males) previously treated with salmeterol or inhaled corticosteroids were treated twice daily with ADVAIR DISKUS (100/50- or 250/50-mcg doses), fluticasone propionate inhalation powder (100- or 250-mcg doses), salmeterol inhalation powder 50 mcg, or placebo. The average duration of exposure was 60 to 79 days in the active treatment groups compared with 42 days in the placebo group.

Table 2. Adverse Reactions With $\geq 3\%$ Incidence With ADVAIR DISKUS in Adult and Adolescent Patients With Asthma

Adverse Event	ADVAIR DISKUS 100/50 (N = 92) %	ADVAIR DISKUS 250/50 (N = 84) %	Fluticasone Propionate 100 mcg (N = 90) %	Fluticasone Propionate 250 mcg (N = 84) %	Salmeterol 50 mcg (N = 180) %	Placebo (N = 175) %
Ear, nose, & throat						
Upper respiratory tract infection	27	21	29	25	19	14
Pharyngitis	13	10	7	12	8	6
Upper respiratory inflammation	7	6	7	8	8	5
Sinusitis	4	5	6	1	3	4
Hoarseness/dysphonia	5	2	2	4	<1	<1
Oral candidiasis	1	4	2	2	0	0
Lower respiratory						
Viral respiratory infections	4	4	4	10	6	3
Bronchitis	2	8	1	2	2	2
Cough	3	6	0	0	3	2
Neurology						
Headaches	12	13	14	8	10	7
Gastrointestinal						
Nausea & vomiting	4	6	3	4	1	1
Gastrointestinal discomfort & pain	4	1	0	2	1	1
Diarrhea	4	2	2	2	1	1
Viral gastrointestinal infections	3	0	3	1	2	2
Non-site specific						
Candidiasis unspecified site	3	0	1	4	0	1
Musculoskeletal						
Musculoskeletal pain	4	2	1	5	3	3

The types of adverse reactions and events reported in Study 3, a 28-week, non-US clinical study of 503 patients previously treated with inhaled corticosteroids who were treated twice daily with ADVAIR DISKUS 500/50, fluticasone propionate inhalation powder 500 mcg and salmeterol inhalation powder 50 mcg used concurrently, or fluticasone propionate inhalation powder 500 mcg, were similar to those reported in Table 2.

Additional Adverse Reactions: Other adverse reactions not previously listed, whether considered drug-related or not by the investigators, that were reported more frequently by patients with asthma treated with ADVAIR DISKUS compared with patients treated with placebo include the following: lymphatic signs and symptoms; muscle injuries; fractures; wounds and lacerations; contusions and hematomas; ear signs and symptoms; nasal signs and symptoms; nasal sinus disorders; keratitis and conjunctivitis; dental discomfort and pain; gastrointestinal signs and symptoms; oral ulcerations; oral discomfort and pain; lower respiratory signs and symptoms; pneumonia; muscle stiffness, tightness, and rigidity; bone and cartilage disorders; sleep disorders; compressed nerve syndromes; viral infections; pain; chest symptoms; fluid retention; bacterial infections; unusual taste; viral skin infections; skin flakiness and acquired ichthyosis; disorders of sweat and sebum.

Pediatric Patients 4 to 11 Years of Age: The safety data for pediatric patients 4 to 11 years of age is based upon 1 US trial of 12 weeks' treatment duration. A total of 203 patients (74 females and 129 males) who were receiving inhaled corticosteroids at study entry were randomized to either ADVAIR DISKUS 100/50 or fluticasone propionate inhalation powder 100 mcg twice daily. Common adverse reactions ($\geq 3\%$ and greater than placebo) seen in the pediatric patients but not reported in the adult and adolescent clinical trials include: throat irritation and ear, nose, and throat infections.

Laboratory Test Abnormalities: Elevation of hepatic enzymes was reported in $\geq 1\%$ of patients in clinical trials. The elevations were transient and did not lead to discontinuation from the studies. In addition, there were no clinically relevant changes noted in glucose or potassium.

6.2 Clinical Trials Experience in Chronic Obstructive Pulmonary Disease

Short-Term (6 Months to 1 Year) Trials: The short-term safety data are based on exposure to ADVAIR DISKUS 250/50 twice daily in one 6-month and two 1-year clinical trials. In the 6-month trial, a total of 723 adult patients (266 females and 457 males) were treated twice daily with ADVAIR DISKUS 250/50, fluticasone propionate inhalation powder 250 mcg, salmeterol inhalation powder, or placebo. The mean age of the patients was 64, and the majority (93%) was Caucasian. In this trial, 70% of the patients treated with ADVAIR DISKUS reported an adverse reaction compared with 64% on placebo. The average duration of exposure to ADVAIR DISKUS 250/50 was 141.3 days compared with 131.6 days for placebo. The incidence of adverse reactions in the 6-month study is shown in Table 3.

Table 3. Overall Adverse Reactions With $\geq 3\%$ Incidence With ADVAIR DISKUS 250/50 in Patients With Chronic Obstructive Pulmonary Disease Associated With Chronic Bronchitis

Adverse Event	ADVAIR DISKUS 250/50 (N = 178) %	Fluticasone Propionate 250 mcg (N = 183) %	Salmeterol 50 mcg (N = 177) %	Placebo (N = 185) %
Ear, nose, & throat				
Candidiasis mouth/throat	10	6	3	1
Throat irritation	8	5	4	7
Hoarseness/dysphonia	5	3	<1	0
Sinusitis	3	8	5	3
Lower respiratory				
Viral respiratory infections	6	4	3	3
Neurology				
Headaches	16	11	10	12
Dizziness	4	<1	3	2
Non-site specific				
Fever	4	3	0	3
Malaise & fatigue	3	2	2	3
Musculoskeletal				
Musculoskeletal pain	9	8	12	9
Muscle cramps & spasms	3	3	1	1

In the two 1-year studies, ADVAIR DISKUS 250/50 was compared with salmeterol in 1,579 patients (863 males and 716 females). The mean age of the patients was 65, and the majority (94%) was Caucasian. To be enrolled, all of the patients had to have had a COPD exacerbation in the previous 12 months. In this trial, 88% of the patients treated with ADVAIR DISKUS and 86% of the patients treated with salmeterol reported an adverse event. The most common events that occurred with a frequency of $>5\%$ and more frequently in the patients treated with ADVAIR DISKUS were nasopharyngitis, upper respiratory tract infection, nasal congestion, back pain, sinusitis, dizziness, nausea, pneumonia, candidiasis, and dysphonia. Overall, 55 (7%) of the patients treated with ADVAIR DISKUS and 25 (3%) of the patients treated with salmeterol developed pneumonia.

The incidence of pneumonia was higher in patients over 65 years of age, 9% in the patients treated with ADVAIR DISKUS compared with 4% in the patients treated with ADVAIR DISKUS less than 65 years of age. In the patients treated with salmeterol, the incidence of pneumonia was the same (3%) in both age-groups. [See *Warnings and Precautions (5.5.)*, *Use in Specific Populations (8.5.)*]

Long-Term (3-Year) Trial: The safety of ADVAIR DISKUS 500/50 was evaluated in a randomized, double-blind, placebo-controlled, multicenter, international, 3-year study in 6,184 adult patients with COPD (4,684 males and 1,500 females). The mean age of the patients was 65, and the majority (82%) was Caucasian. The distribution of adverse events was similar to that seen in the 1-year trials with ADVAIR DISKUS 250/50. In addition, pneumonia was reported in a significantly increased number of patients treated with ADVAIR DISKUS 500/50 and fluticasone propionate 500 mcg (16% and 14%, respectively) compared with patients treated with salmeterol 50 mcg or placebo (11% and 9%, respectively). When adjusted for time on treatment, the rates of pneumonia were 84 and 88 events per 1,000 treatment-years in the groups treated with fluticasone propionate 500 mcg and with ADVAIR DISKUS 500/50, respectively, compared with 52 events per 1,000 treatment-years in the salmeterol and placebo groups. Similar to what was seen in the 1-year studies with ADVAIR DISKUS 250/50, the incidence of pneumonia was higher in patients over 65 years of age (18% with ADVAIR DISKUS 500/50 vs. 10% with placebo) compared with patients less than 65 years of age (14% with ADVAIR DISKUS 500/50 vs. 8% with placebo). *[See Warnings and Precautions (5.5), Use in Specific Populations (8.5).]*

Additional Adverse Reactions: Other adverse reactions not previously listed, whether considered drug-related or not by the investigators, that were reported more frequently by patients with COPD treated with ADVAIR DISKUS compared with patients treated with placebo include the following: syncope; ear, nose, and throat infections; ear signs and symptoms; laryngitis; nasal congestion/blockage; nasal sinus disorders; pharyngitis/throat infection; hypothyroidism; dry eyes; eye infections; gastrointestinal signs and symptoms; oral lesions; abnormal liver function tests; bacterial infections; edema and swelling; viral infections.

Laboratory Abnormalities: There were no clinically relevant changes in these trials. Specifically, no increased reporting of neutrophilia or changes in glucose or potassium was noted.

6.3 Postmarketing Experience

In addition to adverse events reported from clinical trials, the following events have been identified during worldwide use of any formulation of ADVAIR, fluticasone propionate, and/or salmeterol regardless of indication. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, or causal connection to ADVAIR DISKUS, fluticasone propionate, and/or salmeterol or a combination of these factors.

Cardiac Disorders: Arrhythmias (including atrial fibrillation, extrasystoles, supraventricular tachycardia), ventricular tachycardia.

Endocrine Disorders: Cushing syndrome, Cushingoid features, growth velocity reduction in children/adolescents, hypercorticism.

Eye Disorders: Glaucoma.

Gastrointestinal Disorders: Abdominal pain, dyspepsia, xerostomia.

Immune System Disorders: Immediate and delayed hypersensitivity reaction (including very rare anaphylactic reaction). Very rare anaphylactic reaction in patients with severe milk protein allergy.

Metabolic and Nutrition Disorders: Hyperglycemia, weight gain.

Musculoskeletal, Connective Tissue, and Bone Disorders: Arthralgia, cramps, myositis, osteoporosis.

Nervous System Disorders: Paresthesia, restlessness.

Psychiatric Disorders: Agitation, aggression, depression. Behavioral changes, including hyperactivity and irritability, have been reported very rarely and primarily in children.

Reproductive System and Breast Disorders: Dysmenorrhea.

Respiratory, Thoracic, and Mediastinal Disorders: Chest congestion; chest tightness; dyspnea; facial and oropharyngeal edema, immediate bronchospasm; paradoxical bronchospasm; tracheitis; wheezing; reports of upper respiratory symptoms of laryngeal spasm, irritation, or swelling such as stridor or choking.

Skin and Subcutaneous Tissue Disorders: Ecchymoses, photodermatitis.

Vascular Disorders: Pallor.

7 DRUG INTERACTIONS

ADVAIR DISKUS has been used concomitantly with other drugs, including short-acting beta₂-agonists, methylxanthines, and intranasal corticosteroids, commonly used in patients with asthma or COPD, without adverse drug reactions. No formal drug interaction studies have been performed with ADVAIR DISKUS.

7.1 Inhibitors of Cytochrome P450 3A4

Fluticasone propionate and salmeterol, the individual components of ADVAIR DISKUS, are substrates of CYP 3A4. The use of strong CYP 3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, ketoconazole, telithromycin) with ADVAIR DISKUS is not recommended because increased systemic corticosteroid and increased cardiovascular adverse effects may occur.

Ritonavir: Fluticasone Propionate: A drug interaction study with fluticasone propionate aqueous nasal spray in healthy subjects has shown that ritonavir (a strong CYP 3A4 inhibitor) can significantly increase plasma fluticasone propionate exposure, resulting in significantly reduced serum cortisol concentrations [*see Clinical Pharmacology (12.3)*]. During postmarketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing syndrome and adrenal suppression.

Ketoconazole: Fluticasone Propionate: Coadministration of orally inhaled fluticasone propionate (1,000 mcg) and ketoconazole (200 mg once daily) resulted in increased plasma fluticasone propionate exposure and reduced plasma cortisol area under the curve (AUC), but had no effect on urinary excretion of cortisol.

Salmeterol: In a drug interaction study in 20 healthy subjects, coadministration of inhaled salmeterol (50 mcg twice daily) and oral ketoconazole (400 mg once daily) for 7 days resulted in greater systemic exposure to salmeterol (AUC increased 16-fold and C_{max} increased 1.4-fold). Three (3) subjects were withdrawn due to beta₂-agonist side effects (2 with prolonged QTc and 1 with palpitations and sinus tachycardia). Although there was no statistical effect on the mean QTc, coadministration of salmeterol and ketoconazole was associated with more frequent increases in QTc duration compared with salmeterol and placebo administration.

7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

ADVAIR DISKUS should be administered with extreme 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 salmeterol, a component of ADVAIR DISKUS, on the vascular system may be potentiated by these agents.

7.3 Beta-Adrenergic Receptor Blocking Agents

Beta-blockers not only block the pulmonary effect of beta-agonists, such as salmeterol, a component of ADVAIR DISKUS, but may produce severe bronchospasm in patients with reversible obstructive airways disease. Therefore, patients with asthma and COPD 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 for these patients; cardioselective beta-blockers could be considered, although they should be administered with caution.

7.4 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 relevance of these effects is not known, caution is advised in the coadministration of beta-agonists with nonpotassium-sparing diuretics.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C. There are no adequate and well-controlled studies with ADVAIR DISKUS in pregnant women. ADVAIR DISKUS was teratogenic in mice and not in rats, although it lowered fetal weight in rats. Fluticasone propionate alone was teratogenic in mice, rats, and rabbits, and salmeterol alone was teratogenic in rabbits and not in rats. From the reproduction toxicity studies in mice and rats, no evidence of enhanced toxicity was seen using combinations of fluticasone propionate and salmeterol when compared with toxicity data from the components administered separately.

ADVAIR DISKUS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

ADVAIR DISKUS: In the mouse reproduction assay, fluticasone propionate by the subcutaneous route at a dose approximately 3/5 the maximum recommended human daily

inhalation dose (MRHD) on a mg/m^2 basis combined with oral salmeterol at a dose approximately 410 times the MRHD on a mg/m^2 basis produced cleft palate, fetal death, increased implantation loss, and delayed ossification. These observations are characteristic of glucocorticoids. No developmental toxicity was observed at combination doses of fluticasone propionate subcutaneously up to approximately 1/6 the MRHD on a mg/m^2 basis and oral doses of salmeterol up to approximately 55 times the MRHD on a mg/m^2 basis. In rats, combining fluticasone propionate subcutaneously at a dose equivalent to the MRHD on a mg/m^2 basis and an oral dose of salmeterol at approximately 810 times the MRHD on a mg/m^2 basis produced decreased fetal weight, umbilical hernia, delayed ossification, and changes in the occipital bone. No such effects were seen when combining fluticasone propionate subcutaneously at a dose less than the MRHD on a mg/m^2 basis and an oral dose of salmeterol at approximately 80 times the MRHD on a mg/m^2 basis.

Fluticasone Propionate: Subcutaneous studies in the mouse at a dose less than the MRHD on a mg/m^2 basis and in the rat at a dose equivalent to the MRHD on a mg/m^2 basis revealed fetal toxicity characteristic of potent corticosteroid compounds, including embryonic growth retardation, omphalocele, cleft palate, and retarded cranial ossification.

In the rabbit, fetal weight reduction and cleft palate were observed at a subcutaneous dose less than the MRHD on a mg/m^2 basis. However, no teratogenic effects were reported at oral doses up to approximately 5 times the MRHD on a mg/m^2 basis. No fluticasone propionate was detected in the plasma in this study, consistent with the established low bioavailability following oral administration [see *Clinical Pharmacology* (12.3)].

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. In addition, because there is a natural increase in corticosteroid production during pregnancy, most women will require a lower exogenous corticosteroid dose and many will not need corticosteroid treatment during pregnancy.

Salmeterol: No teratogenic effects occurred in rats at oral doses approximately 160 times the MRHD on a mg/m^2 basis. In Dutch rabbits administered oral doses approximately 50 times the MRHD based on comparison of the AUCs, salmeterol exhibited fetal toxic effects characteristically resulting from beta-adrenoceptor stimulation. These included precocious eyelid openings, cleft palate, sternebral fusion, limb and paw flexures, and delayed ossification of the frontal cranial bones. No such effects occurred at an oral dose approximately 20 times the MRHD based on comparison of the AUCs.

New Zealand White rabbits were less sensitive since only delayed ossification of the frontal bones was seen at an oral dose approximately 1,600 times the MRHD on a mg/m^2 basis. Extensive use of other beta-agonists has provided no evidence that these class effects in animals are relevant to their use in humans.

8.2 Labor and Delivery

There are no well-controlled human studies that have investigated effects of ADVAIR DISKUS on preterm labor or labor at term. Because of the potential for beta-agonist interference

with uterine contractility, use of ADVAIR DISKUS during labor should be restricted to those patients in whom the benefits clearly outweigh the risks.

8.3 Nursing Mothers

Plasma levels of salmeterol, a component of ADVAIR DISKUS, after inhaled therapeutic doses are very low. In rats, salmeterol xinafoate is excreted in the milk. There are no data from controlled trials on the use of salmeterol by nursing mothers. It is not known whether fluticasone propionate, a component of ADVAIR DISKUS, is excreted in human breast milk. However, other corticosteroids have been detected in human milk. Subcutaneous administration to lactating rats of tritiated fluticasone propionate resulted in measurable radioactivity in milk.

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

Caution should be exercised when ADVAIR DISKUS is administered to a nursing woman.

8.4 Pediatric Use

Use of ADVAIR DISKUS 100/50 in patients 4 to 11 years of age is supported by extrapolation of efficacy data from older patients and by safety and efficacy data from a study of ADVAIR DISKUS 100/50 in children with asthma aged 4 to 11 years [*see Adverse Reactions (6.1), Clinical Studies (14.1)*]. The safety and effectiveness of ADVAIR DISKUS in children with asthma less than 4 years of age have not been established.

Inhaled corticosteroids, including fluticasone propionate, a component of ADVAIR DISKUS, may cause a reduction in growth velocity in children and adolescents [*see Warnings and Precautions (5.14)*]. The growth of pediatric patients receiving orally inhaled corticosteroids, including ADVAIR DISKUS, should be monitored.

A 52-week placebo-controlled study to assess the potential growth effects of fluticasone propionate inhalation powder (FLOVENT[®] ROTADISK[®]) at 50 and 100 mcg twice daily was conducted in the US in 325 prepubescent children (244 males and 81 females) aged 4 to 11 years. The mean growth velocities at 52 weeks observed in the intent-to-treat population were 6.32 cm/year in the placebo group (N = 76), 6.07 cm/year in the 50-mcg group (N = 98), and 5.66 cm/year in the 100-mcg group (N = 89). An imbalance in the proportion of children entering puberty between groups and a higher dropout rate in the placebo group due to poorly controlled asthma may be confounding factors in interpreting these data. A separate subset analysis of children who remained prepubertal during the study revealed growth rates at 52 weeks of 6.10 cm/year in the placebo group (n = 57), 5.91 cm/year in the 50-mcg group (n = 74), and 5.67 cm/year in the 100-mcg group (n = 79). In children 8.5 years of age, the mean age of children in this study, the range for expected growth velocity is: boys – 3rd percentile = 3.8 cm/year, 50th percentile = 5.4 cm/year, and 97th percentile = 7.0 cm/year; girls – 3rd percentile = 4.2 cm/year, 50th percentile = 5.7 cm/year, and 97th percentile = 7.3 cm/year. The clinical relevance of these growth data is not certain.

If a child or adolescent on any corticosteroid appears to have growth suppression, the possibility that he/she is particularly sensitive to this effect of corticosteroids 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 ADVAIR DISKUS, each patient should be titrated to the lowest strength that effectively controls his/her asthma [*see Dosage and Administration (2.1)*].

8.5 Geriatric Use

Clinical studies of ADVAIR DISKUS for asthma did not include sufficient numbers of patients aged 65 years and older to determine whether older patients with asthma respond differently than younger patients.

Of the total number of patients in clinical studies receiving ADVAIR DISKUS for COPD, 1,621 were 65 years of age or older and 379 were 75 years of age or older. Patients with COPD 65 years of age and older had a higher incidence of serious adverse events compared with patients less than 65 years of age. Although the distribution of adverse events was similar in the 2 age-groups, patients over 65 years of age experienced more severe events. In two 1-year studies, the excess risk of pneumonia that was seen in patients treated with ADVAIR DISKUS compared with those treated with salmeterol was greater in patients over 65 years of age than in patients less than 65 years of age [*see Adverse Reactions (6.2)*]. As with other products containing beta₂-agonists, special caution should be observed when using ADVAIR DISKUS in geriatric patients who have concomitant cardiovascular disease that could be adversely affected by beta₂-agonists. Based on available data for ADVAIR DISKUS or its active components, no adjustment of dosage of ADVAIR DISKUS in geriatric patients is warranted.

No relationship between fluticasone propionate systemic exposure and age was observed in 57 patients with COPD (aged 40 to 82 years) given 250 or 500 mcg twice daily.

8.6 Hepatic Impairment

Formal pharmacokinetic studies using ADVAIR DISKUS have not been conducted in patients with hepatic impairment. However, since both fluticasone propionate and salmeterol are predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of fluticasone propionate and salmeterol in plasma. Therefore, patients with hepatic disease should be closely monitored.

8.7 Renal Impairment

Formal pharmacokinetic studies using ADVAIR DISKUS have not been conducted in patients with renal impairment.

10 OVERDOSAGE

No human overdosage data has been reported for ADVAIR DISKUS.

No deaths occurred in rats given an inhaled single-dose combination of salmeterol 3.6 mg/kg (approximately 290 and 140 times the MRHD for adults and children, respectively, on a mg/m² basis) and 1.9 mg/kg of fluticasone propionate (approximately 15 and 35 times the MRHD for adults and children, respectively, on a mg/m² basis).

Fluticasone Propionate: Chronic overdosage with fluticasone propionate may result in signs/symptoms of hypercorticism [*see Warnings and Precautions (5.7)*]. Inhalation by healthy volunteers of a single dose of 4,000 mcg of fluticasone propionate inhalation powder or single doses of 1,760 or 3,520 mcg of fluticasone propionate inhalation aerosol was well tolerated. Fluticasone propionate given by inhalation aerosol at dosages of 1,320 mcg twice daily for 7 to 15 days to healthy human volunteers was also well tolerated. Repeat oral doses up to 80 mg daily for 10 days in healthy volunteers and repeat oral doses up to 20 mg daily for 42 days in patients were well tolerated. Adverse reactions were of mild or moderate severity, and incidences were similar in active and placebo treatment groups.

No deaths were seen in mice given an oral dose of 1,000 mg/kg (4,100 and 9,600 times the MRHD dose for adults and children, respectively, on a mg/m² basis). No deaths were seen in rats given an oral dose of 1,000 mg/kg (8,100 and 19,200 times the MRHD for adults and children, respectively, on a mg/m² basis).

Salmeterol: The expected signs and symptoms with overdosage of salmeterol are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the following: seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, and insomnia. Overdosage with salmeterol can lead to clinically significant prolongation of the QTc interval, which can produce ventricular arrhythmias. Other signs of overdosage may include hypokalemia and hyperglycemia.

As with all sympathomimetic medications, cardiac arrest and even death may be associated with abuse of salmeterol.

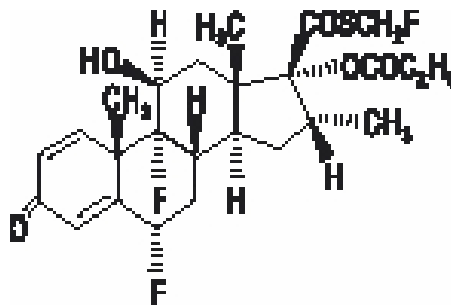
Treatment consists of discontinuation of salmeterol together with appropriate symptomatic therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is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

No deaths were seen in rats given salmeterol at an inhalation dose of 2.9 mg/kg (approximately 240 and 110 times the MRHD for adults and children, respectively, on a mg/m² basis) and in dogs at an inhalation dose of 0.7 mg/kg (approximately 190 and 90 times the MRHD for adults and children, respectively, on a mg/m² basis). By the oral route, no deaths occurred in mice at 150 mg/kg (approximately 6,100 and 2,900 times the MRHD for adults and children, respectively, on a mg/m² basis) and in rats at 1,000 mg/kg (approximately 81,000 and 38,000 times the MRHD for adults and children, respectively, on a mg/m² basis).

11 DESCRIPTION

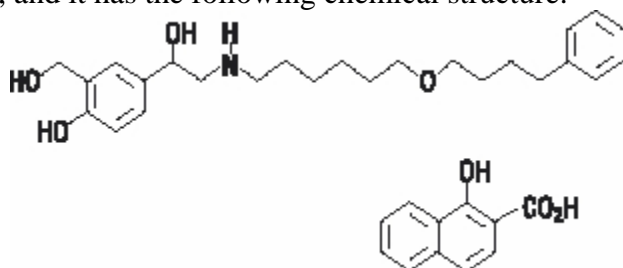
ADVAIR DISKUS 100/50, ADVAIR DISKUS 250/50, and ADVAIR DISKUS 500/50 are combinations of fluticasone propionate and salmeterol xinafoate.

One active component of ADVAIR DISKUS is fluticasone propionate, a corticosteroid having the chemical name *S*-(fluoromethyl) 6 α ,9-difluoro-11 β ,17-dihydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carbothioate, 17-propionate and the following chemical structure:



Fluticasone propionate is a white powder with a molecular weight of 500.6, and the empirical formula is $C_{25}H_{31}F_3O_5S$. It is practically insoluble in water, freely soluble in dimethyl sulfoxide and dimethylformamide, and slightly soluble in methanol and 95% ethanol.

The other active component of ADVAIR DISKUS is salmeterol xinafoate, a beta₂-adrenergic bronchodilator. Salmeterol xinafoate is the racemic form of the 1-hydroxy-2-naphthoic acid salt of salmeterol. The chemical name of salmeterol xinafoate is 4-hydroxy- α^1 -[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol, 1-hydroxy-2-naphthalenecarboxylate, and it has the following chemical structure:



Salmeterol xinafoate is a white powder with a molecular weight of 603.8, and the empirical formula is $C_{25}H_{37}NO_4 \cdot C_{11}H_8O_3$. It is freely soluble in methanol; slightly soluble in ethanol, chloroform, and isopropanol; and sparingly soluble in water.

ADVAIR DISKUS 100/50, ADVAIR DISKUS 250/50, and ADVAIR DISKUS 500/50 are specially designed plastic devices containing a double-foil blister strip of a powder formulation of fluticasone propionate and salmeterol xinafoate intended for oral inhalation only. Each blister on the double-foil strip within the device contains 100, 250, or 500 mcg of microfine fluticasone propionate and 72.5 mcg of microfine salmeterol xinafoate salt, equivalent to 50 mcg of salmeterol base, in 12.5 mg of formulation containing lactose (which contains milk proteins). Each blister contains 1 complete dose of both medications. After a blister containing medication is opened by activating the device, the medication is dispersed into the airstream created by the patient inhaling through the mouthpiece.

Under standardized in vitro test conditions, ADVAIR DISKUS delivers 93, 233, and 465 mcg of fluticasone propionate and 45 mcg of salmeterol base per blister from ADVAIR

DISKUS 100/50, 250/50, and 500/50, respectively, when tested at a flow rate of 60 L/min for 2 seconds. In adult patients with obstructive lung disease and severely compromised lung function (mean FEV₁ 20% to 30% of predicted), mean peak inspiratory flow (PIF) through a DISKUS inhalation device was 82.4 L/min (range, 46.1 to 115.3 L/min).

Inhalation profiles for adolescent (N = 13, aged 12 to 17 years) and adult (N = 17, aged 18 to 50 years) patients with asthma inhaling maximally through the DISKUS[®] device show mean PIF of 122.2 L/min (range, 81.6 to 152.1 L/min). Inhalation profiles for pediatric patients with asthma inhaling maximally through the DISKUS device show a mean PIF of 75.5 L/min (range, 49.0 to 104.8 L/min) for the 4-year-old patient set (N = 20) and 107.3 L/min (range, 82.8 to 125.6 L/min) for the 8-year-old patient set (N = 20).

The actual amount of drug delivered to the lung will depend on patient factors, such as inspiratory flow profile.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

ADVAIR DISKUS: Since ADVAIR DISKUS contains both fluticasone propionate and salmeterol, the mechanisms of action described below for the individual components apply to ADVAIR DISKUS. These drugs represent 2 classes of medications (a synthetic corticosteroid and a selective, long-acting beta-adrenergic receptor agonist) that have different effects on clinical and physiological indices.

Fluticasone Propionate: Fluticasone propionate is a synthetic trifluorinated corticosteroid with potent anti-inflammatory activity. In vitro assays using human lung cytosol preparations have established fluticasone propionate as a human glucocorticoid receptor agonist with an affinity 18 times greater than dexamethasone, almost twice that of beclomethasone-17-monopropionate (BMP), the active metabolite of beclomethasone dipropionate, and over 3 times that of budesonide. Data from the McKenzie vasoconstrictor assay in man are consistent with these results.

Inflammation is an important component in the pathogenesis of asthma. Corticosteroids have been shown to inhibit multiple cell types (e.g., mast cells, eosinophils, basophils, lymphocytes, macrophages, neutrophils) and mediator production or secretion (e.g., histamine, eicosanoids, leukotrienes, cytokines) involved in the asthmatic response. These anti-inflammatory actions of corticosteroids contribute to their efficacy in asthma.

Inflammation is also a component in the pathogenesis of COPD. In contrast to asthma, however, the predominant inflammatory cells in COPD include neutrophils, CD8+ T-lymphocytes, and macrophages. The effects of corticosteroids in the treatment of COPD are not well defined and inhaled corticosteroids and fluticasone propionate when used apart from ADVAIR DISKUS are not indicated for the treatment of COPD.

Salmeterol Xinafoate: Salmeterol is a selective, long-acting beta₂-adrenergic agonist. In vitro studies show salmeterol to be at least 50 times more selective for beta₂-adrenoceptors than albuterol. Although beta₂-adrenoceptors are the predominant adrenergic receptors in bronchial

smooth muscle and β_1 -adrenoceptors are the predominant receptors in the heart, there are also β_2 -adrenoceptors in the human heart comprising 10% to 50% of the total beta-adrenoceptors. The precise function of these receptors has not been established, but they raise the possibility that even highly selective β_2 -agonists may have cardiac effects.

The pharmacologic effects of β_2 -adrenoceptor agonist drugs, including salmeterol, are at least in part attributable to stimulation of intracellular adenylyl 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 salmeterol is a potent and long-lasting inhibitor of the release of mast cell mediators, such as histamine, leukotrienes, and prostaglandin D_2 , from human lung. Salmeterol inhibits histamine-induced plasma protein extravasation and inhibits platelet-activating factor-induced eosinophil accumulation in the lungs of guinea pigs when administered by the inhaled route. In humans, single doses of salmeterol administered via inhalation aerosol attenuate allergen-induced bronchial hyper-responsiveness.

12.2 Pharmacodynamics

ADVAIR DISKUS: Healthy Subjects: Cardiovascular Effects: Since systemic pharmacodynamic effects of salmeterol are not normally seen at the therapeutic dose, higher doses were used to produce measurable effects. Four (4) studies were conducted in healthy adult subjects: (1) a single-dose crossover study using 2 inhalations of ADVAIR DISKUS 500/50, fluticasone propionate powder 500 mcg and salmeterol powder 50 mcg given concurrently, or fluticasone propionate powder 500 mcg given alone, (2) a cumulative dose study using 50 to 400 mcg of salmeterol powder given alone or as ADVAIR DISKUS 500/50, (3) a repeat-dose study for 11 days using 2 inhalations twice daily of ADVAIR DISKUS 250/50, fluticasone propionate powder 250 mcg, or salmeterol powder 50 mcg, and (4) a single-dose study using 5 inhalations of ADVAIR DISKUS 100/50, fluticasone propionate powder 100 mcg alone, or placebo. In these studies no significant differences were observed in the pharmacodynamic effects of salmeterol (pulse rate, blood pressure, QTc interval, potassium, and glucose) whether the salmeterol was given as ADVAIR DISKUS, concurrently with fluticasone propionate from separate inhalers, or as salmeterol alone. The systemic pharmacodynamic effects of salmeterol were not altered by the presence of fluticasone propionate in ADVAIR DISKUS. The potential effect of salmeterol on the effects of fluticasone propionate on the HPA axis was also evaluated in these studies.

HPA Axis Effects: No significant differences across treatments were observed in 24-hour urinary cortisol excretion and, where measured, 24-hour plasma cortisol AUC. The systemic pharmacodynamic effects of fluticasone propionate were not altered by the presence of salmeterol in ADVAIR DISKUS in healthy subjects.

Asthma: Adults and Adolescent Patients: Cardiovascular Effects: In clinical studies with ADVAIR DISKUS in adult and adolescent patients 12 years of age and older with

asthma, no significant differences were observed in the systemic pharmacodynamic effects of salmeterol (pulse rate, blood pressure, QTc interval, potassium, and glucose) whether the salmeterol was given alone or as ADVAIR DISKUS. In 72 adolescent and adult patients with asthma given either ADVAIR DISKUS 100/50 or ADVAIR DISKUS 250/50, continuous 24-hour electrocardiographic monitoring was performed after the first dose and after 12 weeks of therapy, and no clinically significant dysrhythmias were noted.

HPA Axis Effects: In a 28-week study in adolescent and adult patients with asthma, ADVAIR DISKUS 500/50 twice daily was compared with the concurrent use of salmeterol powder 50 mcg plus fluticasone propionate powder 500 mcg from separate inhalers or fluticasone propionate powder 500 mcg alone. No significant differences across treatments were observed in serum cortisol AUC after 12 weeks of dosing or in 24-hour urinary cortisol excretion after 12 and 28 weeks.

In a 12-week study in adolescent and adult patients with asthma, ADVAIR DISKUS 250/50 twice daily was compared with fluticasone propionate powder 250 mcg alone, salmeterol powder 50 mcg alone, and placebo. For most patients, the ability to increase cortisol production in response to stress, as assessed by 30-minute cosyntropin stimulation, remained intact with ADVAIR DISKUS. One patient (3%) who received ADVAIR DISKUS 250/50 had an abnormal response (peak serum cortisol <18 mcg/dL) after dosing, compared with 2 patients (6%) who received placebo, 2 patients (6%) who received fluticasone propionate 250 mcg, and no patients who received salmeterol.

In a repeat-dose, 3-way crossover study, 1 inhalation twice daily of ADVAIR DISKUS 100/50, FLOVENT[®] DISKUS[®] 100 mcg (fluticasone propionate inhalation powder, 100 mcg), or placebo was administered to 20 adolescent and adult patients with asthma. After 28 days of treatment, geometric mean serum cortisol AUC over 12 hours showed no significant difference between ADVAIR DISKUS and FLOVENT DISKUS or between either active treatment and placebo.

Pediatric Patients: HPA Axis Effects: In a 12-week study in patients with asthma aged 4 to 11 years who were receiving inhaled corticosteroids at study entry, ADVAIR DISKUS 100/50 twice daily was compared with fluticasone propionate inhalation powder 100 mcg administered twice daily via the DISKUS. The values for 24-hour urinary cortisol excretion at study entry and after 12 weeks of treatment were similar within each treatment group. After 12 weeks, 24-hour urinary cortisol excretion was also similar between the 2 groups.

Chronic Obstructive Pulmonary Disease: Cardiovascular Effects: In clinical studies with ADVAIR DISKUS in patients with COPD, no significant differences were seen in pulse rate, blood pressure, potassium, and glucose between ADVAIR DISKUS, the individual components of ADVAIR DISKUS, and placebo. In a study of ADVAIR DISKUS 250/50, 8 patients (2 [1.1%] in the group given ADVAIR DISKUS 250/50, 1 [0.5%] in the fluticasone propionate 250-mcg group, 3 [1.7%] in the salmeterol group, and 2 [1.1%] in the placebo group) had QTc intervals >470 msec at least 1 time during the treatment period. Five (5) of these 8 patients had a prolonged QTc interval at baseline.

In a 24-week study, 130 patients with COPD received continuous 24-hour electrocardiographic monitoring prior to the first dose and after 4 weeks of twice-daily treatment with either ADVAIR DISKUS 500/50, fluticasone propionate powder 500 mcg, salmeterol powder 50 mcg, or placebo. No significant differences in ventricular or supraventricular arrhythmias and heart rate were observed among the groups treated with ADVAIR DISKUS 500/50, the individual components, or placebo. One (1) subject in the fluticasone propionate group experienced atrial flutter/atrial fibrillation, and 1 subject in the group given ADVAIR DISKUS 500/50 experienced heart block. There were 3 cases of nonsustained ventricular tachycardia (1 each in the placebo, salmeterol, and fluticasone propionate 500-mcg treatment groups).

In 24-week clinical studies in patients with COPD, the incidence of clinically significant electrocardiogram (ECG) abnormalities (myocardial ischemia, ventricular hypertrophy, clinically significant conduction abnormalities, clinically significant arrhythmias) was lower for patients who received salmeterol (1%, 9 of 688 patients who received either salmeterol 50 mcg or ADVAIR DISKUS) compared with placebo (3%, 10 of 370 patients).

No significant differences with salmeterol 50 mcg alone or in combination with fluticasone propionate as ADVAIR DISKUS 500/50 were observed on pulse rate and systolic and diastolic blood pressure in a subset of patients with COPD who underwent 12-hour serial vital sign measurements after the first dose (N = 183) and after 12 weeks of therapy (N = 149). Median changes from baseline in pulse rate and systolic and diastolic blood pressure were similar to those seen with placebo.

HPA Axis Effects: Short-cosyntropin stimulation testing was performed both at Day 1 and Endpoint in 101 patients with COPD receiving twice-daily ADVAIR DISKUS 250/50, fluticasone propionate powder 250 mcg, salmeterol powder 50 mcg, or placebo. For most patients, the ability to increase cortisol production in response to stress, as assessed by short cosyntropin stimulation, remained intact with ADVAIR DISKUS 250/50. One (1) patient (3%) who received ADVAIR DISKUS 250/50 had an abnormal stimulated cortisol response (peak cortisol <14.5 mcg/dL assessed by high-performance liquid chromatography) after dosing, compared with 2 patients (9%) who received fluticasone propionate 250 mcg, 2 patients (7%) who received salmeterol 50 mcg, and 1 patient (4%) who received placebo following 24 weeks of treatment or early discontinuation from study.

After 36 weeks of dosing, serum cortisol concentrations in a subset of patients with COPD (n = 83) were 22% lower in patients receiving ADVAIR DISKUS 500/50 and 21% lower in patients receiving fluticasone propionate 500 mcg than in patients receiving placebo.

Other Fluticasone Propionate Products: Asthma: HPA Axis Effects: In clinical trials with fluticasone propionate inhalation powder using doses up to and including 250 mcg twice daily, occasional abnormal short cosyntropin tests (peak serum cortisol <18 mcg/dL assessed by radioimmunoassay) were noted both in patients receiving fluticasone propionate and in patients receiving placebo. The incidence of abnormal tests at 500 mcg twice daily was greater than placebo. In a 2-year study carried out with the DISKHALER® inhalation device in

64 patients with mild, persistent asthma (mean FEV₁ 91% of predicted) randomized to fluticasone propionate 500 mcg twice daily or placebo, no patient receiving fluticasone propionate had an abnormal response to 6-hour cosyntropin infusion (peak serum cortisol <18 mcg/dL). With a peak cortisol threshold of <35 mcg/dL, 1 patient receiving fluticasone propionate (4%) had an abnormal response at 1 year; repeat testing at 18 months and 2 years was normal. Another patient receiving fluticasone propionate (5%) had an abnormal response at 2 years. No patient on placebo had an abnormal response at 1 or 2 years.

Chronic Obstructive Pulmonary Disease: HPA Axis Effects: After 4 weeks of dosing, the steady-state fluticasone propionate pharmacokinetics and serum cortisol levels were described in a subset of patients with COPD (n = 86) randomized to twice-daily fluticasone propionate inhalation powder via the DISKUS 500 mcg, fluticasone propionate inhalation powder 250 mcg, or placebo. Serial serum cortisol concentrations were measured across a 12-hour dosing interval. Serum cortisol concentrations following 250- and 500-mcg twice-daily dosing were 10% and 21% lower than placebo, respectively, indicating a dose-dependent increase in systemic exposure to fluticasone propionate.

Other Salmeterol Xinafoate Products: ***Asthma: Cardiovascular Effects:*** Inhaled salmeterol, like other beta-adrenergic agonist drugs, can produce dose-related cardiovascular effects and effects on blood glucose and/or serum potassium [see *Warnings and Precautions* (5.12, 5.18)]. The cardiovascular effects (heart rate, blood pressure) associated with salmeterol occur with similar frequency, and are of similar type and severity, as those noted following albuterol administration.

The effects of rising doses of salmeterol and standard inhaled doses of albuterol were studied in volunteers and in patients with asthma. Salmeterol doses up to 84 mcg administered as inhalation aerosol resulted in heart rate increases of 3 to 16 beats/min, about the same as albuterol dosed at 180 mcg by inhalation aerosol (4 to 10 beats/min). Adolescent and adult patients receiving 50-mcg doses of salmeterol inhalation powder (N = 60) underwent continuous electrocardiographic monitoring during two 12-hour periods after the first dose and after 1 month of therapy, and no clinically significant dysrhythmias were noted.

Concomitant Use of ADVAIR DISKUS With Other Respiratory Medications: ***Short-Acting Beta₂-Agonists:*** In clinical trials with patients with asthma, the mean daily need for albuterol by 166 adult and adolescent patients 12 years of age and older using ADVAIR DISKUS was approximately 1.3 inhalations/day, and ranged from 0 to 9 inhalations/day. Five percent (5%) of patients using ADVAIR DISKUS in these trials averaged 6 or more inhalations per day over the course of the 12-week trials. No increase in frequency of cardiovascular adverse reactions was observed among patients who averaged 6 or more inhalations per day.

In a COPD clinical trial, the mean daily need for albuterol for patients using ADVAIR DISKUS 250/50 was 4.1 inhalations/day. Twenty-six percent (26%) of patients using ADVAIR DISKUS 250/50 averaged 6 or more inhalations per day over the course of the 24-week trial. No increase in frequency of cardiovascular adverse reactions was observed among patients who averaged 6 or more inhalations of albuterol per day.

Methylxanthines: The concurrent use of intravenously or orally administered methylxanthines (e.g., aminophylline, theophylline) by adult and adolescent patients 12 years of age and older receiving ADVAIR DISKUS has not been completely evaluated. In clinical trials with patients with asthma, 39 patients receiving ADVAIR DISKUS 100/50, 250/50, or 500/50 twice daily concurrently with a theophylline product had adverse event rates similar to those in 304 patients receiving ADVAIR DISKUS without theophylline. Similar results were observed in patients receiving salmeterol 50 mcg plus fluticasone propionate 500 mcg twice daily concurrently with a theophylline product (n = 39) or without theophylline (n = 132).

In a COPD clinical trial, 17 patients receiving ADVAIR DISKUS 250/50 twice daily concurrently with a theophylline product had adverse event rates similar to those in 161 patients receiving ADVAIR DISKUS without theophylline. Based on the available data, the concomitant administration of methylxanthines with ADVAIR DISKUS did not alter the observed adverse event profile.

Fluticasone Propionate Nasal Spray: In adult and adolescent patients 12 years of age and older taking ADVAIR DISKUS in clinical trials, no difference in the profile of adverse events or HPA axis effects was noted between patients who were taking FLONASE[®] (fluticasone propionate) Nasal Spray, 50 mcg concurrently (n = 46) and those who were not (n = 130).

12.3 Pharmacokinetics

Absorption: Fluticasone Propionate: Healthy Subjects: Fluticasone propionate acts locally in the lung; therefore, plasma levels do not predict therapeutic effect. Studies using oral dosing of labeled and unlabeled drug have demonstrated that the oral systemic bioavailability of fluticasone propionate is negligible (<1%), primarily due to incomplete absorption and presystemic metabolism in the gut and liver. In contrast, the majority of the fluticasone propionate delivered to the lung is systemically absorbed.

Following administration of ADVAIR DISKUS to healthy adult subjects, peak plasma concentrations of fluticasone propionate were achieved in 1 to 2 hours. In a single-dose crossover study, a higher-than-recommended dose of ADVAIR DISKUS was administered to 14 healthy adult subjects. Two (2) inhalations of the following treatments were administered: ADVAIR DISKUS 500/50, fluticasone propionate powder 500 mcg and salmeterol powder 50 mcg given concurrently, and fluticasone propionate powder 500 mcg alone. Mean peak plasma concentrations of fluticasone propionate averaged 107, 94, and 120 pg/mL, respectively, indicating no significant changes in systemic exposures of fluticasone propionate.

In 15 healthy subjects, systemic exposure to fluticasone propionate from 4 inhalations of ADVAIR[®] HFA 230/21 (fluticasone propionate 230 mcg and salmeterol 21 mcg) Inhalation Aerosol (920/84 mcg) and 2 inhalations of ADVAIR DISKUS 500/50 (1,000/100 mcg) were similar between the 2 inhalers (i.e., 799 vs. 832 pg•hr/mL, respectively), but approximately half the systemic exposure from 4 inhalations of fluticasone propionate CFC inhalation aerosol 220 mcg (880 mcg, AUC = 1,543 pg•hr/mL). Similar results were observed for peak fluticasone propionate plasma concentrations (186 and 182 pg/mL from ADVAIR HFA and ADVAIR

DISKUS, respectively, and 307 pg/mL from the fluticasone propionate CFC inhalation aerosol). Absolute bioavailability of fluticasone propionate was 5.3% and 5.5% following administration of ADVAIR HFA and ADVAIR DISKUS, respectively.

Asthma and COPD Patients: Peak steady-state fluticasone propionate plasma concentrations in adult patients with asthma (N = 11) ranged from undetectable to 266 pg/mL after a 500-mcg twice-daily dose of fluticasone propionate inhalation powder using the DISKUS device. The mean fluticasone propionate plasma concentration was 110 pg/mL.

Full pharmacokinetic profiles were obtained from 9 female and 16 male patients with asthma given fluticasone propionate inhalation powder 500 mcg twice daily using the DISKUS device and from 14 female and 43 male patients with COPD given 250 or 500 mcg twice daily. No overall differences in fluticasone propionate pharmacokinetics were observed.

Peak steady-state fluticasone propionate plasma concentrations in patients with COPD averaged 53 pg/mL (range, 19.3 to 159.3 pg/mL) after treatment with 250 mcg twice daily (N = 30) and 84 pg/mL (range, 24.3 to 197.1 pg/mL) after treatment with 500 mcg twice daily (N = 27) via the fluticasone propionate DISKUS device. In another study in patients with COPD, peak steady-state fluticasone propionate plasma concentrations averaged 115 pg/mL (range, 52.6 to 366.0 pg/mL) after treatment with 500 mcg twice daily via the fluticasone propionate DISKUS device (N = 15) and 105 pg/mL (range, 22.5 to 299.0 pg/mL) via ADVAIR DISKUS (N = 24).

Salmeterol Xinafoate: Healthy Subjects: Salmeterol xinafoate, an ionic salt, dissociates in solution so that the salmeterol and 1-hydroxy-2-naphthoic acid (xinafoate) moieties are absorbed, distributed, metabolized, and eliminated independently. Salmeterol acts locally in the lung; therefore, plasma levels do not predict therapeutic effect.

Following administration of ADVAIR DISKUS to healthy adult subjects, peak plasma concentrations of salmeterol were achieved in about 5 minutes.

In 15 healthy subjects receiving ADVAIR HFA 230/21 Inhalation Aerosol (920/84 mcg) and ADVAIR DISKUS 500/50 (1,000/100 mcg), systemic exposure to salmeterol was higher (317 vs. 169 pg•hr/mL) and peak salmeterol concentrations were lower (196 vs. 223 pg/mL) following ADVAIR HFA compared with ADVAIR DISKUS, although pharmacodynamic results were comparable.

Asthma Patients: Because of the small therapeutic dose, systemic levels of salmeterol are low or undetectable after inhalation of recommended doses (50 mcg of salmeterol inhalation powder twice daily). Following chronic administration of an inhaled dose of 50 mcg of salmeterol inhalation powder twice daily, salmeterol was detected in plasma within 5 to 45 minutes in 7 patients with asthma; plasma concentrations were very low, with mean peak concentrations of 167 pg/mL at 20 minutes and no accumulation with repeated doses.

Distribution: Fluticasone Propionate: Following intravenous administration, the initial disposition phase for fluticasone propionate was rapid and consistent with its high lipid solubility and tissue binding. The volume of distribution averaged 4.2 L/kg.

The percentage of fluticasone propionate bound to human plasma proteins averages 91%. Fluticasone propionate is weakly and reversibly bound to erythrocytes and is not significantly bound to human transcortin.

Salmeterol: The percentage of salmeterol bound to human plasma proteins averages 96% in vitro over the concentration range of 8 to 7,722 ng of salmeterol base per milliliter, much higher concentrations than those achieved following therapeutic doses of salmeterol.

Metabolism: Fluticasone Propionate: The total clearance of fluticasone propionate is high (average, 1,093 mL/min), with renal clearance accounting for less than 0.02% of the total. The only circulating metabolite detected in man is the 17 β -carboxylic acid derivative of fluticasone propionate, which is formed through the CYP 3A4 pathway. This metabolite had less affinity (approximately 1/2,000) than the parent drug for the glucocorticoid receptor of human lung cytosol in vitro and negligible pharmacological activity in animal studies. Other metabolites detected in vitro using cultured human hepatoma cells have not been detected in man.

Salmeterol: Salmeterol base is extensively metabolized by hydroxylation, with subsequent elimination predominantly in the feces. No significant amount of unchanged salmeterol base was detected in either urine or feces.

An in vitro study using human liver microsomes showed that salmeterol is extensively metabolized to α -hydroxysalmeterol (aliphatic oxidation) by CYP 3A4. Ketoconazole, a strong inhibitor of CYP 3A4, essentially completely inhibited the formation of α -hydroxysalmeterol in vitro.

Elimination: Fluticasone Propionate: Following intravenous dosing, fluticasone propionate showed polyexponential kinetics and had a terminal elimination half-life of approximately 7.8 hours. Less than 5% of a radiolabeled oral dose was excreted in the urine as metabolites, with the remainder excreted in the feces as parent drug and metabolites. Terminal half-life estimates of fluticasone propionate for ADVAIR HFA, ADVAIR DISKUS, and fluticasone propionate CFC inhalation aerosol were similar and averaged 5.6 hours.

Salmeterol: In 2 healthy adult subjects who received 1 mg of radiolabeled salmeterol (as salmeterol xinafoate) orally, approximately 25% and 60% of the radiolabeled salmeterol was eliminated in urine and feces, respectively, over a period of 7 days. The terminal elimination half-life was about 5.5 hours (1 volunteer only).

The xinafoate moiety has no apparent pharmacologic activity. The xinafoate moiety is highly protein bound (>99%) and has a long elimination half-life of 11 days. No terminal half-life estimates were calculated for salmeterol following administration of ADVAIR DISKUS.

Special Populations: A population pharmacokinetic analysis was performed for fluticasone propionate and salmeterol utilizing data from 9 controlled clinical trials that included 350 patients with asthma aged 4 to 77 years who received treatment with ADVAIR DISKUS, the combination of HFA-propelled fluticasone propionate and salmeterol inhalation aerosol (ADVAIR HFA), fluticasone propionate inhalation powder (FLOVENT DISKUS), HFA-propelled fluticasone propionate inhalation aerosol (FLOVENT[®] HFA), or CFC-propelled fluticasone propionate inhalation aerosol. The population pharmacokinetic analyses for

fluticasone propionate and salmeterol showed no clinically relevant effects of age, gender, race, body weight, body mass index, or percent of predicted FEV₁ on apparent clearance and apparent volume of distribution.

Age: When the population pharmacokinetic analysis for fluticasone propionate was divided into subgroups based on fluticasone propionate strength, formulation, and age (adolescents/adults and children), there were some differences in fluticasone propionate exposure. Higher fluticasone propionate exposure from ADVAIR DISKUS 100/50 compared with FLOVENT DISKUS 100 mcg was observed in adolescents and adults (ratio 1.52 [90% CI: 1.08, 2.13]). However, in clinical studies of up to 12 weeks' duration comparing ADVAIR DISKUS 100/50 and FLOVENT DISKUS 100 mcg in adolescents and adults, no differences in systemic effects of corticosteroid treatment (e.g., HPA axis effects) were observed. Similar fluticasone propionate exposure was observed from ADVAIR DISKUS 500/50 and FLOVENT DISKUS 500 mcg (ratio 0.83 [90% CI: 0.65, 1.07]) in adolescents and adults.

Steady-state systemic exposure to salmeterol when delivered as ADVAIR DISKUS 100/50, ADVAIR DISKUS 250/50, or ADVAIR HFA 115/21 (fluticasone propionate 115 mcg and salmeterol 21 mcg) Inhalation Aerosol was evaluated in 127 patients aged 4 to 57 years. The geometric mean AUC was 325 pg•hr/mL [90% CI: 309, 341] in adolescents and adults.

The population pharmacokinetic analysis included 160 patients with asthma aged 4 to 11 years who received ADVAIR DISKUS 100/50 or FLOVENT DISKUS 100 mcg. Higher fluticasone propionate exposure (AUC) was observed in children from ADVAIR DISKUS 100/50 compared with FLOVENT DISKUS 100 mcg (ratio 1.20 [90% CI: 1.06, 1.37]). Higher fluticasone propionate exposure (AUC) from ADVAIR DISKUS 100/50 was observed in children compared with adolescents and adults (ratio 1.63 [90% CI: 1.35, 1.96]). However, in clinical studies of up to 12 weeks' duration comparing ADVAIR DISKUS 100/50 and FLOVENT DISKUS 100 mcg in both adolescents and adults and in children, no differences in systemic effects of corticosteroid treatment (e.g., HPA axis effects) were observed.

Exposure to salmeterol was higher in children compared with adolescents and adults who received ADVAIR DISKUS 100/50 (ratio 1.23 [90% CI: 1.10, 1.38]). However, in clinical studies of up to 12 weeks' duration with ADVAIR DISKUS 100/50 in both adolescents and adults and in children, no differences in systemic effects of beta₂-agonist treatment (e.g., cardiovascular effects, tremor) were observed.

Gender: The population pharmacokinetic analysis involved 202 males and 148 females with asthma who received fluticasone propionate alone or in combination with salmeterol and showed no gender differences for fluticasone propionate pharmacokinetics.

The population pharmacokinetic analysis involved 76 males and 51 females with asthma who received salmeterol in combination with fluticasone propionate and showed no gender differences for salmeterol pharmacokinetics.

Hepatic and Renal Impairment: Formal pharmacokinetic studies using ADVAIR DISKUS have not been conducted in patients with hepatic or renal impairment. However, since both fluticasone propionate and salmeterol are predominantly cleared by hepatic metabolism,

impairment of liver function may lead to accumulation of fluticasone propionate and salmeterol in plasma. Therefore, patients with hepatic disease should be closely monitored.

Drug Interactions: In the repeat- and single-dose studies, there was no evidence of significant drug interaction in systemic exposure between fluticasone propionate and salmeterol when given as ADVAIR DISKUS. The population pharmacokinetic analysis from 9 controlled clinical trials in 350 patients with asthma showed no significant effects on fluticasone propionate or salmeterol pharmacokinetics following co-administration with beta₂-agonists, corticosteroids, antihistamines, or theophyllines.

Inhibitors of Cytochrome P450 3A4: Ritonavir: Fluticasone Propionate:

Fluticasone propionate is a substrate of CYP 3A4. Coadministration of fluticasone propionate and the strong CYP 3A4 inhibitor ritonavir is not recommended based upon a multiple-dose, crossover drug interaction study in 18 healthy subjects. Fluticasone propionate aqueous nasal spray (200 mcg once daily) was coadministered for 7 days with ritonavir (100 mg twice daily). Plasma fluticasone propionate concentrations following fluticasone propionate aqueous nasal spray alone were undetectable (<10 pg/mL) in most subjects, and when concentrations were detectable peak levels (C_{max}) averaged 11.9 pg/mL (range, 10.8 to 14.1 pg/mL) and $AUC_{(0-\tau)}$ averaged 8.43 pg•hr/mL (range, 4.2 to 18.8 pg•hr/mL). Fluticasone propionate C_{max} and $AUC_{(0-\tau)}$ increased to 318 pg/mL (range, 110 to 648 pg/mL) and 3,102.6 pg•hr/mL (range, 1,207.1 to 5,662.0 pg•hr/mL), respectively, after coadministration of ritonavir with fluticasone propionate aqueous nasal spray. This significant increase in plasma fluticasone propionate exposure resulted in a significant decrease (86%) in serum cortisol AUC.

Ketoconazole: Fluticasone Propionate: In a placebo-controlled, crossover study in 8 healthy adult volunteers, coadministration of a single dose of orally inhaled fluticasone propionate (1,000 mcg) with multiple doses of ketoconazole (200 mg) to steady state resulted in increased plasma fluticasone propionate exposure, a reduction in plasma cortisol AUC, and no effect on urinary excretion of cortisol.

Salmeterol: In a placebo-controlled, crossover drug interaction study in 20 healthy male and female subjects, coadministration of salmeterol (50 mcg twice daily) and the strong CYP 3A4 inhibitor ketoconazole (400 mg once daily) for 7 days resulted in a significant increase in plasma salmeterol exposure as determined by a 16-fold increase in AUC (ratio with and without ketoconazole 15.76 [90% CI: 10.66, 23.31]) mainly due to increased bioavailability of the swallowed portion of the dose. Peak plasma salmeterol concentrations were increased by 1.4-fold [90% CI: 1.23, 1.68]. Three (3) out of 20 subjects (15%) were withdrawn from salmeterol and ketoconazole coadministration due to beta-agonist-mediated systemic effects (2 with QTc prolongation and 1 with palpitations and sinus tachycardia). Coadministration of salmeterol and ketoconazole did not result in a clinically significant effect on mean heart rate, mean blood potassium, or mean blood glucose. Although there was no statistical effect on the mean QTc, coadministration of salmeterol and ketoconazole was associated with more frequent increases in QTc duration compared with salmeterol and placebo administration.

Erythromycin: Fluticasone Propionate: In a multiple-dose drug interaction study, coadministration of orally inhaled fluticasone propionate (500 mcg twice daily) and erythromycin (333 mg 3 times daily) did not affect fluticasone propionate pharmacokinetics.

Salmeterol: In a repeat-dose study in 13 healthy subjects, concomitant administration of erythromycin (a moderate CYP 3A4 inhibitor) and salmeterol inhalation aerosol resulted in a 40% increase in salmeterol C_{\max} at steady state (ratio with and without erythromycin 1.4 [90% CI: 0.96, 2.03], $p = 0.12$), a 3.6-beat/min increase in heart rate ([95% CI: 0.19, 7.03], $p < 0.04$), a 5.8-msec increase in QTc interval ([95% CI: -6.14, 17.77], $p = 0.34$), and no change in plasma potassium.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Fluticasone Propionate: Fluticasone propionate demonstrated no tumorigenic potential in mice at oral doses up to 1,000 mcg/kg (approximately 4 and 10 times the MRHD for adults and children, respectively, on a mg/m^2 basis) for 78 weeks or in rats at inhalation doses up to 57 mcg/kg (less than and approximately equivalent to the MRHD for adults and children, respectively, on a mg/m^2 basis) for 104 weeks.

Fluticasone propionate did not induce gene mutation in prokaryotic or eukaryotic cells in vitro. No significant clastogenic effect was seen in cultured human peripheral lymphocytes in vitro or in the in vivo mouse micronucleus test.

No evidence of impairment of fertility was observed in reproductive studies conducted in rats at subcutaneous doses up to 50 mcg/kg (less than the MRHD on a mg/m^2 basis). Prostate weight was significantly reduced.

Salmeterol: In an 18-month carcinogenicity study in CD-mice, salmeterol at oral doses of 1.4 mg/kg and above (approximately 20 times the MRHD for adults and children based on comparison of the plasma AUCs) caused a dose-related increase in the incidence of smooth muscle hyperplasia, cystic glandular hyperplasia, leiomyomas of the uterus, and cysts in the ovaries. No tumors were seen at 0.2 mg/kg (approximately 3 times the MRHD for adults and children based on comparison of the AUCs).

In a 24-month oral and inhalation carcinogenicity study in Sprague Dawley rats, salmeterol caused a dose-related increase in the incidence of mesovarian leiomyomas and ovarian cysts at doses of 0.68 mg/kg and above (approximately 55 and 25 times the MRHD for adults and children, respectively, on a mg/m^2 basis). No tumors were seen at 0.21 mg/kg (approximately 15 and 8 times the MRHD for adults and children, respectively, on a mg/m^2 basis). These findings in rodents are similar to those reported previously for other beta-adrenergic agonist drugs. The relevance of these findings to human use is unknown.

Salmeterol produced no detectable or reproducible increases in microbial and mammalian gene mutation in vitro. No clastogenic activity occurred in vitro in human lymphocytes or in vivo in a rat micronucleus test. No effects on fertility were identified in rats treated with salmeterol at oral doses up to 2 mg/kg (approximately 160 times the MRHD for adults on a mg/m^2 basis).

13.2 Animal Toxicology and/or Pharmacology

Preclinical: 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 relevance of these findings is unknown.

Reproductive Toxicology Studies: ADVAIR DISKUS: In mice, combining 150 mcg/kg subcutaneously of fluticasone propionate (less than the MRHD on a mg/m^2 basis) with 10 mg/kg orally of salmeterol (approximately 410 times the MRHD on a mg/m^2 basis) produced cleft palate, fetal death, increased implantation loss, and delayed ossification. No such effects were observed at combination subcutaneous doses up to 40 mcg/kg subcutaneously of fluticasone propionate (less than the MRHD on a mg/m^2 basis) and up to 1.4 mg/kg orally doses of salmeterol (approximately 55 times the MRHD on a mg/m^2 basis).

In rats, combining 100 mcg/kg subcutaneously of fluticasone propionate (equivalent to the MRHD on a mg/m^2 basis) and 10 mg/kg orally of salmeterol (approximately 810 times the MRHD on a mg/m^2 basis) produced decreased fetal weight, umbilical hernia, delayed ossification, and changes in the occipital bone. No such effects were observed at combination doses up to 30 mcg/kg subcutaneously of fluticasone propionate (less than the MRHD on a mg/m^2 basis) and up to 1 mg/kg orally of salmeterol (approximately 80 times the MRHD on a mg/m^2 basis).

Fluticasone Propionate: Subcutaneous studies in the mouse and rat at 45 and 100 mcg/kg (less than and equivalent to the MRHD on a mg/m^2 basis), respectively, revealed fetal toxicity characteristic of potent corticosteroid compounds, including embryonic growth retardation, omphalocele, cleft palate, and retarded cranial ossification.

In the rabbit, fetal weight reduction and cleft palate were observed at a subcutaneous dose of 4 mcg/kg (less than the MRHD on a mg/m^2 basis). However, no teratogenic effects were reported at oral doses up to 300 mcg/kg (approximately 5 times the MRHD on a mg/m^2 basis) of fluticasone propionate. No fluticasone propionate was detected in the plasma in this study, consistent with the established low bioavailability following oral administration [*see Clinical Pharmacology (12.3)*].

Fluticasone propionate crossed the placenta following subcutaneous administration to mice and rats and oral administration to rabbits.

Salmeterol: No teratogenic effects occurred in rats at oral doses up to 2 mg/kg (approximately 160 times the MRHD on a mg/m^2 basis).

In Dutch rabbits administered oral doses of 1 mg/kg and above (approximately 50 times and above the MRHD based on comparison of the AUCs), salmeterol exhibited fetal toxic effects characteristically resulting from beta-adrenoceptor stimulation. These included precocious eyelid openings, cleft palate, sternebral fusion, limb and paw flexures, and delayed ossification of the frontal cranial bones. No such effects occurred at an oral dose of 0.6 mg/kg (approximately 20 times the MRHD based on comparison of the AUCs). New Zealand White rabbits were less

sensitive since only delayed ossification of the frontal bones was seen at an oral dose of 10 mg/kg (approximately 1,600 times the MRHD on a mg/m² basis).

Salmeterol crossed the placenta following oral administration to mice and rats.

14 CLINICAL STUDIES

14.1 Asthma

Adult and Adolescent Patients 12 Years of Age and Older: In clinical trials comparing ADVAIR DISKUS with its individual components, improvements in most efficacy endpoints were greater with ADVAIR DISKUS than with the use of either fluticasone propionate or salmeterol alone. In addition, clinical trials showed similar results between ADVAIR DISKUS and the concurrent use of fluticasone propionate plus salmeterol at corresponding doses from separate inhalers.

Studies Comparing ADVAIR DISKUS to Fluticasone Propionate Alone or Salmeterol Alone: Three (3) double-blind, parallel-group clinical trials were conducted with ADVAIR DISKUS in 1,208 adolescent and adult patients (≥12 years, baseline FEV₁ 63% to 72% of predicted normal) with asthma that was not optimally controlled on their current therapy. All treatments were inhalation powders given as 1 inhalation from the DISKUS device twice daily, and other maintenance therapies were discontinued.

Study 1: Clinical Trial With ADVAIR DISKUS 100/50: This placebo-controlled, 12-week, US study compared ADVAIR DISKUS 100/50 with its individual components, fluticasone propionate 100 mcg and salmeterol 50 mcg. The study was stratified according to baseline asthma maintenance therapy; patients were using either inhaled corticosteroids (N = 250) (daily doses of beclomethasone dipropionate 252 to 420 mcg; flunisolide 1,000 mcg; fluticasone propionate inhalation aerosol 176 mcg; or triamcinolone acetonide 600 to 1,000 mcg) or salmeterol (N = 106). Baseline FEV₁ measurements were similar across treatments: ADVAIR DISKUS 100/50, 2.17 L; fluticasone propionate 100 mcg, 2.11 L; salmeterol, 2.13 L; and placebo, 2.15 L.

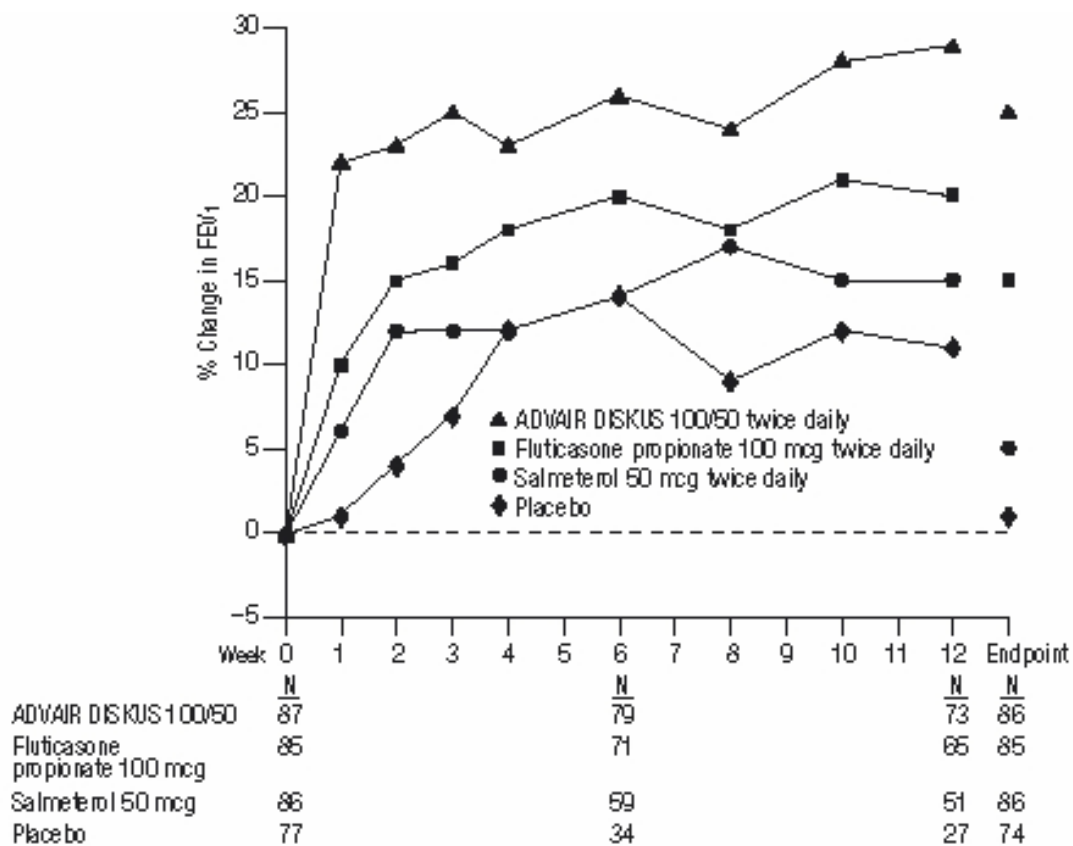
Predefined withdrawal criteria for lack of efficacy, an indicator of worsening asthma, were utilized for this placebo-controlled study. Worsening asthma was defined as a clinically important decrease in FEV₁ or PEF, increase in use of VENTOLIN[®] (albuterol, USP) Inhalation Aerosol, increase in night awakenings due to asthma, emergency intervention or hospitalization due to asthma, or requirement for asthma medication not allowed by the protocol. As shown in Table 4, statistically significantly fewer patients receiving ADVAIR DISKUS 100/50 were withdrawn due to worsening asthma compared with fluticasone propionate, salmeterol, and placebo.

Table 4. Percent of Patients Withdrawn Due to Worsening Asthma in Patients Previously Treated With Either Inhaled Corticosteroids or Salmeterol (Study 1)

ADVAIR DISKUS 100/50 (N = 87)	Fluticasone Propionate 100 mcg (N = 85)	Salmeterol 50 mcg (N = 86)	Placebo (N = 77)
3%	11%	35%	49%

The FEV₁ results are displayed in Figure 2. Because this trial used predetermined criteria for worsening asthma, which caused more patients in the placebo group to be withdrawn, FEV₁ results at Endpoint (last available FEV₁ result) are also provided. Patients receiving ADVAIR DISKUS 100/50 had significantly greater improvements in FEV₁ (0.51 L, 25%) compared with fluticasone propionate 100 mcg (0.28 L, 15%), salmeterol (0.11 L, 5%), and placebo (0.01 L, 1%). These improvements in FEV₁ with ADVAIR DISKUS were achieved regardless of baseline asthma maintenance therapy (inhaled corticosteroids or salmeterol).

Figure 2. Mean Percent Change From Baseline in FEV₁ in Patients With Asthma Previously Treated With Either Inhaled Corticosteroids or Salmeterol (Study 1)



The effect of ADVAIR DISKUS 100/50 on morning and evening PEF endpoints is shown in Table 5.

Table 5. Peak Expiratory Flow Results for Patients With Asthma Previously Treated With Either Inhaled Corticosteroids or Salmeterol (Study 1)

Efficacy Variable*	ADVAIR DISKUS 100/50 (N = 87)	Fluticasone Propionate 100 mcg (N = 85)	Salmeterol 50 mcg (N = 86)	Placebo (N = 77)
AM PEF (L/min)				
Baseline	393	374	369	382
Change from baseline	53	17	-2	-24
PM PEF (L/min)				
Baseline	418	390	396	398
Change from baseline	35	18	-7	-13

*Change from baseline = change from baseline at Endpoint (last available data).

The subjective impact of asthma on patients' perception of health was evaluated through use of an instrument called the Asthma Quality of Life Questionnaire (AQLQ) (based on a 7-point scale where 1 = maximum impairment and 7 = none). Patients receiving ADVAIR DISKUS 100/50 had clinically meaningful improvements in overall asthma-specific quality of life as defined by a difference between groups of ≥ 0.5 points in change from baseline AQLQ scores (difference in AQLQ score of 1.25 compared with placebo).

Study 2: Clinical Trial With ADVAIR DISKUS 250/50: This placebo-controlled, 12-week, US study compared ADVAIR DISKUS 250/50 with its individual components, fluticasone propionate 250 mcg and salmeterol 50 mcg, in 349 patients with asthma using inhaled corticosteroids (daily doses of beclomethasone dipropionate 462 to 672 mcg; flunisolide 1,250 to 2,000 mcg; fluticasone propionate inhalation aerosol 440 mcg; or triamcinolone acetonide 1,100 to 1,600 mcg). Baseline FEV₁ measurements were similar across treatments: ADVAIR DISKUS 250/50, 2.23 L; fluticasone propionate 250 mcg, 2.12 L; salmeterol, 2.20 L; and placebo, 2.19 L.

Efficacy results in this study were similar to those observed in Study 1. Patients receiving ADVAIR DISKUS 250/50 had significantly greater improvements in FEV₁ (0.48 L, 23%) compared with fluticasone propionate 250 mcg (0.25 L, 13%), salmeterol (0.05 L, 4%), and placebo (decrease of 0.11 L, decrease of 5%). Statistically significantly fewer patients receiving ADVAIR DISKUS 250/50 were withdrawn from this study for worsening asthma (4%) compared with fluticasone propionate (22%), salmeterol (38%), and placebo (62%). In addition, ADVAIR DISKUS 250/50 was superior to fluticasone propionate, salmeterol, and placebo for improvements in morning and evening PEF. Patients receiving ADVAIR DISKUS 250/50 also

had clinically meaningful improvements in overall asthma-specific quality of life as described in Study 1 (difference in AQLQ score of 1.29 compared with placebo).

Study 3: Clinical Trial With ADVAIR DISKUS 500/50: This 28-week, non-US study compared ADVAIR DISKUS 500/50 with fluticasone propionate 500 mcg alone and concurrent therapy (salmeterol 50 mcg plus fluticasone propionate 500 mcg administered from separate inhalers) twice daily in 503 patients with asthma using inhaled corticosteroids (daily doses of beclomethasone dipropionate 1,260 to 1,680 mcg; budesonide 1,500 to 2,000 mcg; flunisolide 1,500 to 2,000 mcg; or fluticasone propionate inhalation aerosol 660 to 880 mcg [750 to 1,000 mcg inhalation powder]). The primary efficacy parameter, morning PEF, was collected daily for the first 12 weeks of the study. The primary purpose of weeks 13 to 28 was to collect safety data.

Baseline PEF measurements were similar across treatments: ADVAIR DISKUS 500/50, 359 L/min; fluticasone propionate 500 mcg, 351 L/min; and concurrent therapy, 345 L/min. Morning PEF improved significantly with ADVAIR DISKUS 500/50 compared with fluticasone propionate 500 mcg over the 12-week treatment period. Improvements in morning PEF observed with ADVAIR DISKUS 500/50 were similar to improvements observed with concurrent therapy.

Onset 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 placebo-controlled US trials. Following the first dose, the median time to onset of clinically significant bronchodilatation ($\geq 15\%$ improvement in FEV_1) in most patients was seen within 30 to 60 minutes. Maximum improvement in FEV_1 generally occurred within 3 hours, and clinically significant improvement was maintained for 12 hours (see Figure 3). Following the initial dose, predose FEV_1 relative to Day 1 baseline improved markedly over the first week of treatment and continued to improve over the 12 weeks of treatment in both studies. No diminution in the 12-hour bronchodilator effect was observed with either ADVAIR DISKUS 100/50 (Figures 3 and 4) or ADVAIR DISKUS 250/50 as assessed by FEV_1 following 12 weeks of therapy.

Figure 3. Percent Change in Serial 12-hour FEV₁ in Patients With Asthma Previously Using Either Inhaled Corticosteroids or Salmeterol (Study 1)

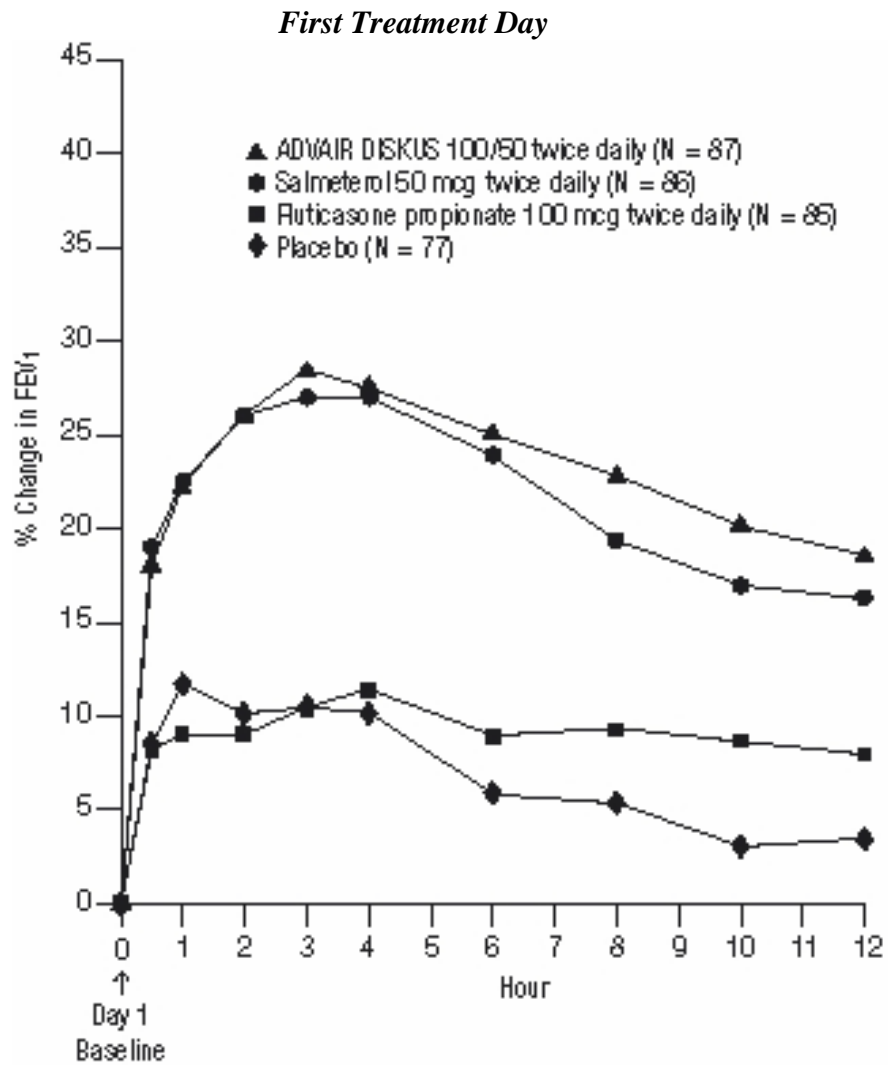
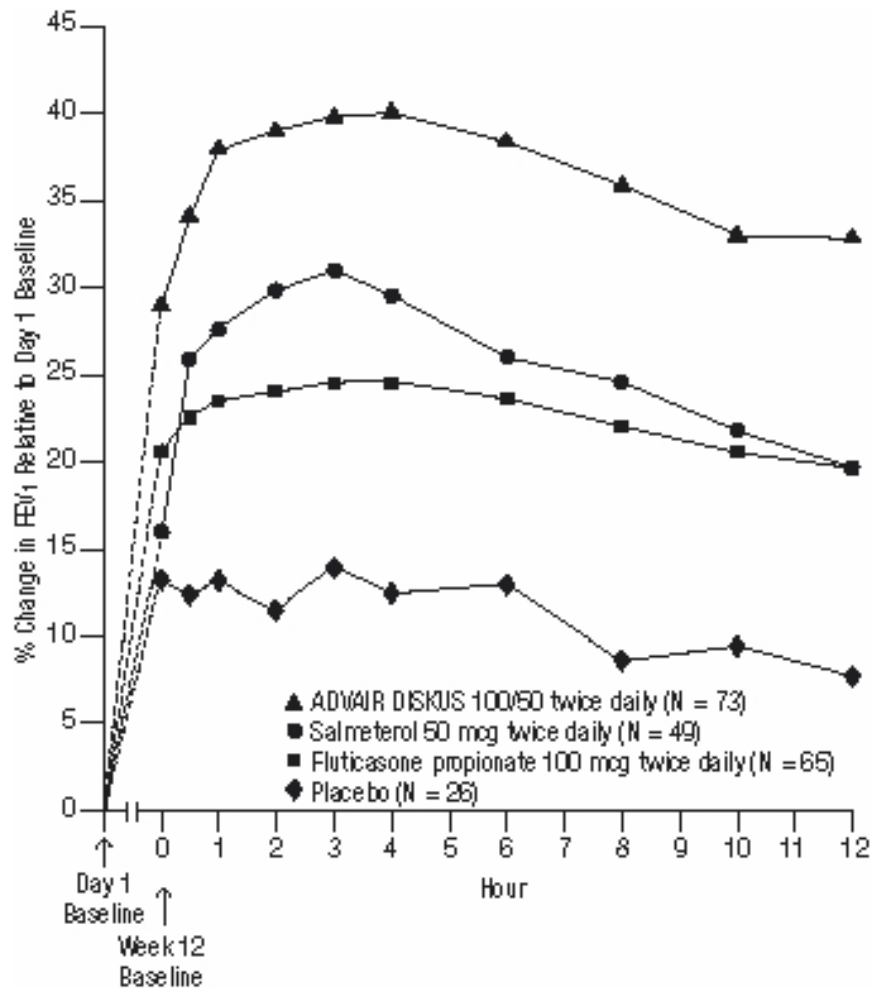


Figure 4. Percent Change in Serial 12-hour FEV₁ in Patients With Asthma Previously Using Either Inhaled Corticosteroids or Salmeterol (Study 1)

Last Treatment Day (Week 12)



Reduction in asthma symptoms, use of rescue VENTOLIN Inhalation Aerosol, and improvement in morning and evening PEF also occurred within the first day of treatment with ADVAIR DISKUS, and continued to improve over the 12 weeks of therapy in both studies.

Pediatric Patients: In a 12-week US study, ADVAIR DISKUS 100/50 twice daily was compared with fluticasone propionate inhalation powder 100 mcg twice daily in 203 children with asthma aged 4 to 11 years. At study entry, the children were symptomatic on low doses of inhaled corticosteroids (beclomethasone dipropionate 252 to 336 mcg/day; budesonide 200 to 400 mcg/day; flunisolide 1,000 mcg/day; triamcinolone acetonide 600 to 1,000 mcg/day; or fluticasone propionate 88 to 250 mcg/day). The primary objective of this study was to determine the safety of ADVAIR DISKUS 100/50 compared with fluticasone propionate inhalation powder

100 mcg in this age-group; however, the study also included secondary efficacy measures of pulmonary function. Morning predose FEV₁ was obtained at baseline and Endpoint (last available FEV₁ result) in children aged 6 to 11 years. In patients receiving ADVAIR DISKUS 100/50, FEV₁ increased from 1.70 L at baseline (N = 79) to 1.88 L at Endpoint (N = 69) compared with an increase from 1.65 L at baseline (N = 83) to 1.77 L at Endpoint (N = 75) in patients receiving fluticasone propionate 100 mcg.

The findings of this study, along with extrapolation of efficacy data from patients 12 years of age and older, support the overall conclusion that ADVAIR DISKUS 100/50 is efficacious in the maintenance treatment of asthma in patients aged 4 to 11 years.

14.2 Chronic Obstructive Pulmonary Disease

The efficacy of ADVAIR DISKUS 250/50 and ADVAIR DISKUS 500/50 in the treatment of patients with COPD was evaluated in 6 randomized, double-blind, parallel-group clinical trials in adult patients 40 years of age and older. These trials were primarily designed to evaluate the efficacy of ADVAIR DISKUS on lung function (3 trials), exacerbations (2 trials), and survival (1 trial).

Lung Function: Two of the 3 clinical trials primarily designed to evaluate the efficacy of ADVAIR DISKUS on lung function were conducted in 1,414 patients with COPD associated with chronic bronchitis. In these 2 trials, all the patients had a history of cough productive of sputum that was not attributable to another disease process on most days for at least 3 months of the year for at least 2 years. The trials were randomized, double-blind, parallel-group, 24-week treatment duration. One trial evaluated the efficacy of ADVAIR DISKUS 250/50 compared with its components fluticasone propionate 250 mcg and salmeterol 50 mcg and to placebo, and the other trial evaluated the efficacy of ADVAIR DISKUS 500/50 compared with its components fluticasone propionate 500 mcg salmeterol 50 mcg and to placebo. Study treatments were inhalation powders given as 1 inhalation from the DISKUS device twice daily. Maintenance COPD therapies were discontinued, with the exception of theophylline. The patients had a mean pre-bronchodilator FEV₁ of 41% and 20% reversibility at study entry. Percent reversibility was calculated as 100 times (FEV₁ post-albuterol minus FEV₁ pre-albuterol)/FEV₁ pre-albuterol.

Improvements in lung function (as defined by predose and postdose FEV₁) were significantly greater with ADVAIR DISKUS than with fluticasone propionate, salmeterol, or placebo. The improvement in lung function with ADVAIR DISKUS 500/50 was similar to the improvement seen with ADVAIR DISKUS 250/50.

Figures 5 and 6 display predose and 2-hour postdose, respectively, FEV₁ results for the study with ADVAIR DISKUS 250/50. To account for patient withdrawals during the study, FEV₁ at Endpoint (last evaluable FEV₁) was evaluated. Patients receiving ADVAIR DISKUS 250/50 had significantly greater improvements in predose FEV₁ at Endpoint (165 mL, 17%) compared with salmeterol 50 mcg (91 mL, 9%) and placebo (1 mL, 1%), demonstrating the contribution of fluticasone propionate to the improvement in lung function with ADVAIR DISKUS (Figure 5). Patients receiving ADVAIR DISKUS 250/50 had significantly greater improvements in postdose FEV₁ at Endpoint (281 mL, 27%) compared with fluticasone

propionate 250 mcg (147 mL, 14%) and placebo (58 mL, 6%), demonstrating the contribution of salmeterol to the improvement in lung function with ADVAIR DISKUS (Figure 6).

Figure 5. Predose FEV₁: Mean Percent Change From Baseline in Patients With Chronic Obstructive Pulmonary Disease

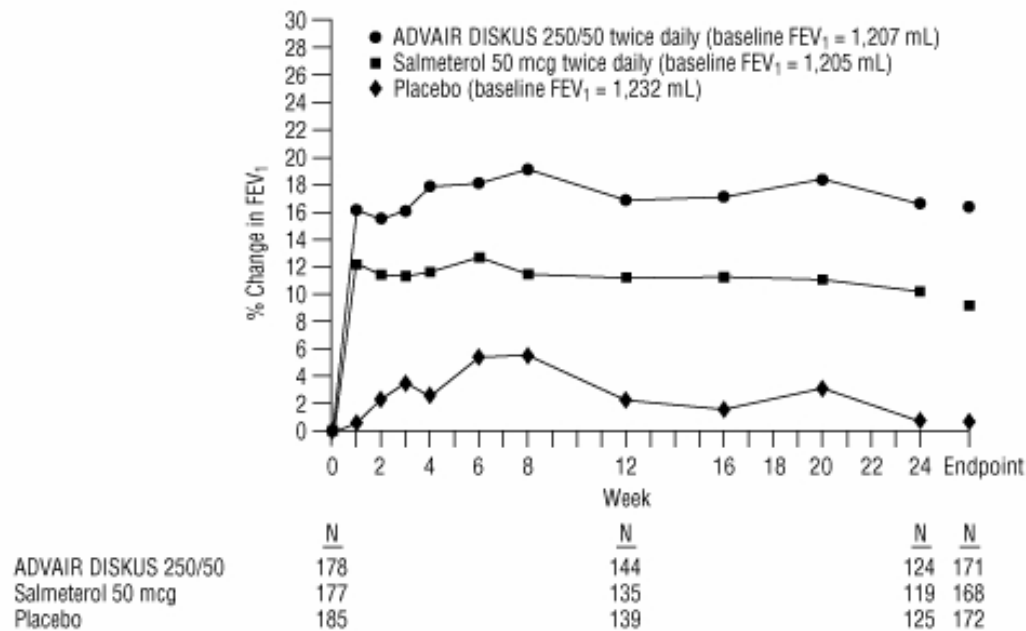
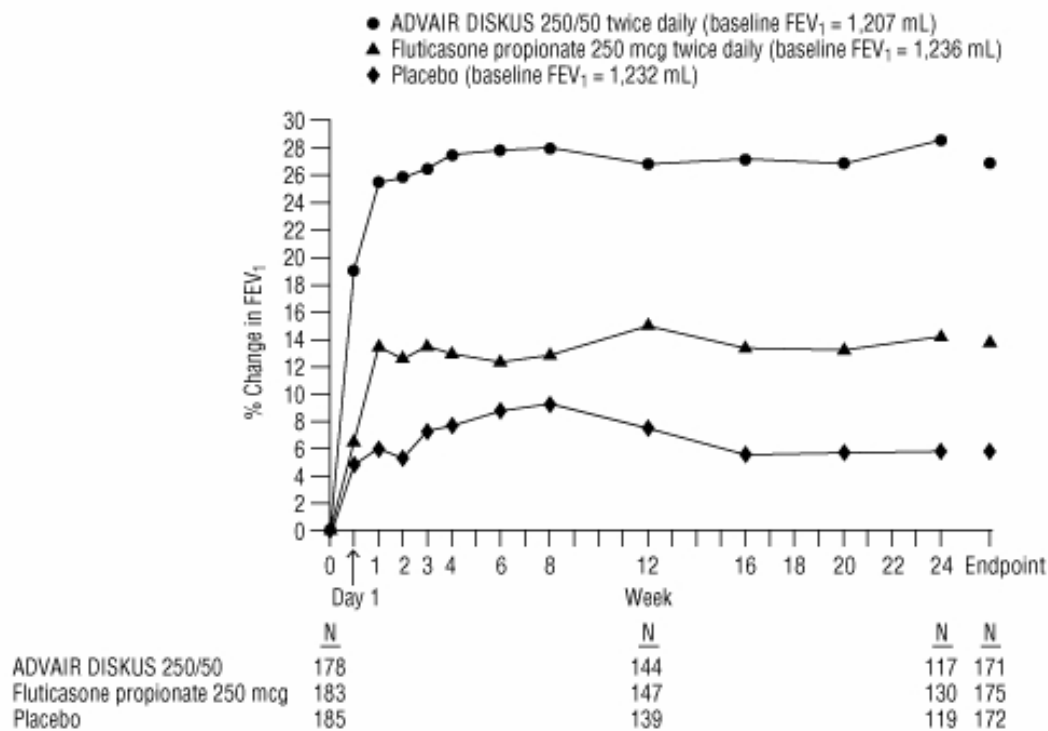


Figure 6. Two-Hour Postdose FEV₁: Mean Percent Changes From Baseline Over Time in Patients With Chronic Obstructive Pulmonary Disease



The third trial was a 1-year study that evaluated ADVAIR DISKUS 500/50, fluticasone propionate 500 mcg, salmeterol 50 mcg, and placebo in 1,465 patients. The patients had an established history of COPD and exacerbations, a pre-bronchodilator FEV₁ <70% of predicted at study entry, and 8.3% reversibility. The primary endpoint was the comparison of pre-bronchodilator FEV₁ in the groups receiving ADVAIR DISKUS 500/50 or placebo. Patients treated with ADVAIR DISKUS 500/50 had greater improvements in FEV₁ (113 mL, 10%) compared with fluticasone propionate 500 mcg (7 mL, 2%), salmeterol (15 mL, 2%), and placebo (-60 mL, -3%).

Exacerbations: Two studies were primarily designed to evaluate the effect of ADVAIR DISKUS 250/50 on exacerbations. In these 2 studies, exacerbations were defined as worsening of 2 or more major symptoms (dyspnea, sputum volume, and sputum purulence) or worsening of any 1 major symptom together with any 1 of the following minor symptoms: sore throat, colds (nasal discharge and/or nasal congestion), fever without other cause, and increased cough or wheeze for at least 2 consecutive days. COPD exacerbations were considered of moderate severity if treatment with systemic corticosteroids and/or antibiotics was required and were considered severe if hospitalization was required.

Exacerbations were also evaluated as a secondary outcome in the 1- and 3-year trials with ADVAIR DISKUS 500/50. There was not a symptomatic definition of exacerbation in these 2

trials. Exacerbations were defined in terms of severity requiring treatment with antibiotics and/or systemic corticosteroids (moderately severe) or requiring hospitalization (severe).

The 2 exacerbation trials with ADVAIR DISKUS 250/50 were identical studies designed to evaluate the effect of ADVAIR DISKUS 250/50 and salmeterol 50 mcg, each given twice daily, on exacerbations of COPD over a 12-month period. A total of 1,579 patients had an established history of COPD (but no other significant respiratory disorders). Patients had a pre-bronchodilator FEV₁ of 33% of predicted, a mean reversibility of 23% at baseline, and a history of ≥ 1 COPD exacerbation in the previous year that was moderate or severe. All patients were treated with ADVAIR DISKUS 250/50 twice daily during a 4-week run-in period prior to being assigned study treatment with twice-daily ADVAIR DISKUS 250/50 or salmeterol 50 mcg. In both studies, treatment with ADVAIR DISKUS 250/50 resulted in a significantly lower annual rate of moderate/severe COPD exacerbations compared with salmeterol (30.5% reduction [95% CI: 17.0, 41.8], $p < 0.001$) in the first study and (30.4% reduction [95% CI: 16.9, 41.7], $p < 0.001$) in the second study. Patients treated with ADVAIR DISKUS 250/50 also had a significantly lower annual rate of exacerbations requiring treatment with oral corticosteroids compared with patients treated with salmeterol (39.7% reduction [95% CI: 22.8, 52.9], $p < 0.001$) in the first study, and (34.3% reduction [95% CI: 18.6, 47.0], $p < 0.001$) in the second study. Secondary endpoints including pulmonary function and symptom scores improved more in patients treated with ADVAIR DISKUS 250/50 than with salmeterol 50 mcg in both studies.

Exacerbations were evaluated in the 1- and the 3-year trials with ADVAIR DISKUS 500/50 as 1 of the secondary efficacy endpoints. In the 1-year trial, the group receiving ADVAIR DISKUS 500/50 had a significantly lower rate of moderate and severe exacerbations compared with placebo (25.4% reduction compared with placebo [95% CI: 13.5, 35.7]) but not when compared with its components (7.5% reduction compared with fluticasone propionate [95% CI: -7.3, 20.3] and 7% reduction compared with salmeterol [95% CI: -8.0, 19.9]). In the 3-year trial, the group receiving ADVAIR DISKUS 500/50 had a significantly lower rate of moderate and severe exacerbations compared with each of the other treatment groups (25.1% reduction compared with placebo [95% CI: 18.6, 31.1], 9.0% reduction compared with fluticasone propionate [95% CI: 1.2, 16.2], and 12.2% reduction compared with salmeterol [95% CI: 4.6, 19.2]).

There were no studies conducted to directly compare the efficacy of ADVAIR DISKUS 250/50 with ADVAIR DISKUS 500/50 on exacerbations. Across studies, the reduction in exacerbations seen with ADVAIR DISKUS 500/50 was not greater than the reduction in exacerbations seen with ADVAIR DISKUS 250/50.

Survival: A 3-year multicenter, international study evaluated the efficacy of ADVAIR DISKUS 500/50 compared with fluticasone propionate 500 mcg, salmeterol 50 mcg, and placebo on survival in 6,112 patients with COPD. During the study patients were permitted usual COPD therapy with the exception of other inhaled corticosteroids and long-acting bronchodilators. The patients were 40 to 80 years of age with an established history of COPD, a pre-bronchodilator FEV₁ $< 60\%$ of predicted at study entry, and $< 10\%$ of predicted reversibility. Each patient who

withdrew from double-blind treatment for any reason was followed for the full 3-year study period to determine survival status. The primary efficacy endpoint was all-cause mortality. Survival with ADVAIR DISKUS 500/50 was not significantly improved compared with placebo, or the individual components (all-cause mortality rate 12.6% ADVAIR DISKUS vs. 15.2% placebo). The rates for all-cause mortality were 13.5% and 16.0% in the groups treated with salmeterol 50 mcg and fluticasone propionate 500 mcg, respectively. Secondary outcomes, including pulmonary function (post-bronchodilator FEV₁), improved with ADVAIR DISKUS 500/50, salmeterol, and fluticasone propionate 500/50 compared with placebo.

16 HOW SUPPLIED/STORAGE AND HANDLING

ADVAIR DISKUS 100/50 is supplied as a disposable purple device containing 60 blisters. The DISKUS inhalation device is packaged within a purple, plastic-coated, moisture-protective foil pouch (NDC 0173-0695-00). ADVAIR DISKUS 100/50 is also supplied in an institutional pack of 1 disposable purple device containing 28 blisters. The DISKUS inhalation device is packaged within a purple, plastic-coated, moisture-protective foil pouch (NDC 0173-0695-02).

ADVAIR DISKUS 250/50 is supplied as a disposable purple device containing 60 blisters. The DISKUS inhalation device is packaged within a purple, plastic-coated, moisture-protective foil pouch (NDC 0173-0696-00). ADVAIR DISKUS 250/50 is also supplied in an institutional pack of 1 disposable purple device containing 28 blisters. The DISKUS inhalation device is packaged within a purple, plastic-coated, moisture-protective foil pouch (NDC 0173-0696-02).

ADVAIR DISKUS 500/50 is supplied as a disposable purple device containing 60 blisters. The DISKUS inhalation device is packaged within a purple, plastic-coated, moisture-protective foil pouch (NDC 0173-0697-00). ADVAIR DISKUS 500/50 is also supplied in an institutional pack of 1 disposable purple device containing 28 blisters. The DISKUS inhalation device is packaged within a purple, plastic-coated, moisture-protective foil pouch (NDC 0173-0697-02).

Store at controlled room temperature (see USP), 20° to 25°C (68° to 77°F), in a dry place away from direct heat or sunlight. Keep out of reach of children. The DISKUS inhalation device is not reusable. The device should be discarded 1 month after removal from the moisture-protective foil overwrap pouch or after all blisters have been used (when the dose indicator reads “0”), whichever comes first. Do not attempt to take the device apart.

17 PATIENT COUNSELING INFORMATION

See Medication Guide (17.6).

17.1 Asthma-Related Death

Patients with asthma should be informed that salmeterol, one of the active ingredients in ADVAIR DISKUS, may increase the risk of asthma-related death. They should also be informed that data are not adequate to determine whether the concurrent use of

inhaled corticosteroids, such as fluticasone propionate, the other component of ADVAIR DISKUS, or other asthma-controller therapy modifies this risk.

17.2 Not for Acute Symptoms

ADVAIR DISKUS is not meant to relieve acute asthma symptoms or exacerbations of COPD and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting beta₂-agonist such as albuterol. (The physician should provide the patient with such medication and instruct the patient in how it should be used.)

Patients should be instructed to notify their physician immediately if they experience any of the following:

- Decreasing effectiveness of inhaled, short-acting beta₂-agonists
- Need for more inhalations than usual of inhaled, short-acting beta₂-agonists
- Significant decrease in lung function as outlined by the physician

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

17.3 Do Not Use Additional Long-Acting Beta₂-Agonists

When patients are prescribed ADVAIR DISKUS, other long-acting beta₂-agonists for asthma and COPD should not be used.

17.4 Risks Associated With Corticosteroid Therapy

Local Effects: Patients should be advised that localized infections with *Candida albicans* occurred in the mouth and pharynx in some patients. If oropharyngeal candidiasis develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while still continuing therapy with ADVAIR DISKUS, but at times therapy with ADVAIR DISKUS may need to be temporarily interrupted under close medical supervision. Rinsing the mouth after inhalation is advised.

Pneumonia: Patients with COPD have a higher risk of pneumonia and should be instructed to contact their healthcare provider if they develop symptoms of pneumonia.

Immunosuppression: Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles and, if exposed, to consult their physician without delay. Patients should be informed of potential worsening of existing tuberculosis, fungal, bacterial, viral, or parasitic infections, or ocular herpes simplex.

Hypercorticism and Adrenal Suppression: Patients should be advised that ADVAIR DISKUS may cause systemic corticosteroid effects of hypercorticism and adrenal suppression. Additionally, patients should be instructed that deaths due to adrenal insufficiency have occurred during and after transfer from systemic corticosteroids. Patients should taper slowly from systemic corticosteroids if transferring to ADVAIR DISKUS.

Reduction in Bone Mineral Density: Patients who are at an increased risk for decreased BMD should be advised that the use of corticosteroids may pose an additional risk.

Reduced Growth Velocity: Patients should be informed that orally inhaled corticosteroids, including fluticasone propionate, a component of ADVAIR DISKUS, may cause

a reduction in growth velocity when administered to pediatric patients. Physicians should closely follow the growth of children and adolescents taking corticosteroids by any route.

Ocular Effects: Long-term use of inhaled corticosteroids may increase the risk of some eye problems (cataracts or glaucoma); regular eye examinations should be considered.

17.5 Risks Associated With Beta-Agonist Therapy

Patients should be informed of adverse effects associated with beta₂-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.

17.6 Medication Guide

MEDICATION GUIDE

ADVAIR [*ad'vair*] DISKUS[®] 100/50

(fluticasone propionate 100 mcg and salmeterol 50 mcg inhalation powder)

ADVAIR DISKUS[®] 250/50

(fluticasone propionate 250 mcg and salmeterol 50 mcg inhalation powder)

ADVAIR DISKUS[®] 500/50

(fluticasone propionate 500 mcg and salmeterol 50 mcg inhalation powder)

Read the Medication Guide that comes with ADVAIR DISKUS 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 ADVAIR DISKUS?

- **ADVAIR DISKUS contains 2 medicines:**
 - **fluticasone propionate (the same medicine found in FLOVENT[®]),** an inhaled corticosteroid medicine. Inhaled corticosteroids help to decrease inflammation in the lungs. Inflammation in the lungs can lead to asthma symptoms.
 - **salmeterol (the same medicine found in SEREVENT[®]),** a long-acting beta₂-agonist medicine or LABA. LABA medicines are used in patients with asthma and chronic obstructive pulmonary disease (COPD). LABA medicines help the muscles around the airways in your lungs stay relaxed to prevent 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 cause death if not treated right away.
- **In patients with asthma, LABA medicines, such as salmeterol (one of the medicines in ADVAIR DISKUS), may increase the chance of death from asthma problems.** In a large asthma study, more patients who used salmeterol died from asthma problems compared with patients who did not use salmeterol. It is not known whether fluticasone propionate, the other medicine in ADVAIR DISKUS, changes your chance of death from asthma problems seen

with salmeterol. Talk with your healthcare provider about this risk and the benefits of treating your asthma with ADVAIR DISKUS.

- **ADVAIR DISKUS does not relieve sudden symptoms. Always have a short-acting beta₂-agonist medicine with you to treat sudden symptoms. If you do not have an inhaled, short-acting bronchodilator, contact your healthcare provider to have one prescribed for you.**
- **Do not stop using ADVAIR DISKUS unless told to do so by your healthcare provider because your symptoms might get worse.**
- **ADVAIR DISKUS 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 ADVAIR DISKUS. 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 ADVAIR DISKUS?

ADVAIR DISKUS combines an inhaled corticosteroid medicine, fluticasone propionate (the same medicine found in FLOVENT) and a long-acting beta₂-agonist medicine, salmeterol (the same medicine found in SEREVENT). ADVAIR DISKUS is used for asthma and chronic obstructive pulmonary disease (COPD) as follows:

Asthma

ADVAIR DISKUS is used long term, twice a day to control symptoms of asthma and to prevent symptoms such as wheezing in adults and children ages 4 and older.

ADVAIR DISKUS contains salmeterol (the same medicine found in SEREVENT). Because LABA medicines, such as salmeterol, may increase the chance of death from asthma problems, ADVAIR DISKUS is not for adults and children 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

Chronic Obstructive Pulmonary Disease

COPD is a chronic lung disease that includes chronic bronchitis, emphysema, or both. ADVAIR DISKUS 250/50 is used long term, twice a day to help improve lung function for better breathing in adults with COPD. ADVAIR DISKUS 250/50 has been shown to decrease the number of flare-ups and worsening of COPD symptoms (exacerbations).

Who should not use ADVAIR DISKUS?

Do not use ADVAIR DISKUS:

- to treat sudden, severe symptoms of asthma or COPD
- if you have a severe allergy to milk proteins. Ask your doctor if you are not sure.

What should I tell my healthcare provider before using ADVAIR DISKUS?

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 ADVAIR DISKUS may harm your unborn baby.
- **are breastfeeding.** It is not known if ADVAIR DISKUS passes into your milk and if it can harm your baby.
- **are allergic to any of the ingredients in ADVAIR DISKUS, any other medicines, or food products.** See the end of this Medication Guide for a complete list of the ingredients in ADVAIR DISKUS.
- **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. ADVAIR DISKUS and certain other medicines may interact with each other. This may cause serious side effects. Especially, tell your healthcare provider if you take ritonavir. The anti-HIV medicines NORVIR[®] (ritonavir capsules) Soft Gelatin, NORVIR (ritonavir oral solution), and KALETRA[®] (lopinavir/ritonavir) Tablets contain ritonavir.

Know 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 ADVAIR DISKUS?

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

- Children should use ADVAIR DISKUS with an adult's help, as instructed by the child's healthcare provider.
- Use ADVAIR DISKUS exactly as prescribed. **Do not use ADVAIR DISKUS more often than prescribed.** ADVAIR DISKUS comes in 3 strengths. Your healthcare provider will prescribe the one that is best for your condition.
- The usual dosage of ADVAIR DISKUS is 1 inhalation twice a day (morning and evening). The 2 doses should be about 12 hours apart. Rinse your mouth with water after using ADVAIR DISKUS.
- If you take more ADVAIR DISKUS than your doctor has prescribed, get medical help right away if you have any unusual symptoms, such as worsening shortness of breath, chest pain, increased heart rate, or shakiness.
- If you miss a dose of ADVAIR DISKUS, just skip that dose. Take your next dose at your usual time. Do not take 2 doses at one time.
- Do not use a spacer device with ADVAIR DISKUS.
- Do not breathe into ADVAIR DISKUS.
- **While you are using ADVAIR DISKUS twice a day, do not use other medicines that contain a long-acting beta₂-agonist or LABA for any reason. Ask your healthcare provider or pharmacist if any of your other medicines are LABA medicines.**
- 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 ADVAIR DISKUS.
- **Call your healthcare provider or get medical care right away if:**
 - your breathing problems worsen with ADVAIR DISKUS

- you need to use your short-acting beta₂-agonist medicine more often than usual
- your short-acting beta₂-agonist medicine does not work as well for you at relieving symptoms
- you need to use 4 or more inhalations of your short-acting beta₂-agonist medicine for 2 or more days in a row
- you use 1 whole canister of your short-acting beta₂-agonist medicine in 8 weeks' time
- your peak flow meter results decrease. Your healthcare provider will tell you the numbers that are right for you.
- you have asthma and your symptoms do not improve after using ADVAIR DISKUS regularly for 1 week

What are the possible side effects with ADVAIR DISKUS?

- **ADVAIR DISKUS contains salmeterol (the same medicine found in SEREVENT). In patients with asthma, LABA medicines, such as salmeterol, may increase the chance of death from asthma problems.** See “What is the most important information I should know about ADVAIR DISKUS?”
- Patients with COPD have a higher chance of getting pneumonia. ADVAIR DISKUS may increase the chance of getting pneumonia. **Call your healthcare provider if you notice any of the following symptoms:**
 - increase in mucus (sputum) production
 - change in mucus color
 - fever
 - chills
 - increased cough
 - increased breathing problems.

Other possible side effects with ADVAIR DISKUS include:

- **serious allergic reactions.** Call your healthcare provider or get emergency medical care if you get any of the following symptoms of a serious allergic reaction, including:
 - rash
 - hives
 - swelling of the face, mouth, and tongue
 - breathing problems
- **increased blood pressure**
- **a fast and irregular heartbeat**
- **chest pain**
- **headache**
- **tremor**
- **nervousness**
- **weakened immune system and a higher chance of infections**

- **lower bone mineral density.** This may be a problem for people who already have a higher chance of low bone density (osteoporosis).
- **eye problems including glaucoma and cataracts.** You should have regular eye exams while using ADVAIR DISKUS.
- **slowed growth in children.** A child's growth should be checked often.

The most common side effects with ADVAIR DISKUS include:

Asthma in adults and children:

- upper respiratory tract infection
- throat irritation
- hoarseness and voice changes
- thrush in the mouth and throat
- bronchitis
- cough
- headache
- nausea and vomiting

In children with asthma, infections in the ear, nose, and throat are also common.

COPD:

- thrush in the mouth and throat
- throat irritation
- hoarseness and voice changes
- viral respiratory infections
- headache
- muscle and bone pain

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 ADVAIR DISKUS. Ask your healthcare provider or pharmacist for more information.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How do I store ADVAIR DISKUS?

- Store ADVAIR DISKUS at room temperature between 68° to 77° F (20° to 25° C). Keep in a dry place away from heat and sunlight.
- Safely discard ADVAIR DISKUS 1 month after you remove it from the foil pouch, or after the dose indicator reads "0", whichever comes first.
- **Keep ADVAIR DISKUS and all medicines out of the reach of children.**

General Information about ADVAIR DISKUS

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

This Medication Guide summarizes the most important information about ADVAIR DISKUS. If you would like more information, talk with your healthcare provider or pharmacist. You can ask your healthcare provider or pharmacist for information about ADVAIR DISKUS that was written for healthcare professionals. You can also contact the company that makes ADVAIR DISKUS (toll free) at 1-888-825-5249 or at www.advair.com.

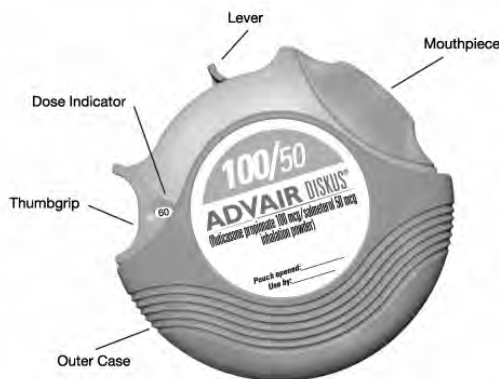
What are the ingredients in ADVAIR DISKUS?

Active ingredients: fluticasone propionate, salmeterol xinafoate

Inactive ingredient: lactose (contains milk proteins)

Instructions for Using ADVAIR DISKUS

Follow the instructions below for using your ADVAIR DISKUS. **You will breathe in (inhale) the medicine from the DISKUS®.** If you have any questions, ask your healthcare provider or pharmacist.



Take ADVAIR DISKUS out of the box and foil pouch. Write the “**Pouch opened**” and “**Use by**” dates on the label on top of the DISKUS. The “**Use by**” date is 1 month from date of opening the pouch.

- The DISKUS will be in the closed position when the pouch is opened.
- The **dose indicator** on the top of the DISKUS tells you how many doses are left. The dose indicator number will decrease each time you use the DISKUS. After you have used 55 doses from the DISKUS, the numbers 5 to 0 will appear in **red** to warn you that there are only a few doses left (*see Figure 1*). If you are using a “sample” DISKUS, the numbers 5 to 0 will appear in red after 23 doses.



Figure 1

Taking a dose from the DISKUS requires the following 3 simple steps: Open, Click, Inhale.

1. OPEN

Hold the DISKUS in one hand and put the thumb of your other hand on the **thumbgrip**. Push your thumb away from you as far as it will go until the mouthpiece appears and snaps into position (*see Figure 2*).



Figure 2

2. CLICK

Hold the DISKUS in a level, flat position with the mouthpiece towards you. Slide the **lever** away from you as far as it will go until it **clicks** (*see Figure 3*). The DISKUS is now ready to use.



Figure 3

Every time the **lever** is pushed back, a dose is ready to be inhaled. This is shown by a decrease in numbers on the dose counter. **To avoid releasing or wasting doses once the DISKUS is ready:**

- **Do not close the DISKUS.**
- **Do not tilt the DISKUS.**
- **Do not play with the lever.**
- **Do not move the lever more than once.**

3. INHALE

Before inhaling your dose from the DISKUS, breathe out (exhale) fully while holding the DISKUS level and away from your mouth (*see Figure 4*). **Remember, never breathe out into the DISKUS mouthpiece.**



Figure 4

Put the mouthpiece to your lips (*see Figure 5*). Breathe in quickly and deeply through the DISKUS. Do not breathe in through your nose.



Figure 5

Remove the DISKUS from your mouth. Hold your breath for about 10 seconds, or for as long as is comfortable. Breathe out slowly.

The DISKUS delivers your dose of medicine as a very fine powder. Most patients can taste or feel the powder. Do not use another dose from the DISKUS if you do not feel or taste the medicine.

Rinse your mouth with water after breathing-in the medicine. Spit the water out. Do not swallow.

4. **Close the DISKUS** when you are finished taking a dose so that the **DISKUS** will be ready for you to take your next dose. Put your thumb on the thumbgrip and slide the thumbgrip back towards you as far as it will go (*see Figure 6*). The DISKUS will click shut. The lever will automatically return to its original position. The DISKUS is now ready for you to take your next scheduled dose, due in about 12 hours. (Repeat steps 1 to 4.)



Figure 6

Remember:

- Never breathe into the DISKUS.
- Never take the DISKUS apart.
- Always ready and use the DISKUS in a level, flat position.
- Do not use the DISKUS with a spacer device.
- After each dose, rinse your mouth with water and spit the water out. Do not swallow.
- Never wash the mouthpiece or any part of the DISKUS. **Keep it dry.**
- Always keep the DISKUS in a dry place.
- Never take an extra dose, even if you did not taste or feel the medicine.

April 2008

ADD:4MG

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

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GlaxoSmithKline

Research Triangle Park, NC 27709

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PRESCRIBING INFORMATION

ADVAIR[®] HFA 45/21

(fluticasone propionate 45 mcg and salmeterol 21 mcg*)

Inhalation Aerosol

ADVAIR[®] HFA 115/21

(fluticasone propionate 115 mcg and salmeterol 21 mcg*)

Inhalation Aerosol

ADVAIR[®] HFA 230/21

(fluticasone propionate 230 mcg and salmeterol 21 mcg*)

Inhalation Aerosol

*As salmeterol xinafoate salt 30.45 mcg, equivalent to salmeterol base 21 mcg

For Oral Inhalation Only

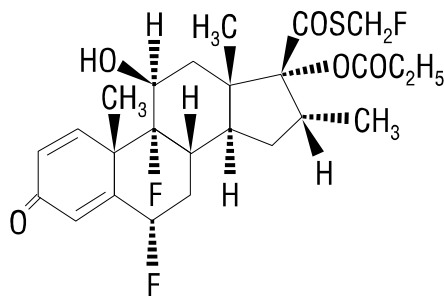
WARNING

Long-acting beta₂-adrenergic agonists, such as salmeterol, one of the active ingredients in ADVAIR HFA, may increase the risk of asthma-related death. Therefore, when treating patients with asthma, physicians should only prescribe ADVAIR HFA 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 2 maintenance therapies. Data from a large placebo-controlled US study that compared the safety of salmeterol (SEREVENT[®] Inhalation Aerosol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176 patients treated for 28 weeks on salmeterol versus 3 deaths out of 13,179 patients on placebo) (see WARNINGS).

DESCRIPTION

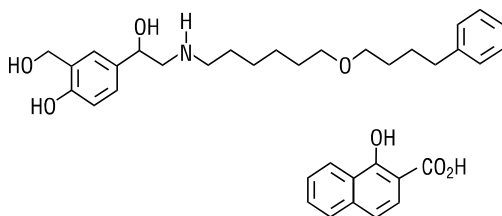
ADVAIR HFA 45/21 Inhalation Aerosol, ADVAIR HFA 115/21 Inhalation Aerosol, and ADVAIR HFA 230/21 Inhalation Aerosol are combinations of fluticasone propionate and salmeterol xinafoate.

One active component of ADVAIR HFA is fluticasone propionate, a corticosteroid having the chemical name *S*-(fluoromethyl) 6 α ,9-difluoro-11 β ,17-dihydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carbothioate, 17-propionate and the following chemical structure:



Fluticasone propionate is a white powder with a molecular weight of 500.6, and the empirical formula is $C_{25}H_{31}F_3O_5S$. It is practically insoluble in water, freely soluble in dimethyl sulfoxide and dimethylformamide, and slightly soluble in methanol and 95% ethanol.

The other active component of ADVAIR HFA is salmeterol xinafoate, a β_2 -adrenergic bronchodilator. Salmeterol xinafoate is the racemic form of the 1-hydroxy-2-naphthoic acid salt of salmeterol. The chemical name of salmeterol xinafoate is 4-hydroxy- α^1 -[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol, 1-hydroxy-2-naphthalenecarboxylate, and it has the following chemical structure:



Salmeterol xinafoate is a white powder with a molecular weight of 603.8, and the empirical formula is $C_{25}H_{37}NO_4 \cdot C_{11}H_8O_3$. It is freely soluble in methanol; slightly soluble in ethanol, chloroform, and isopropanol; and sparingly soluble in water.

ADVAIR HFA 45/21 Inhalation Aerosol, ADVAIR HFA 115/21 Inhalation Aerosol, and ADVAIR HFA 230/21 Inhalation Aerosol are pressurized metered-dose aerosol units fitted with a counter. ADVAIR HFA is intended for oral inhalation only. Each unit contains a microcrystalline suspension of fluticasone propionate (micronized) and salmeterol xinafoate (micronized) in propellant HFA-134a (1,1,1,2-tetrafluoroethane). It contains no other excipients.

After priming, each actuation of the inhaler delivers 50, 125, or 250 mcg of fluticasone propionate and 25 mcg of salmeterol in 75 mg of suspension from the valve. Each actuation delivers 45, 115, or 230 mcg of fluticasone propionate and 21 mcg of salmeterol from the actuator. Twenty-one micrograms (21 mcg) of salmeterol base is equivalent to 30.45 mcg of salmeterol xinafoate. The actual amount of drug delivered to the lung may depend on patient factors, such as the coordination between the actuation of the device and inspiration through the delivery system.

Each 12-g canister provides 120 inhalations.

ADVAIR HFA should be primed before using for the first time by releasing 4 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 4 weeks or when it has been dropped, prime the inhaler again by releasing 2 test sprays into the air away from the face, shaking well for 5 seconds before each spray.

This product does not contain any chlorofluorocarbon (CFC) as the propellant.

CLINICAL PHARMACOLOGY

Mechanism of Action: ADVAIR HFA Inhalation Aerosol: Since ADVAIR HFA contains both fluticasone propionate and salmeterol, the mechanisms of action described below for the individual components apply to ADVAIR HFA. These drugs represent 2 classes of medications (a synthetic corticosteroid and a selective, long-acting beta₂-adrenergic receptor agonist) that have different effects on clinical, physiologic, and inflammatory indices of asthma.

Fluticasone Propionate: Fluticasone propionate is a synthetic trifluorinated corticosteroid with potent anti-inflammatory activity. In vitro assays using human lung cytosol preparations have established fluticasone propionate as a human glucocorticoid receptor agonist with an affinity 18 times greater than dexamethasone, almost twice that of beclomethasone-17-monopropionate (BMP), the active metabolite of beclomethasone dipropionate, and over 3 times that of budesonide. Data from the McKenzie vasoconstrictor assay in man are consistent with these results.

Inflammation is an important component in the pathogenesis of asthma. Corticosteroids have been shown to inhibit multiple cell types (e.g., mast cells, eosinophils, basophils, lymphocytes, macrophages, and neutrophils) and mediator production or secretion (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in the asthmatic response. These anti-inflammatory actions of corticosteroids contribute to their efficacy in asthma.

Salmeterol Xinafoate: Salmeterol is a long-acting beta₂-adrenergic agonist. In vitro studies and in vivo pharmacologic studies demonstrate that salmeterol is selective for beta₂-adrenoceptors compared with isoproterenol, which has approximately equal agonist activity on beta₁- and beta₂-adrenoceptors. In vitro studies show salmeterol to be at least 50 times more selective for beta₂-adrenoceptors than albuterol. Although beta₂-adrenoceptors are the predominant adrenergic receptors in bronchial smooth muscle and beta₁-adrenoceptors are the predominant receptors in the heart, there are also beta₂-adrenoceptors in the human heart comprising 10% to 50% of the total beta-adrenoceptors. The precise function of these receptors has not been established, but their presence raises the possibility that even selective beta₂-agonists may have cardiac effects.

The pharmacologic effects of beta₂-adrenoceptor agonist drugs, including salmeterol, are at least in part attributable to stimulation of intracellular adenylyl 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 salmeterol is a potent and long-lasting inhibitor of the release of mast cell mediators, such as histamine, leukotrienes, and prostaglandin D₂, from human lung. Salmeterol inhibits histamine-induced plasma protein extravasation and inhibits platelet activating factor-induced eosinophil accumulation in the lungs of guinea pigs when administered by the inhaled route. In humans, single doses of salmeterol administered via inhalation aerosol attenuate allergen-induced bronchial hyper-responsiveness.

Preclinical: In animals and humans, propellant HFA-134a was found to be rapidly absorbed and rapidly eliminated, with an elimination half-life of 3 to 27 minutes in animals and 5 to 7 minutes in humans. Time to maximum plasma concentration (T_{max}) and mean residence time are both extremely short, leading to a transient appearance of HFA-134a in the blood with no evidence of accumulation.

Propellant HFA-134a is devoid of pharmacological activity except at very high doses in animals (i.e., 380 to 1,300 times the maximum human exposure based on comparisons of area under the plasma concentration versus time curve [AUC] values), primarily producing ataxia, tremors, dyspnea, or salivation. These events are similar to effects produced by the structurally related CFCs, which have been used extensively in metered-dose inhalers. In drug interaction studies in male and female dogs, there was a slight increase in the salmeterol-related effect on heart rate (a known effect of beta₂-agonists) when given in combination with high doses of fluticasone propionate. This effect was not observed in clinical studies.

Pharmacokinetics: ADVAIR HFA Inhalation Aerosol: Three single-dose, placebo-controlled, crossover studies were conducted in healthy subjects: (1) a study using 4 inhalations of ADVAIR HFA 230/21, salmeterol CFC inhalation aerosol 21 mcg, or fluticasone propionate CFC inhalation aerosol 220 mcg, (2) a study using 8 inhalations of ADVAIR HFA 45/21, ADVAIR HFA 115/21, or ADVAIR HFA 230/21, and (3) a study using 4 inhalations of ADVAIR HFA 230/21; 2 inhalations of ADVAIR DISKUS[®] 500/50 (fluticasone propionate 500 mcg and salmeterol 50 mcg inhalation powder); 4 inhalations of fluticasone propionate CFC inhalation aerosol 220 mcg; or 1,010 mcg of fluticasone propionate given intravenously. Peak plasma concentrations of fluticasone propionate were achieved in 0.33 to 1.5 hours and those of salmeterol were achieved in 5 to 10 minutes.

Peak plasma concentrations of fluticasone propionate (N = 20 subjects) following 8 inhalations of ADVAIR HFA 45/21, ADVAIR HFA 115/21, and ADVAIR HFA 230/21 averaged 41, 108, and 173 pg/mL, respectively. Peak plasma salmeterol concentrations ranged from 220 to 470 pg/mL.

Systemic exposure (N = 20 subjects) from 4 inhalations of ADVAIR HFA 230/21 was 53% of the value from the individual inhaler for fluticasone propionate CFC inhalation aerosol and 42% of the value from the individual inhaler for salmeterol CFC inhalation aerosol. Peak plasma concentrations from ADVAIR HFA for fluticasone propionate (86 vs. 120 pg/mL) and salmeterol (170 vs. 510 pg/mL) were significantly lower compared with individual inhalers.

In 15 healthy subjects, systemic exposure to fluticasone propionate from 4 inhalations of ADVAIR HFA 230/21 (920/84 mcg) and 2 inhalations of ADVAIR DISKUS 500/50

(1,000/100 mcg) were similar between the 2 inhalers (i.e., 799 vs. 832 pg•h/mL, respectively) but approximately half the systemic exposure from 4 inhalations of fluticasone propionate CFC inhalation aerosol 220 mcg (880 mcg, AUC = 1,543 pg•h/mL). Similar results were observed for peak fluticasone propionate plasma concentrations (186 and 182 pg/mL from ADVAIR HFA and ADVAIR DISKUS, respectively, and 307 pg/mL from the fluticasone propionate CFC inhalation aerosol). Systemic exposure to salmeterol was higher (317 vs. 169 pg•h/mL) and peak salmeterol concentrations were lower (196 vs. 223 pg/mL) following ADVAIR HFA compared with ADVAIR DISKUS, although pharmacodynamic results were comparable.

Absolute bioavailability of fluticasone propionate from ADVAIR HFA in 15 healthy subjects was 5.3%. Terminal half-life estimates of fluticasone propionate for ADVAIR HFA, ADVAIR DISKUS, and fluticasone propionate CFC inhalation aerosol were similar and averaged 5.6 hours. No terminal half-life estimates were calculated for salmeterol.

A double-blind crossover study was conducted in 13 adult patients with asthma to evaluate the steady-state pharmacokinetics of fluticasone propionate and salmeterol following administration of 2 inhalations of ADVAIR HFA 115/21 twice daily or 1 inhalation of ADVAIR DISKUS 250/50 twice daily for 4 weeks. Systemic exposure (AUC) to fluticasone propionate was similar for ADVAIR HFA (274 pg•h/mL [95% CI 150, 502]) and ADVAIR DISKUS (338 pg•h/mL [95% CI 197, 581]). Systemic exposure to salmeterol was also similar for ADVAIR HFA (53 pg•h/mL [95% CI 17, 164]) and ADVAIR DISKUS (70 pg•h/mL [95% CI 19, 254]).

Special Populations: Hepatic and Renal Impairment: Formal pharmacokinetic studies using ADVAIR HFA have not been conducted to examine gender differences or in special populations, such as elderly patients or patients with hepatic or renal impairment. However, since both fluticasone propionate and salmeterol are predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of fluticasone propionate and salmeterol in plasma. Therefore, patients with hepatic disease should be closely monitored.

Drug Interactions: In repeat- and single-dose studies, there was no evidence of significant drug interaction on systemic exposure to fluticasone propionate and salmeterol when given alone or in combination via the DISKUS. Similar definitive studies have not been performed with ADVAIR HFA.

Fluticasone Propionate: Absorption: Fluticasone propionate acts locally in the lung; therefore, plasma levels do not predict therapeutic effect. Studies using oral dosing of labeled and unlabeled drug have demonstrated that the oral systemic bioavailability of fluticasone propionate is negligible (<1%), primarily due to incomplete absorption and presystemic metabolism in the gut and liver. In contrast, the majority of the fluticasone propionate delivered to the lung is systemically absorbed.

Distribution: Following intravenous administration, the initial disposition phase for fluticasone propionate was rapid and consistent with its high lipid solubility and tissue binding. The volume of distribution averaged 4.2 L/kg.

The percentage of fluticasone propionate bound to human plasma proteins averages 99%. Fluticasone propionate is weakly and reversibly bound to erythrocytes and is not significantly bound to human transcortin.

Metabolism: The total clearance of fluticasone propionate is high (average, 1,093 mL/min), with renal clearance accounting for less than 0.02% of the total. The only circulating metabolite detected in man is the 17 β -carboxylic acid derivative of fluticasone propionate, which is formed through the cytochrome P450 3A4 pathway. This metabolite had less affinity (approximately 1/2,000) than the parent drug for the glucocorticoid receptor of human lung cytosol in vitro and negligible pharmacological activity in animal studies. Other metabolites detected in vitro using cultured human hepatoma cells have not been detected in man.

Elimination: Following intravenous dosing, fluticasone propionate showed polyexponential kinetics and had a terminal elimination half-life of approximately 7.8 hours. Less than 5% of a radiolabeled oral dose was excreted in the urine as metabolites, with the remainder excreted in the feces as parent drug and metabolites.

Special Populations: Gender: In 19 male and 33 female patients with asthma, systemic exposure was similar from 2 inhalations of fluticasone propionate CFC inhalation aerosol 44, 110, and 220 mcg twice daily.

Drug Interactions: Fluticasone propionate is a substrate of cytochrome P450 3A4. Coadministration of fluticasone propionate and the strong cytochrome P450 3A4 inhibitor ritonavir is not recommended based upon a multiple-dose, crossover drug interaction study in 18 healthy subjects. Fluticasone propionate aqueous nasal spray (200 mcg once daily) was coadministered for 7 days with ritonavir (100 mg twice daily). Plasma fluticasone propionate concentrations following fluticasone propionate aqueous nasal spray alone were undetectable (<10 pg/mL) in most subjects, and when concentrations were detectable, peak levels (C_{max}) averaged 11.9 pg/mL (range, 10.8 to 14.1 pg/mL) and $AUC_{(0-\tau)}$ averaged 8.43 pg•hr/mL (range, 4.2 to 18.8 pg•hr/mL). Fluticasone propionate C_{max} and $AUC_{(0-\tau)}$ increased to 318 pg/mL (range, 110 to 648 pg/mL) and 3,102.6 pg•hr/mL (range, 1,207.1 to 5,662.0 pg•hr/mL), respectively, after coadministration of ritonavir with fluticasone propionate aqueous nasal spray. This significant increase in systemic fluticasone propionate exposure resulted in a significant decrease (86%) in serum cortisol AUC.

Caution should be exercised when other strong cytochrome P450 3A4 inhibitors are coadministered with fluticasone propionate. In a drug interaction study, coadministration of orally inhaled fluticasone propionate (1,000 mcg) and ketoconazole (200 mg once daily) resulted in increased systemic fluticasone propionate exposure and reduced plasma cortisol AUC, but had no effect on urinary excretion of cortisol.

In another multiple-dose drug interaction study, coadministration of orally inhaled fluticasone propionate (500 mcg twice daily) and erythromycin (333 mg 3 times daily) did not affect fluticasone propionate pharmacokinetics.

Salmeterol Xinafoate: Salmeterol xinafoate, an ionic salt, dissociates in solution so that the salmeterol and 1-hydroxy-2-naphthoic acid (xinafoate) moieties are absorbed, distributed, metabolized, and excreted independently. Salmeterol acts locally in the lung; therefore, plasma levels do not predict therapeutic effect.

Absorption: Because of the small therapeutic dose, systemic levels of salmeterol are low or undetectable after inhalation of recommended dosages (42 mcg of salmeterol inhalation aerosol twice daily). Following chronic administration of an inhaled dosage of 42 mcg twice daily, salmeterol was detected in plasma within 5 to 10 minutes in 6 patients with asthma; plasma concentrations were very low, with mean peak concentrations of 150 pg/mL and no accumulation with repeated doses.

Distribution: The percentage of salmeterol bound to human plasma proteins averages 96% in vitro over the concentration range of 8 to 7,722 ng of salmeterol base per milliliter, much higher concentrations than those achieved following therapeutic doses of salmeterol.

Metabolism: Salmeterol base is extensively metabolized by hydroxylation, with subsequent elimination predominately in the feces. No significant amount of unchanged salmeterol base was detected in either urine or feces.

An in vitro study using human liver microsomes showed that salmeterol is extensively metabolized to α -hydroxysalmeterol (aliphatic oxidation) by cytochrome P450 3A4 (CYP3A4). Ketoconazole, a strong inhibitor of CYP3A4, essentially completely inhibited the formation of α -hydroxysalmeterol in vitro.

Elimination: In 2 healthy adult subjects who received 1 mg of radiolabeled salmeterol (as salmeterol xinafoate) orally, approximately 25% and 60% of the radiolabeled salmeterol was eliminated in urine and feces, respectively, over a period of 7 days. The terminal elimination half-life was about 5.5 hours (1 volunteer only).

The xinafoate moiety has no apparent pharmacologic activity. The xinafoate moiety is highly protein bound (>99%) and has a long elimination half-life of 11 days.

Drug Interactions: Salmeterol is a substrate of CYP3A4.

Inhibitors of Cytochrome P450 3A4: Ketoconazole: In a placebo-controlled, crossover drug interaction study in 20 healthy male and female subjects, coadministration of salmeterol (50 mcg twice daily) and the strong CYP3A4 inhibitor ketoconazole (400 mg once daily) for 7 days resulted in a significant increase in plasma salmeterol exposure as determined by a 16-fold increase in AUC (ratio with and without ketoconazole 15.76; 90% CI: 10.66, 23.31) mainly due to increased bioavailability of the swallowed portion of the dose. Peak plasma salmeterol concentrations were increased by 1.4-fold (90% CI: 1.23, 1.68). Three (3) out of 20 subjects (15%) were withdrawn from salmeterol and ketoconazole coadministration due to beta-agonist-mediated systemic effects (2 with QTc prolongation and 1 with palpitations and sinus tachycardia). Coadministration of salmeterol and ketoconazole did not result in a clinically significant effect on mean heart rate, mean blood potassium, or mean blood glucose. Although there was no statistical effect on the mean QTc, coadministration of salmeterol and ketoconazole was associated with more frequent increases in QTc duration compared with salmeterol and

261 placebo administration. Due to the potential increased risk of cardiovascular adverse events, the
262 concomitant use of salmeterol with strong CYP3A4 inhibitors (e.g., ketoconazole, ritonavir,
263 atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir,
264 telithromycin) is not recommended.

265 **Erythromycin:** In a repeat-dose study in 13 healthy subjects, concomitant
266 administration of erythromycin (a moderate CYP3A4 inhibitor) and salmeterol inhalation aerosol
267 resulted in a 40% increase in salmeterol C_{max} at steady state (ratio with and without erythromycin
268 1.4; 90% CI: 0.96, 2.03; $p = 0.12$), a 3.6-beat/min increase in heart rate (95% CI: 0.19, 7.03;
269 $p < 0.04$), a 5.8-msec increase in QTc interval (95% CI: -6.14, 17.77; $p = 0.34$), and no change in
270 plasma potassium.

271 **Pharmacodynamics: ADVAIR HFA Inhalation Aerosol:** Since systemic
272 pharmacodynamic effects of salmeterol are not normally seen at the therapeutic dose, higher
273 doses were used to produce measurable effects. Four placebo-controlled, crossover studies were
274 conducted in healthy subjects: (1) a cumulative-dose study using 42 to 336 mcg of salmeterol
275 CFC inhalation aerosol given alone or as ADVAIR HFA 115/21, (2) a single-dose study using
276 4 inhalations of ADVAIR HFA 230/21, salmeterol CFC inhalation aerosol 21 mcg, or
277 fluticasone propionate CFC inhalation aerosol 220 mcg, (3) a single-dose study using
278 8 inhalations of ADVAIR HFA 45/21, ADVAIR HFA 115/21, or ADVAIR HFA 230/21, and
279 (4) a single-dose study using 4 inhalations of ADVAIR HFA 230/21; 2 inhalations of ADVAIR
280 DISKUS 500/50; 4 inhalations of fluticasone propionate CFC inhalation aerosol 220 mcg; or
281 1,010 mcg of fluticasone propionate given intravenously. In these studies pulse rate, blood
282 pressure, QTc interval, glucose, and/or potassium were measured. Comparable or lower effects
283 were observed for ADVAIR HFA compared with ADVAIR DISKUS or salmeterol alone. The
284 effect of salmeterol on pulse rate and potassium was not altered by the presence of different
285 amounts of fluticasone propionate in ADVAIR HFA. The potential effect of salmeterol on the
286 effects of fluticasone propionate on the hypothalamic-pituitary-adrenal (HPA) axis was also
287 evaluated in 3 of these studies. Compared with fluticasone propionate CFC inhalation aerosol,
288 ADVAIR HFA had less effect on 24-hour urinary cortisol excretion and less or comparable
289 effect on 24-hour serum cortisol. In these crossover studies in healthy subjects, ADVAIR HFA
290 and ADVAIR DISKUS had similar effects on urinary and serum cortisol.

291 In clinical studies with ADVAIR HFA in patients with asthma, systemic pharmacodynamic
292 effects of salmeterol (pulse rate, blood pressure, QTc interval, potassium, and glucose) were
293 similar to or slightly lower in patients treated with ADVAIR HFA compared with patients treated
294 with salmeterol CFC inhalation aerosol 21 mcg. In 61 adolescent and adult patients with asthma
295 given ADVAIR HFA (45/21 or 115/21 mcg), continuous 24-hour electrocardiographic
296 monitoring was performed after the first dose and after 12 weeks of twice-daily therapy, and no
297 clinically significant dysrhythmias were noted.

298 A 4-way crossover study in 13 patients with asthma compared pharmacodynamics at steady
299 state following 4 weeks of twice-daily treatment with 2 inhalations of ADVAIR HFA 115/21,
300 1 inhalation of ADVAIR DISKUS 250/50 mcg, 2 inhalations of fluticasone propionate HFA

inhalation aerosol 110 mcg, and placebo. No significant differences in serum cortisol AUC were observed between active treatments and placebo. Mean 12-hour serum cortisol AUC ratios comparing active treatment with placebo ranged from 0.9 to 1.2. No statistically or clinically significant increases in heart rate or QTc interval were observed for any active treatment compared with placebo.

In a 12-week study (see CLINICAL TRIALS: Studies Comparing ADVAIR HFA With Fluticasone Propionate Alone or Salmeterol Alone: *Study 3*) in patients with asthma, ADVAIR HFA 115/21 was compared with the individual components, fluticasone propionate CFC inhalation aerosol 110 mcg and salmeterol CFC inhalation aerosol 21 mcg, and placebo. All treatments were administered as 2 inhalations twice daily. After 12 weeks of treatment with these therapeutic doses, the geometric mean ratio of urinary cortisol excretion compared with baseline was 0.9 for ADVAIR HFA and fluticasone propionate and 1.0 for placebo and salmeterol. In addition, the ability to increase cortisol production in response to stress, as assessed by 30-minute cosyntropin stimulation in 23 to 32 patients per treatment group, remained intact for the majority of patients and was similar across treatments. Three patients who received ADVAIR HFA 115/21 had an abnormal response (peak serum cortisol <18 mcg/dL) after dosing, compared with 1 patient who received placebo, 2 patients who received fluticasone propionate 110 mcg, and 1 patient who received salmeterol.

In another 12-week study (see CLINICAL TRIALS: Studies Comparing ADVAIR HFA With Fluticasone Propionate Alone or Salmeterol Alone: *Study 4*) in patients with asthma, ADVAIR HFA 230/21 (2 inhalations twice daily) was compared with ADVAIR DISKUS 500/50 (1 inhalation twice daily) and fluticasone propionate CFC inhalation aerosol 220 mcg (2 inhalations twice daily). The geometric mean ratio of 24-hour urinary cortisol excretion at week 12 compared with baseline was 0.9 for all 3 treatment groups.

Fluticasone Propionate: In clinical trials with fluticasone propionate inhalation powder using dosages up to and including 250 mcg twice daily, occasional abnormal short cosyntropin tests (peak serum cortisol <18 mcg/dL) were noted both in patients receiving fluticasone propionate and in patients receiving placebo. The incidence of abnormal tests at 500 mcg twice daily was greater than placebo. In a 2-year study carried out in 64 patients with mild, persistent asthma (mean FEV₁ 91% of predicted) randomized to fluticasone propionate 500 mcg twice daily or placebo, no patient receiving fluticasone propionate had an abnormal response to 6-hour cosyntropin infusion (peak serum cortisol <18 mcg/dL). With a peak cortisol threshold of <35 mcg/dL, 1 patient receiving fluticasone propionate (4%) had an abnormal response at 1 year; repeat testing at 18 months and 2 years was normal. Another patient receiving fluticasone propionate (5%) had an abnormal response at 2 years. No patient on placebo had an abnormal response at 1 or 2 years.

Salmeterol Xinafoate: Inhaled salmeterol, like other beta-adrenergic agonist drugs, can produce dose-related cardiovascular effects and effects on blood glucose and/or serum potassium in some patients (see PRECAUTIONS). The cardiovascular effects (heart rate, blood pressure)

associated with salmeterol occur with similar frequency, and are of similar type and severity, as those noted following albuterol administration.

The effects of rising inhaled doses of salmeterol and standard inhaled doses of albuterol were studied in volunteers and in patients with asthma. Salmeterol doses up to 84 mcg resulted in heart rate increases of 3 to 16 beats/min, about the same as albuterol dosed at 180 mcg by inhalation aerosol (4 to 10 beats/min). In 2 double-blind asthma studies, patients receiving either 42 mcg of salmeterol inhalation aerosol twice daily (n = 81) or 180 mcg of albuterol inhalation aerosol 4 times daily (n = 80) underwent continuous electrocardiographic monitoring during four 24-hour periods; no clinically significant dysrhythmias were noted.

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.

CLINICAL TRIALS

ADVAIR HFA has been studied in patients with asthma 12 years of age and older. ADVAIR HFA has not been studied in patients under 12 years of age or in patients with chronic obstructive pulmonary disease (COPD). In clinical trials comparing ADVAIR HFA Inhalation Aerosol with the individual components, improvements in most efficacy endpoints were greater with ADVAIR HFA than with the use of either fluticasone propionate or salmeterol alone. In addition, clinical trials showed comparable results between ADVAIR HFA and ADVAIR DISKUS.

Studies Comparing ADVAIR HFA With Fluticasone Propionate Alone or Salmeterol Alone: Four (4) double-blind, parallel-group clinical trials were conducted with ADVAIR HFA in 1,517 adolescent and adult patients (≥ 12 years, mean baseline forced expiratory volume in 1 second [FEV₁] 65% to 75% of predicted normal) with asthma that was not optimally controlled on their current therapy. All metered-dose inhaler treatments were inhalation aerosols given as 2 inhalations twice daily, and other maintenance therapies were discontinued.

Study 1: Clinical Trial With ADVAIR HFA 45/21 Inhalation Aerosol: This placebo-controlled, 12-week, US study compared ADVAIR HFA 45/21 with fluticasone propionate CFC inhalation aerosol 44 mcg or salmeterol CFC inhalation aerosol 21 mcg, each given as 2 inhalations twice daily. The primary efficacy endpoints were predose FEV₁ and withdrawals due to worsening asthma. This study was stratified according to baseline asthma therapy: patients using beta-agonists (albuterol alone [n = 142], salmeterol [n = 84], or inhaled corticosteroids [n = 134] [daily doses of beclomethasone dipropionate 252 to 336 mcg; budesonide 400 to 600 mcg; flunisolide 1,000 mcg; fluticasone propionate inhalation aerosol 176 mcg; fluticasone propionate inhalation powder 200 mcg; or triamcinolone acetonide 600 to 800 mcg]). Baseline FEV₁ measurements were similar across treatments: ADVAIR HFA 45/21, 2.29 L; fluticasone propionate 44 mcg, 2.20 L; salmeterol, 2.33 L; and placebo, 2.27 L.

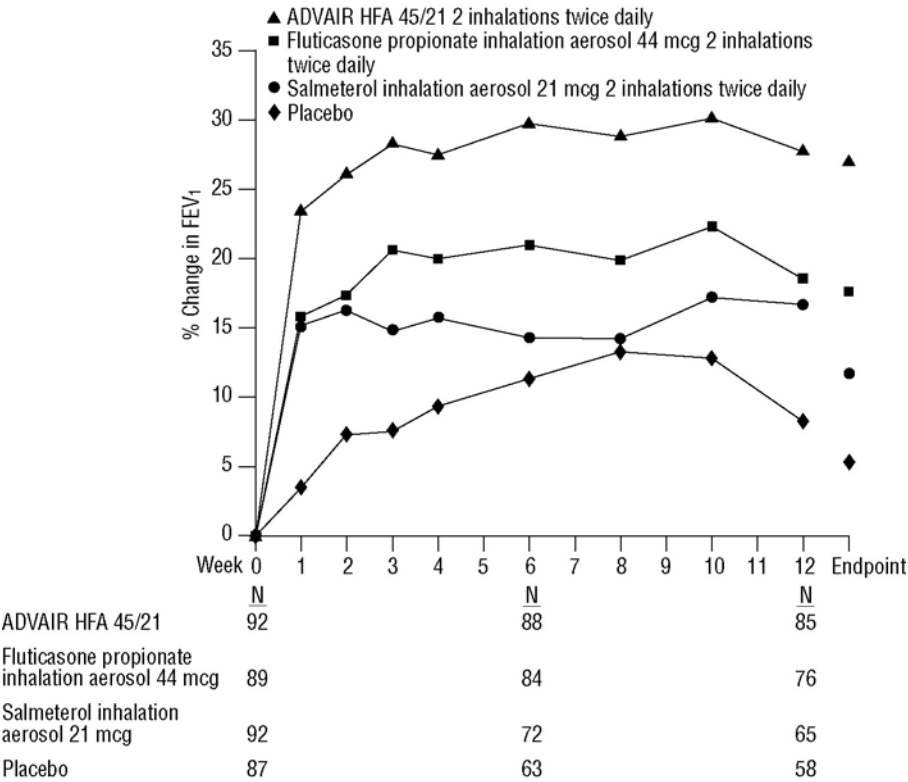
Predefined withdrawal criteria for lack of efficacy, an indicator of worsening asthma, were utilized for this placebo-controlled study. Worsening asthma was defined as a clinically important decrease in FEV₁ or peak expiratory flow (PEF), increase in use of VENTOLIN[®] (albuterol, USP) Inhalation Aerosol, increase in night awakenings due to asthma, emergency intervention or hospitalization due to asthma, or requirement for asthma medication not allowed by the protocol. As shown in Table 1, statistically significantly fewer patients receiving ADVAIR HFA 45/21 were withdrawn due to worsening asthma compared with salmeterol and placebo. Fewer patients receiving ADVAIR HFA 45/21 were withdrawn due to worsening asthma compared with fluticasone propionate 44 mcg; however, the difference was not statistically significant.

Table 1. Percent of Patients Withdrawn Due to Worsening Asthma in Patients Previously Treated With Beta₂-Agonists (Albuterol or Salmeterol) or Inhaled Corticosteroids (Study 1)

ADVAIR HFA 45/21 (n = 92)	Fluticasone Propionate CFC Inhalation Aerosol 44 mcg (n = 89)	Salmeterol CFC Inhalation Aerosol 21 mcg (n = 92)	Placebo HFA Inhalation Aerosol (n = 87)
2%	8%	25%	28%

The FEV₁ results are displayed in Figure 1. Because this trial used predetermined criteria for worsening asthma, which caused more patients in the placebo group to be withdrawn, FEV₁ results at Endpoint (last available FEV₁ result) are also provided. Patients receiving ADVAIR HFA 45/21 had significantly greater improvements in FEV₁ (0.58 L, 27%) compared with fluticasone propionate 44 mcg (0.36 L, 18%), salmeterol (0.25 L, 12%), and placebo (0.14 L, 5%). These improvements in FEV₁ with ADVAIR HFA 45/21 were achieved regardless of baseline asthma therapy (albuterol alone, salmeterol, or inhaled corticosteroids).

Figure 1. Mean Percent Change From Baseline in FEV₁ in Patients Previously Treated With Either Beta₂-Agonists (Albuterol or Salmeterol) or Inhaled Corticosteroids (Study 1)



The effect of ADVAIR HFA 45/21 on the secondary efficacy parameters, including morning and evening PEF, usage of VENTOLIN Inhalation Aerosol, and asthma symptoms over 24 hours on a scale of 0 to 5 is shown in Table 2.

Table 2. Secondary Efficacy Variable Results for Patients Previously Treated With Beta₂-Agonists (Albuterol or Salmeterol) or Inhaled Corticosteroids (Study 1)

Efficacy Variable *	ADVAIR HFA 45/21 (n = 92)	Fluticasone Propionate CFC Inhalation Aerosol 44 mcg (n = 89)	Salmeterol CFC Inhalation Aerosol 21 mcg (n = 92)	Placebo HFA Inhalation Aerosol (n = 87)
AM PEF (L/min)				
Baseline	377	369	381	382
Change from baseline	58	27	25	1
PM PEF (L/min)				
Baseline	397	387	402	407
Change from baseline	48	20	16	3
Use of VENTOLIN Inhalation Aerosol (inhalations/day)				
Baseline	3.1	2.4	2.7	2.7
Change from baseline	-2.1	-0.4	-0.8	0.2
Asthma symptom score/day				
Baseline	1.8	1.6	1.7	1.7
Change from baseline	-1.0	-0.3	-0.4	0

* Change from baseline = change from baseline at Endpoint (last available data).

The subjective impact of asthma on patients' perceptions of health was evaluated through use of an instrument called the Asthma Quality of Life Questionnaire (AQLQ) (based on a 7-point scale where 1 = maximum impairment and 7 = none). Patients receiving ADVAIR HFA 45/21 had clinically meaningful improvements in overall asthma-specific quality of life as defined by a difference between groups of ≥ 0.5 points in change from baseline AQLQ scores (difference in AQLQ score of 1.14 [95% CI 0.85, 1.44] compared with placebo).

Study 2: Clinical Trial With ADVAIR HFA 45/21 Inhalation Aerosol: This active-controlled, 12-week, US study compared ADVAIR HFA 45/21 with fluticasone propionate CFC inhalation aerosol 44 mcg and salmeterol CFC inhalation aerosol 21 mcg, each given as 2 inhalations twice daily, in 283 patients using as-needed albuterol alone. The primary efficacy endpoint was predose FEV₁. Baseline FEV₁ measurements were similar across treatments: ADVAIR HFA 45/21, 2.37 L; fluticasone propionate 44 mcg, 2.31 L; and salmeterol, 2.34 L.

Efficacy results in this study were similar to those observed in Study 1. Patients receiving ADVAIR HFA 45/21 had significantly greater improvements in FEV₁ (0.69 L, 33%) compared with fluticasone propionate 44 mcg (0.51 L, 25%) and salmeterol (0.47 L, 22%).

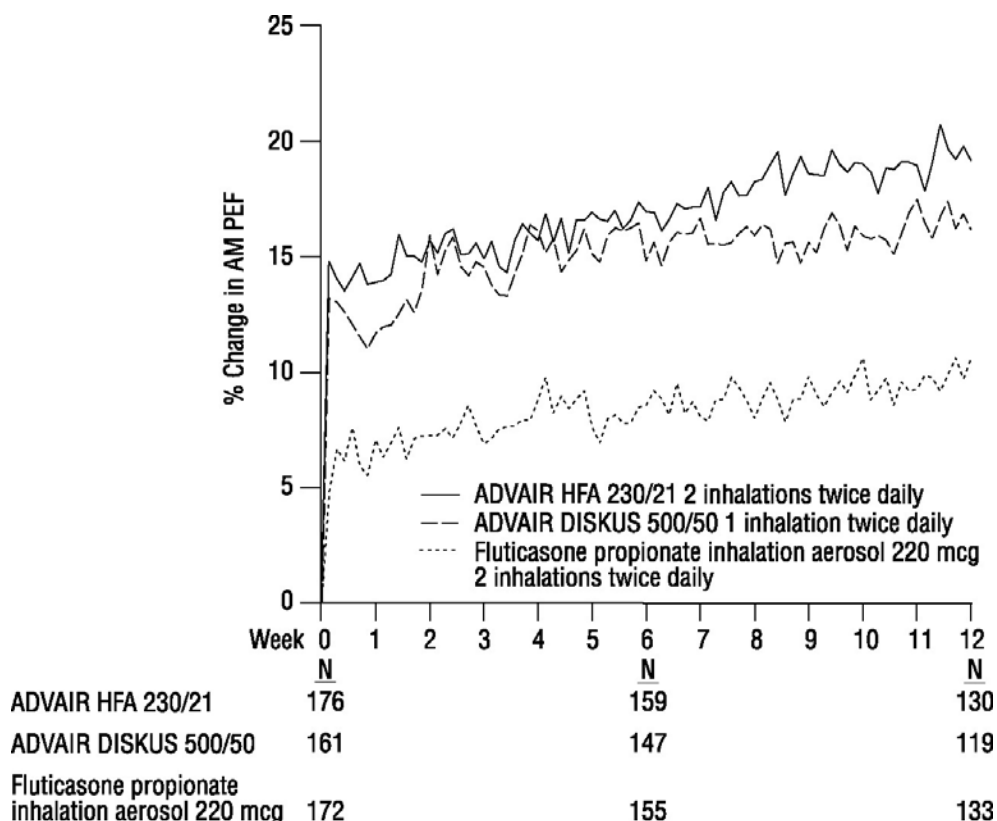
Study 3: Clinical Trial With ADVAIR HFA 115/21 Inhalation Aerosol: This placebo-controlled, 12-week, US study compared ADVAIR HFA 115/21 with fluticasone propionate CFC inhalation aerosol 110 mcg or salmeterol CFC inhalation aerosol 21 mcg, each given as 2 inhalations twice daily, in 365 patients using inhaled corticosteroids (daily doses of beclomethasone dipropionate 378 to 840 mcg; budesonide 800 to 1,200 mcg; flunisolide 1,250 to 2,000 mcg; fluticasone propionate inhalation aerosol 440 to 660 mcg; fluticasone propionate inhalation powder 400 to 600 mcg; or triamcinolone acetonide 900 to 1,600 mcg). The primary efficacy endpoints were predose FEV₁ and withdrawals due to worsening asthma. Baseline FEV₁ measurements were similar across treatments: ADVAIR HFA 115/21, 2.23 L; fluticasone propionate 110 mcg, 2.18 L; salmeterol, 2.22 L; and placebo, 2.17 L.

Efficacy results in this study were similar to those observed in Studies 1 and 2. Patients receiving ADVAIR HFA 115/21 had significantly greater improvements in FEV₁ (0.41 L, 20%) compared with fluticasone propionate 110 mcg (0.19 L, 9%), salmeterol (0.15 L, 8%), and placebo (-0.12 L, -6%). Significantly fewer patients receiving ADVAIR HFA 115/21 were withdrawn from this study for worsening asthma (7%) compared with salmeterol (24%) and placebo (54%). Fewer patients receiving ADVAIR HFA 115/21 were withdrawn due to worsening asthma (7%) compared with fluticasone propionate 110 mcg (11%); however, the difference was not statistically significant.

Study 4: Clinical Trial With ADVAIR HFA 230/21 Inhalation Aerosol: This active-controlled, 12-week, non-US study compared ADVAIR HFA 230/21 with fluticasone propionate CFC inhalation aerosol 220 mcg, each given as 2 inhalations twice daily, and with ADVAIR DISKUS 500/50 given as 1 inhalation twice daily in 509 patients using inhaled corticosteroids (daily doses of beclomethasone dipropionate CFC inhalation aerosol 1,500 to 2,000 mcg; budesonide 1,500 to 2,000 mcg; flunisolide 1,500 to 2,000 mcg; fluticasone propionate inhalation aerosol 660 to 880 mcg; or fluticasone propionate inhalation powder 750 to 1,000 mcg). The primary efficacy endpoint was morning PEF.

Baseline morning PEF measurements were similar across treatments: ADVAIR HFA 230/21, 327 L/min; ADVAIR DISKUS 500/50, 341 L/min; and fluticasone propionate 220 mcg, 345 L/min. As shown in Figure 2, morning PEF improved significantly with ADVAIR HFA 230/21 compared with fluticasone propionate 220 mcg over the 12-week treatment period. Improvements in morning PEF observed with ADVAIR HFA 230/21 were similar to improvements observed with ADVAIR DISKUS 500/50.

Figure 2. Mean Percent Change From Baseline in Morning Peak Expiratory Flow in Patients Previously Treated With Inhaled Corticosteroids (Study 4)



One-Year Safety Study: *Clinical Trial With ADVAIR HFA 45/21, 115/21, and 230/21*

Inhalation Aerosol: This 1-year, open-label, non-US study evaluated the safety of ADVAIR HFA 45/21, 115/21, and 230/21 given as 2 inhalations twice daily in 325 patients. This study was stratified into 3 groups according to baseline asthma therapy: patients using short-acting beta₂-agonists alone (n = 42), salmeterol (n = 91), or inhaled corticosteroids (n = 277). Patients treated with short-acting beta₂-agonists alone, salmeterol, or low doses of inhaled corticosteroids with or without concurrent salmeterol received ADVAIR HFA 45/21. Patients treated with moderate doses of inhaled corticosteroids with or without concurrent salmeterol received ADVAIR HFA 115/21. Patients treated with high doses of inhaled corticosteroids with or without concurrent salmeterol received ADVAIR HFA 230/21. Baseline FEV₁ measurements ranged from 2.3 to 2.6 L.

Improvements in FEV₁ (0.17 to 0.35 L at 4 weeks) were seen across all 3 treatments and were sustained throughout the 52-week treatment period. Few patients (3%) were withdrawn due to worsening asthma over 1 year.

Onset of Action and Progression of Improvement in Asthma Control: The onset of action and progression of improvement in asthma control were evaluated in 2 placebo-controlled

US trials and 1 active-controlled US trial. Following the first dose, the median time to onset of clinically significant bronchodilatation ($\geq 15\%$ improvement in FEV₁) in most patients was seen within 30 to 60 minutes. Maximum improvement in FEV₁ occurred within 4 hours, and clinically significant improvement was maintained for 12 hours (see Figure 3).

Following the initial dose, predose FEV₁ relative to day 1 baseline improved markedly over the first week of treatment and continued to improve over the 12 weeks of treatment in all 3 studies.

No diminution in the 12-hour bronchodilator effect was observed with either ADVAIR HFA 45/21 (Figures 3 and 4) or ADVAIR HFA 230/21 as assessed by FEV₁ following 12 weeks of therapy.

Figure 3. Percent Change in Serial 12-Hour FEV₁ in Patients Previously Using Either Beta₂-Agonists (Albuterol or Salmeterol) or Inhaled Corticosteroids (Study 1)

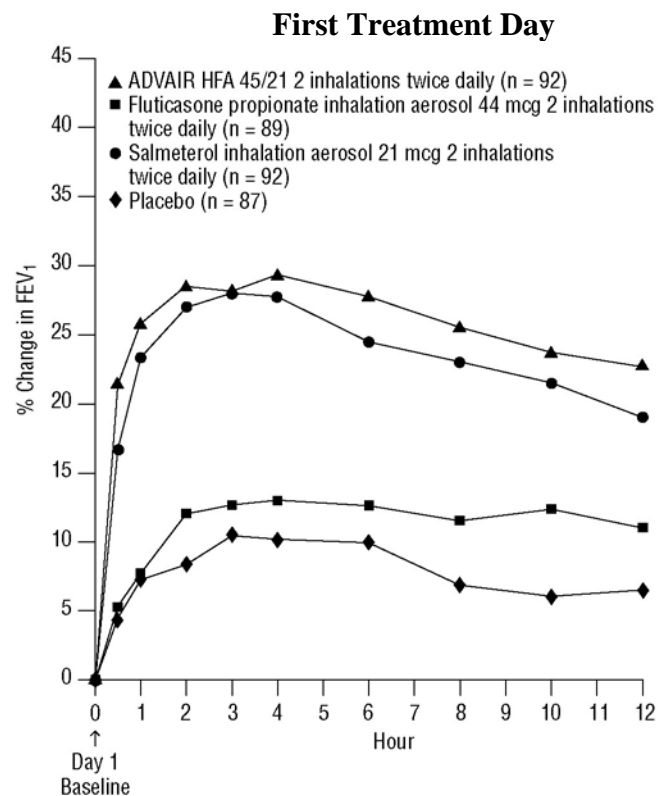
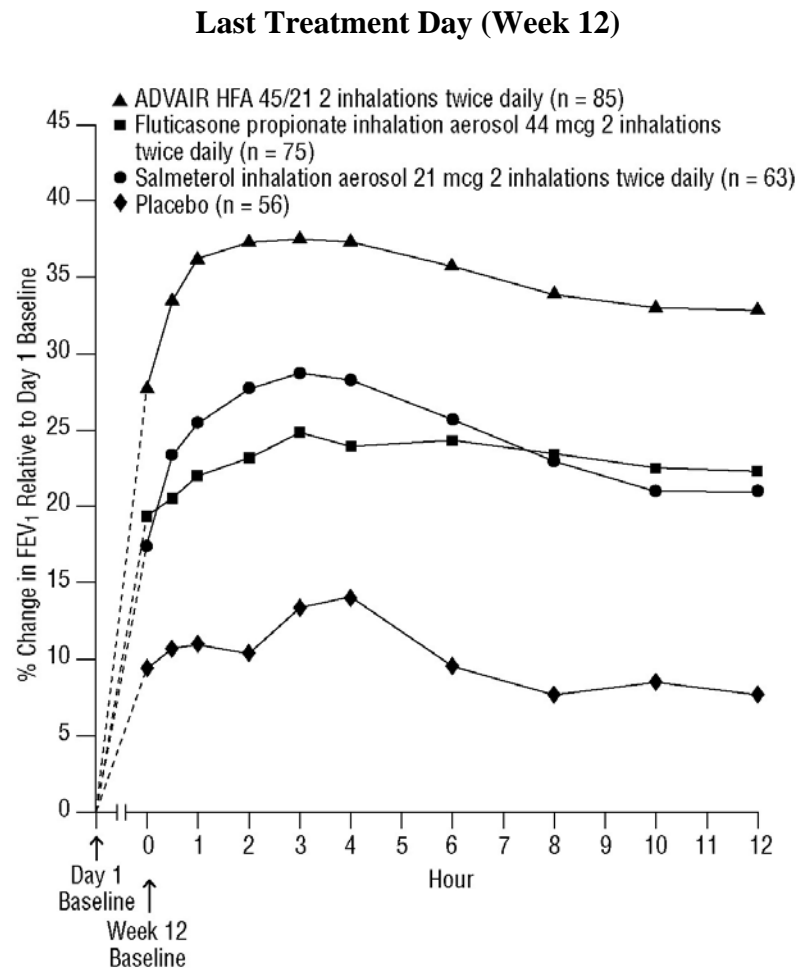


Figure 4. Percent Change in Serial 12-Hour FEV₁ in Patients Previously Using Either Beta₂-Agonists (Albuterol or Salmeterol) or Inhaled Corticosteroids (Study 1)



Reduction in asthma symptoms and use of rescue VENTOLIN Inhalation Aerosol and improvement in morning and evening PEF also occurred within the first day of treatment with ADVAIR HFA, and continued to improve over the 12 weeks of therapy in all 3 studies.

INDICATIONS AND USAGE

ADVAIR HFA is indicated for the long-term, twice-daily maintenance treatment of asthma in patients 12 years of age and older.

Long-acting beta₂-adrenergic agonists, such as salmeterol, one of the active ingredients in ADVAIR HFA, may increase the risk of asthma-related death (see WARNINGS). Therefore, when treating patients with asthma, physicians should only prescribe ADVAIR HFA 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 2

524 maintenance therapies. ADVAIR HFA is not indicated in patients whose asthma can be
525 successfully managed by inhaled corticosteroids along with occasional use of inhaled,
526 short-acting beta₂-agonists.

527 ADVAIR HFA is NOT indicated for the relief of acute bronchospasm.

528 **CONTRAINDICATIONS**

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

531 Hypersensitivity to any of the ingredients of these preparations contraindicates their use.

532 **WARNINGS**

533 **Long-acting beta₂-adrenergic agonists, such as salmeterol, one of the active ingredients**
534 **in ADVAIR HFA, may increase the risk of asthma-related death. Therefore, when treating**
535 **patients with asthma, physicians should only prescribe ADVAIR HFA for patients not**
536 **adequately controlled on other asthma-controller medications (e.g., low- to medium-dose**
537 **inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment**
538 **with 2 maintenance therapies.**

539 A large placebo-controlled US study that compared the safety of salmeterol with placebo,
540 each added to usual asthma therapy, showed an increase in asthma-related deaths in patients
541 receiving salmeterol. The Salmeterol Multi-center Asthma Research Trial (SMART) was a
542 randomized, double-blind study that enrolled long-acting beta₂-agonist-naïve patients with
543 asthma to assess the safety of salmeterol (SEREVENT Inhalation Aerosol) 42 mcg twice daily
544 over 28 weeks compared with placebo when added to usual asthma therapy. A planned interim
545 analysis was conducted when approximately half of the intended number of patients had been
546 enrolled (N = 26,355), which led to premature termination of the study. The results of the interim
547 analysis showed that patients receiving salmeterol were at increased risk for fatal asthma events
548 (see Table 3 and Figure 5). In the total population, a higher rate of asthma-related death occurred
549 in patients treated with salmeterol than those treated with placebo (0.10% vs. 0.02%; relative risk
550 4.37 [95% CI 1.25, 15.34]).

551 Post-hoc subpopulation analyses were performed. In Caucasians, asthma-related death
552 occurred at a higher rate in patients treated with salmeterol than in patients treated with placebo
553 (0.07% vs. 0.01%; relative risk 5.82 [95% CI 0.70, 48.37]). In African Americans also,
554 asthma-related death occurred at a higher rate in patients treated with salmeterol than those
555 treated with placebo (0.31% vs. 0.04%; relative risk 7.26 [95% CI 0.89, 58.94]). Although the
556 relative risks of asthma-related death were similar in Caucasians and African Americans, the
557 estimate of excess deaths in patients treated with salmeterol was greater in African Americans
558 because there was a higher overall rate of asthma-related death in African American patients (see
559 Table 3). Given the similar basic mechanisms of action of beta₂-agonists, it is possible that the
560 findings seen in the SMART study represent a class effect.

The data from the SMART study are not adequate to determine whether concurrent use of inhaled corticosteroids, such as fluticasone propionate, the other active ingredient in ADVAIR HFA, or other asthma-controller therapy modifies the risk of asthma-related death.

Table 3: Asthma-Related Deaths in the 28-Week Salmeterol Multi-center Asthma Research Trial (SMART)

	Salmeterol n (% [*])	Placebo n (% [*])	Relative Risk [†] (95% Confidence Interval)	Excess Deaths Expressed per 10,000 Patients [‡] (95% Confidence Interval)
Total Population[§] Salmeterol: N = 13,176 Placebo: N = 13,179	13 (0.10%)	3 (0.02%)	4.37 (1.25, 15.34)	8 (3, 13)
Caucasian Salmeterol: N = 9,281 Placebo: N = 9,361	6 (0.07%)	1 (0.01%)	5.82 (0.70, 48.37)	6 (1, 10)
African American Salmeterol: N = 2,366 Placebo: N = 2,319	7 (0.31%)	1 (0.04%)	7.26 (0.89, 58.94)	27 (8, 46)

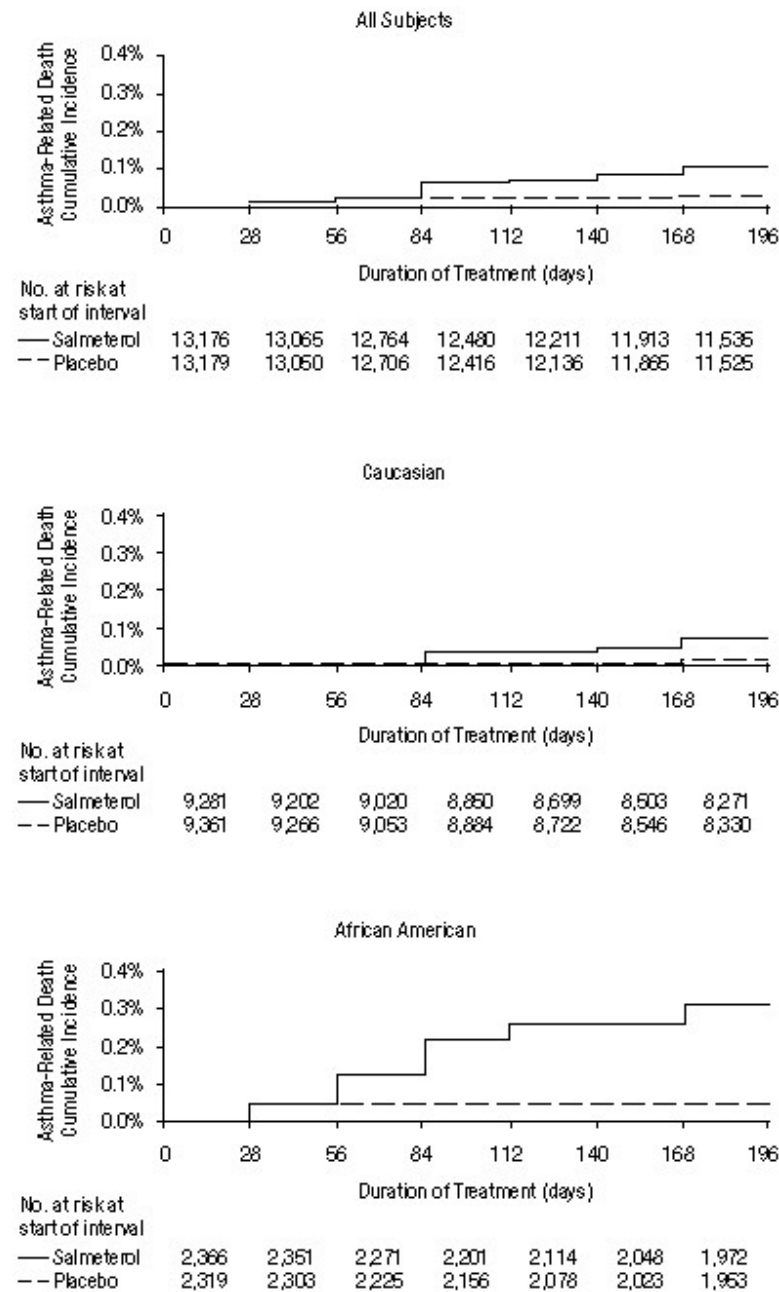
^{*} Life-table 28-week estimate, adjusted according to the patients' actual lengths of exposure to study treatment to account for early withdrawal of patients from the study.

[†] Relative risk is the ratio of the rate of asthma-related death in the salmeterol group and the rate in the placebo group. The relative risk indicates how many more times likely an asthma-related death occurred in the salmeterol group than in the placebo group in a 28-week treatment period.

[‡] Estimate of the number of additional asthma-related deaths in patients treated with salmeterol in SMART, assuming 10,000 patients received salmeterol for a 28-week treatment period. Estimate calculated as the difference between the salmeterol and placebo groups in the rates of asthma-related death multiplied by 10,000.

[§] The Total Population includes the following ethnic origins listed on the case report form: Caucasian, African American, Hispanic, Asian, and "Other." In addition, the Total Population includes those patients whose ethnic origin was not reported. The results for Caucasian and African American subpopulations are shown above. No asthma-related deaths occurred in the Hispanic (salmeterol n = 996, placebo n = 999), Asian (salmeterol n = 173, placebo n = 149), or "Other" (salmeterol n = 230, placebo n = 224) subpopulations. One asthma-related death occurred in the placebo group in the subpopulation whose ethnic origin was not reported (salmeterol n = 130, placebo n = 127).

Figure 5. Cumulative Incidence of Asthma-Related Deaths in the 28-Week Salmeterol Multi-center Asthma Research Trial (SMART), by Duration of Treatment



A 16-week clinical study performed in the United Kingdom, the Salmeterol Nationwide Surveillance (SNS) study, showed results similar to the SMART study. In the SNS study, the rate of asthma-related death was numerically, though not statistically significantly, greater in patients with asthma treated with salmeterol (42 mcg twice daily) than those treated with albuterol (180 mcg 4 times daily) added to usual asthma therapy.

The following additional WARNINGS about ADVAIR HFA should be noted.

1. ADVAIR HFA should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of asthma. Serious acute respiratory events, including fatalities, have been reported both in the United States and worldwide when salmeterol, a component of ADVAIR HFA, has been initiated in patients with significantly worsening or acutely deteriorating asthma. In most cases, these have occurred in patients with severe asthma (e.g., patients with a history of corticosteroid dependence, low pulmonary function, intubation, mechanical ventilation, frequent hospitalizations, or previous life-threatening acute asthma exacerbations) and/or in some patients in whom asthma has been acutely deteriorating (e.g., unresponsive to usual medications; increasing need for inhaled, short-acting beta₂-agonists; increasing need for systemic corticosteroids; significant increase in symptoms; recent emergency room visits; sudden or progressive deterioration in pulmonary function). However, they have occurred in a few patients with less severe asthma as well. It was not possible from these reports to determine whether salmeterol contributed to these events.

2. ADVAIR HFA should not be used to treat acute symptoms. An inhaled, short-acting beta₂-agonist, not ADVAIR HFA, should be used to relieve acute symptoms of shortness of breath. When prescribing ADVAIR HFA, the physician must also provide the patient with an inhaled, short-acting beta₂-agonist (e.g., albuterol) for treatment of shortness of breath that occurs acutely, despite regular twice-daily (morning and evening) use of ADVAIR HFA.

When beginning treatment with ADVAIR HFA, 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 taking ADVAIR HFA, inhaled, short-acting beta₂-agonists should only be used for symptomatic relief of acute symptoms of shortness of breath (see PRECAUTIONS: Information for Patients).

3. Increasing use of inhaled, short-acting beta₂-agonists is a marker of deteriorating asthma. The physician and patient should be alert to such changes. The patient's condition 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, this may be a marker of destabilization of the disease. In this setting, the patient requires immediate reevaluation with reassessment of the treatment regimen, giving special consideration to the possible need for replacing the current strength of ADVAIR HFA with a higher strength, adding additional inhaled corticosteroid, or initiating systemic corticosteroids. Patients should not use more than 2 inhalations twice daily (morning and evening) of ADVAIR HFA.

4. ADVAIR HFA should not be used for transferring patients from systemic corticosteroid therapy. Particular care is needed for patients who have been transferred from systemically active corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months are 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 corticosteroids may provide control of asthma symptoms during these episodes, in recommended doses they supply less than normal physiologic amounts of glucocorticoid (cortisol) systemically and do 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 warning card indicating that they may need supplementary systemic corticosteroids during periods of stress or a severe asthma attack.

5. ADVAIR HFA should not be used in conjunction with an inhaled, long-acting beta₂-agonist.

Patients who are receiving ADVAIR HFA twice daily should not use additional salmeterol or other long-acting beta₂-agonists (e.g., formoterol) for prevention of exercise-induced bronchospasm (EIB) or the maintenance treatment of asthma. Additional benefit would not be gained from using supplemental salmeterol or formoterol for prevention of EIB since ADVAIR HFA already contains an inhaled, long-acting beta₂-agonist.

6. The recommended dosage should not be exceeded. ADVAIR HFA 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. Large doses of inhaled or oral salmeterol (12 to 20 times the recommended dose) have been associated with clinically significant prolongation of the QTc interval, which has the potential for producing ventricular arrhythmias.

7. Paradoxical bronchospasm. As with other inhaled asthma medications, ADVAIR HFA can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with ADVAIR HFA, it should be treated immediately with an inhaled, short-acting bronchodilator; ADVAIR HFA should be discontinued immediately; and alternative therapy should be instituted.

8. Immediate hypersensitivity reactions. Immediate hypersensitivity reactions may occur after administration of ADVAIR HFA, as demonstrated by cases of urticaria, angioedema, rash, and bronchospasm.

9. Upper airway symptoms. Symptoms of laryngeal spasm, irritation, or swelling, such as stridor and choking, have been reported in patients receiving fluticasone propionate and salmeterol, components of ADVAIR HFA.

10. Cardiovascular disorders. ADVAIR HFA, like all products containing sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension. Salmeterol, a component of ADVAIR HFA, can 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 salmeterol 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.

11. Discontinuation of systemic corticosteroids. Transfer of patients from systemic corticosteroid therapy to ADVAIR HFA may unmask conditions previously suppressed by the systemic corticosteroid therapy, e.g., rhinitis, conjunctivitis, eczema, arthritis, and eosinophilic conditions.

12. 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. How the dose, route, and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled 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.

13. Pneumonia. Lower respiratory tract infections, including pneumonia, have been reported in patients with COPD following the inhaled administration of corticosteroids, including fluticasone propionate and ADVAIR DISKUS. In 2 replicate 12-month studies of 1,579 patients with COPD, there was a higher incidence of pneumonia reported in patients receiving ADVAIR DISKUS 250/50 (7%) than in those receiving salmeterol 50 mcg (3%). The incidence of pneumonia in the patients treated with ADVAIR DISKUS was higher in patients over 65 years of age (9%) compared with the incidence in patients less than 65 years of age (4%).

In a 3-year study of 6,184 patients with COPD, there was a higher incidence of pneumonia reported in patients receiving ADVAIR DISKUS 500/50 compared with placebo (16% with ADVAIR DISKUS 500/50, 14% with fluticasone propionate 500 mcg, 11% with salmeterol 50 mcg, and 9% with placebo). Similar to what was seen in the 1-year studies with ADVAIR DISKUS 250/50, the incidence of pneumonia was higher in patients over 65 years of age (18% with ADVAIR DISKUS 500/50 versus 10% with placebo) compared with patients less than 65 years of age (14% with ADVAIR DISKUS 500/50 versus 8% with placebo).

14. Potential drug interactions with CYP 3A4 inhibitors. Both fluticasone propionate and salmeterol are substrates of CYP 3A4.

Fluticasone Propionate: A drug interaction study in healthy subjects has shown that ritonavir (a strong cytochrome P450 3A4 inhibitor) can significantly increase systemic fluticasone propionate exposure (AUC), resulting in significantly reduced serum cortisol concentrations (see CLINICAL PHARMACOLOGY: Pharmacokinetics: *Fluticasone Propionate: Drug Interactions* and PRECAUTIONS: Drug Interactions: *Inhibitors of Cytochrome P450*). During postmarketing

use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing syndrome and adrenal suppression. Therefore, coadministration of fluticasone propionate and ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.

Salmeterol: Because of the potential for drug interactions and the potential for increased risk of cardiovascular adverse events, the concomitant use of ADVAIR HFA with strong CYP 3A4 inhibitors (e.g., ketoconazole, ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) is not recommended (see CLINICAL PHARMACOLOGY: Pharmacokinetics: *Salmeterol Xinafoate: Drug Interactions*).

PRECAUTIONS

General: Cardiovascular Effects: Cardiovascular and central nervous system effects seen with all sympathomimetic drugs (e.g., increased blood pressure, heart rate, excitement) can occur after use of salmeterol, a component of ADVAIR HFA, and may require discontinuation of ADVAIR HFA. ADVAIR HFA, 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 or thyrotoxicosis; and in patients who are unusually responsive to sympathomimetic amines.

As has been described with other beta-adrenergic agonist bronchodilators, clinically significant changes in ECGs have been seen infrequently in individual patients in controlled clinical studies with ADVAIR HFA and salmeterol. Clinically significant changes in systolic and/or diastolic blood pressure and pulse rate have been seen infrequently in individual patients in controlled clinical studies with salmeterol, a component of ADVAIR HFA.

Metabolic and Other Effects: Long-term use of orally inhaled corticosteroids 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 of osteoporosis, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants and corticosteroids), ADVAIR HFA 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. Beta-adrenergic agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation.

Clinically significant changes in blood glucose and/or serum potassium were seen infrequently during clinical studies with ADVAIR HFA 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.

Fluticasone propionate, a component of ADVAIR HFA, will often help control asthma symptoms with less suppression of HPA function than therapeutically equivalent oral doses of prednisone. Since fluticasone propionate is absorbed into the circulation and can be systemically active at higher doses, the beneficial effects of ADVAIR HFA in minimizing HPA dysfunction may be expected only when recommended dosages are not exceeded and individual patients are titrated to the lowest effective dose. A relationship between plasma levels of fluticasone propionate and inhibitory effects on stimulated cortisol production has been shown after 4 weeks of treatment with fluticasone propionate inhalation aerosol. Since individual sensitivity to effects on cortisol production exists, physicians should consider this information when prescribing ADVAIR HFA.

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

It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression (including adrenal crisis) may appear in a small number of patients, particularly when fluticasone propionate is administered at higher than recommended doses over prolonged periods of time. If such effects occur, the dosage of ADVAIR HFA should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids and for management of asthma.

A reduction of growth velocity in children and adolescents may occur as a result of poorly controlled asthma or from the therapeutic use of corticosteroids, including inhaled corticosteroids (see PRECAUTIONS: Pediatric Use). The effects of long-term treatment of children and adolescents with inhaled corticosteroids, including fluticasone propionate, on final adult height are not known. Patients should be maintained on the lowest strength of ADVAIR HFA that effectively controls their asthma.

The long-term effects of ADVAIR HFA in human subjects are not fully known. In particular, the effects resulting from chronic use of fluticasone propionate on developmental or immunologic processes in the mouth, pharynx, trachea, and lung are unknown. Some patients received inhaled fluticasone propionate on a continuous basis in a clinical study for up to 4 years. In clinical studies with patients treated for 2 years with inhaled fluticasone propionate, no apparent differences in the type or severity of adverse reactions were observed after long- versus short-term treatment.

Glaucoma, increased intraocular pressure, and cataracts have been reported in patients following the long-term administration of inhaled corticosteroids, including fluticasone propionate, a component of ADVAIR HFA.

Lower respiratory tract infections, including pneumonia, have been reported following the inhaled administration of corticosteroids, including fluticasone propionate, a component of ADVAIR HFA.

In clinical studies with ADVAIR HFA, the development of localized infections of the pharynx with *Candida albicans* has occurred. When such an infection develops, it should be treated with appropriate local or systemic (i.e., oral antifungal) therapy while remaining on treatment with ADVAIR HFA, but at times therapy with ADVAIR HFA may need to be interrupted.

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

Eosinophilic Conditions: In rare cases, patients on inhaled fluticasone propionate, a component of ADVAIR HFA, may present with systemic eosinophilic conditions, with some patients presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of fluticasone propionate. Cases of serious eosinophilic conditions have also been reported with other inhaled corticosteroids in this clinical setting. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal relationship between fluticasone propionate and these underlying conditions has not been established (see ADVERSE REACTIONS: Observed During Clinical Practice: *Eosinophilic Conditions*).

Information for Patients: Patients should be instructed to read the accompanying Medication Guide with each new prescription and refill. The complete text of the Medication Guide is reprinted at the end of this document.

Patients being treated with ADVAIR HFA should receive the following information and instructions. This information is intended to aid them in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. It is important that patients understand how to use ADVAIR HFA in relation to other asthma medications they are taking.

- 1. Patients should be informed that salmeterol, one of the active ingredients in ADVAIR HFA, may increase the risk of asthma-related death.** They should also be informed that data are not adequate to determine whether the concurrent use of inhaled corticosteroids, such as fluticasone propionate, the other component of ADVAIR HFA, or other asthma-controller therapy modifies this risk.
- ADVAIR HFA 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 beta₂-agonist such as albuterol (the physician should provide the patient with such medication and instruct the patient in how it should be used).
- The physician should be notified immediately if any of the following signs of seriously worsening asthma occur:
 - decreasing effectiveness of inhaled, short-acting beta₂-agonists;
 - need for more inhalations than usual of inhaled, short-acting beta₂-agonists;
 - significant decrease in lung function as outlined by the physician.

4. Patients should not stop therapy with ADVAIR HFA without physician/provider guidance since symptoms may recur after discontinuation.
5. Patients should be cautioned regarding common adverse effects associated with beta₂-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.
6. Long-term use of inhaled corticosteroids, including fluticasone propionate, a component of ADVAIR HFA, may increase the risk of some eye problems (cataracts or glaucoma). Regular eye examinations should be considered.
7. When patients are prescribed ADVAIR HFA, other medications for asthma should be used only as directed by the physician.
8. Patients who are pregnant or nursing should contact the physician about the use of ADVAIR HFA.
9. Patients should use ADVAIR HFA at regular intervals as directed. Results of clinical trials indicated significant improvement may occur within the first 30 minutes of taking the first dose; however, the full benefit may not be achieved until treatment has been administered for 1 week or longer. The patient should not use more than the prescribed dosage but should contact the physician if symptoms do not improve or if the condition worsens.
10. The bronchodilation from a single dose of ADVAIR HFA may last up to 12 hours or longer. The recommended dosage (2 inhalations twice daily, morning and evening) should not be exceeded. Patients who are receiving ADVAIR HFA twice daily should not use salmeterol or other inhaled, long-acting beta₂-agonists (e.g., formoterol) for prevention of EIB or maintenance treatment of asthma.
11. Patients should be warned to avoid exposure to chickenpox or measles and, if they are exposed to consult the physician without delay.
12. Prime the inhaler before using for the first time by releasing 4 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 4 weeks or when it has been dropped, prime the inhaler again by releasing 2 test sprays into the air away from the face, shaking well for 5 seconds before each spray.
13. After inhalation, rinse the mouth with water and spit out. Do not swallow.
14. Clean the inhaler at least once a week after the evening dose. Keeping the canister and plastic actuator clean is important to prevent medicine buildup. (See the cleaning instructions in the “How to use your ADVAIR HFA” section of the Medication Guide accompanying the product.)
15. Use ADVAIR HFA only with the actuator supplied with the product. When the counter reads 020, contact the pharmacist for a refill of medication or consult the physician to determine whether a prescription refill is needed. Discard the inhaler when the counter reads 000. Never try to alter the numbers or remove the counter from the metal canister.
16. For important summary information and instructions for the proper use of ADVAIR HFA, the patient should carefully read and follow the Medication Guide accompanying the product.

Drug Interactions: ADVAIR HFA has been used concomitantly with other drugs, including short-acting beta₂-agonists, methylxanthines, and intranasal corticosteroids, commonly used in patients with asthma, without adverse drug reactions. No formal drug interaction studies have been performed with ADVAIR HFA.

Short-Acting Beta₂-Agonists: In three 12-week US clinical trials, the mean daily need for additional beta₂-agonist use in 277 patients receiving ADVAIR HFA was approximately 1.2 inhalations/day and ranged from 0 to 9 inhalations/day. Two percent (2%) of patients receiving ADVAIR HFA in these trials averaged 6 or more inhalations per day over the course of the 12-week trials. No increase in frequency of cardiovascular events was observed among patients who averaged 6 or more inhalations per day.

Methylxanthines: The concurrent use of intravenously or orally administered methylxanthines (e.g., aminophylline, theophylline) by patients receiving ADVAIR HFA has not been completely evaluated. In five 12-week clinical trials (3 US and 2 non-US), 45 patients receiving ADVAIR HFA 45/21, 115/21, or 230/21 twice daily concurrently with a theophylline product had adverse event rates similar to those in 577 patients receiving ADVAIR HFA without theophylline.

Fluticasone Propionate Nasal Spray: In patients receiving ADVAIR HFA in three 12-week US clinical trials, no difference in the profile of adverse events or HPA axis effects was noted between patients receiving FLONASE[®] (fluticasone propionate) Nasal Spray, 50 mcg concurrently (n = 89) and those who were not (n = 192).

Monoamine Oxidase Inhibitors and Tricyclic Antidepressants: ADVAIR HFA should be administered with extreme 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 salmeterol, a component of ADVAIR HFA, on the vascular system may be potentiated by these agents.

Beta-Adrenergic Receptor Blocking Agents: Beta-blockers not only block the pulmonary effect of beta-agonists, such as salmeterol, a component of ADVAIR HFA, 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 beta-agonists with nonpotassium-sparing diuretics.

Inhibitors of Cytochrome P450: Fluticasone propionate and salmeterol are substrates of cytochrome P450 3A4.

Fluticasone propionate: A drug interaction study with fluticasone propionate aqueous nasal spray in healthy subjects has shown that ritonavir (a strong cytochrome P450 3A4 inhibitor) can significantly increase plasma fluticasone propionate exposure, resulting in significantly reduced serum cortisol concentrations (see CLINICAL PHARMACOLOGY: Pharmacokinetics: *Fluticasone Propionate: Drug Interactions*). During postmarketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing's syndrome and adrenal suppression. Therefore, coadministration of fluticasone propionate and ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.

In a placebo-controlled, crossover study in 8 healthy adult volunteers, coadministration of a single dose of orally inhaled fluticasone propionate (1,000 mcg) with multiple doses of ketoconazole (200 mg) to steady state resulted in increased systemic fluticasone propionate exposure, a reduction in plasma cortisol AUC, and no effect on urinary excretion of cortisol.

Salmeterol: In a drug interaction study in 20 healthy subjects, coadministration of inhaled salmeterol (50 mcg twice daily) and oral ketoconazole (400 mg once daily) for 7 days resulted in greater systemic exposure to salmeterol (AUC increased 16-fold and C_{max} increased 1.4-fold). Three (3) subjects were withdrawn due to β_2 -agonist side effects (2 with prolonged QTc and 1 with palpitations and sinus tachycardia). Although there was no statistical effect on the mean QTc, coadministration of salmeterol and ketoconazole was associated with more frequent increases in QTc duration compared with salmeterol and placebo administration. Due to the potential increased risk of cardiovascular adverse events, the concomitant use of salmeterol with strong CYP3A4 inhibitors (e.g., ketoconazole, ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) is not recommended (see CLINICAL PHARMACOLOGY: Pharmacokinetics: *Salmeterol Xinafoate: Drug Interactions*).

Carcinogenesis, Mutagenesis, Impairment of Fertility: Fluticasone Propionate: Fluticasone propionate demonstrated no tumorigenic potential in mice at oral doses up to 1,000 mcg/kg (approximately 4 times the maximum recommended human daily inhalation dose on a mcg/m² basis) for 78 weeks or in rats at inhalation doses up to 57 mcg/kg (less than the maximum recommended human daily inhalation dose on a mcg/m² basis) for 104 weeks.

Fluticasone propionate did not induce gene mutation in prokaryotic or eukaryotic cells in vitro. No significant clastogenic effect was seen in cultured human peripheral lymphocytes in vitro or in the mouse micronucleus test.

No evidence of impairment of fertility was observed in reproductive studies conducted in male and female rats at subcutaneous doses up to 50 mcg/kg (less than the maximum recommended human daily inhalation dose on a mcg/m² basis). Prostate weight was significantly reduced at a subcutaneous dose of 50 mcg/kg.

Salmeterol: In an 18-month oral carcinogenicity study in CD-mice, salmeterol at oral doses of 1.4 mg/kg and above (approximately 10 times the maximum recommended human daily inhalation dose based on comparison of the AUCs) caused a dose-related increase in the

incidence of smooth muscle hyperplasia, cystic glandular hyperplasia, leiomyomas of the uterus, and ovarian cysts. The incidence of leiomyosarcomas was not statistically significant. No tumors were seen at 0.2 mg/kg (approximately 2 times the maximum recommended human daily inhalation dose in adults based on comparison of the AUCs).

In a 24-month oral and inhalation carcinogenicity study in Sprague Dawley rats, salmeterol caused a dose-related increase in the incidence of mesovarian leiomyomas and ovarian cysts at doses of 0.68 mg/kg and above (approximately 65 times the maximum recommended human daily inhalation dose on a mg/m² basis). No tumors were seen at 0.21 mg/kg (approximately 20 times the maximum recommended human daily inhalation dose on a mg/m² basis). These findings in rodents are similar to those reported previously for other beta-adrenergic agonist drugs. The relevance of these findings to human use is unknown.

Salmeterol produced no detectable or reproducible increases in microbial and mammalian gene mutation in vitro. No clastogenic activity occurred in vitro in human lymphocytes or in vivo in a rat micronucleus test. No effects on fertility were identified in male and female rats treated with salmeterol at oral doses up to 2 mg/kg (approximately 190 times the maximum recommended human daily inhalation dose on a mg/m² basis).

Pregnancy: Teratogenic Effects: ADVAIR HFA Inhalation Aerosol: Pregnancy Category C. From the reproduction toxicity studies in mice and rats, no evidence of enhanced toxicity was seen using combinations of fluticasone propionate and salmeterol compared with toxicity data from the components administered separately. In mice combining 150 mcg/kg subcutaneously of fluticasone propionate (less than the maximum recommended human daily inhalation dose on a mcg/m² basis) with 10 mg/kg orally of salmeterol (approximately 480 times the maximum recommended human daily inhalation dose on a mg/m² basis) were teratogenic. Cleft palate, fetal death, increased implantation loss and delayed ossification was seen. These observations are characteristic of glucocorticoids. No developmental toxicity was observed at combination doses up to 40 mcg/kg subcutaneously of fluticasone propionate (less than the maximum recommended human daily inhalation dose on a mcg/m² basis) and up to 1.4 mg/kg orally of salmeterol (approximately 70 times the maximum recommended human daily inhalation dose on a mg/m² basis). In rats, no teratogenicity was observed at combination doses up to 30 mcg/kg subcutaneously of fluticasone propionate (less than the maximum recommended human daily inhalation dose on a mcg/m² basis) and up to 1 mg/kg of salmeterol (approximately 95 times the maximum recommended human daily inhalation dose on a mg/m² basis). Combining 100 mcg/kg subcutaneously of fluticasone propionate (equivalent to the maximum recommended human daily inhalation dose on a mcg/m² basis) with 10 mg/kg orally of salmeterol (approximately 970 times the maximum recommended human daily inhalation dose on a mg/m² basis) produced maternal toxicity, decreased placental weight, decreased fetal weight, umbilical hernia, delayed ossification, and changes in the occipital bone.

There are no adequate and well-controlled studies with ADVAIR HFA in pregnant women. ADVAIR HFA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Fluticasone Propionate: Pregnancy Category C. Subcutaneous studies in the mouse and rat at 45 and 100 mcg/kg, respectively (less than and equivalent to, respectively, the maximum recommended human daily inhalation dose on a mcg/m² basis), revealed fetal toxicity characteristic of potent corticosteroid compounds, including embryonic growth retardation, omphalocele, cleft palate, and retarded cranial ossification. No teratogenicity was seen in the rat at inhalation doses up to 68.7 mcg/kg (less than the maximum recommended human daily inhalation dose on a mcg/m² basis).

In the rabbit, fetal weight reduction and cleft palate were observed at a subcutaneous dose of 4 mcg/kg (less than the maximum recommended human daily inhalation dose on a mcg/m² basis). However, no teratogenic effects were reported at oral doses up to 300 mcg/kg (approximately 5 times the maximum recommended human daily inhalation dose on a mcg/m² basis) of fluticasone propionate. No fluticasone propionate was detected in the plasma in this study, consistent with the established low bioavailability following oral administration (see CLINICAL PHARMACOLOGY: Pharmacokinetics: *Fluticasone Propionate: Absorption*).

Fluticasone propionate crossed the placenta following administration of a subcutaneous dose of 100 mcg/kg to mice (less than the maximum recommended human daily inhalation dose on a mcg/m² basis), a subcutaneous or an oral dose of 100 mcg/kg to rats (equivalent to the maximum recommended human daily inhalation dose on a mcg/m² basis), and an oral dose of 300 mcg/kg to rabbits (approximately 5 times the maximum recommended human daily inhalation dose on a mcg/m² basis).

There are no adequate and well-controlled studies in pregnant women. ADVAIR HFA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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. In addition, because there is a natural increase in corticosteroid production during pregnancy, most women will require a lower exogenous corticosteroid dose and many will not need corticosteroid treatment during pregnancy.

Salmeterol: Pregnancy Category C. No teratogenic effects occurred in the rat at oral doses up to 2 mg/kg (approximately 190 times the maximum recommended human daily inhalation dose on a mg/m² basis). In pregnant Dutch rabbits administered oral doses of 1 mg/kg and above (approximately 25 times the maximum recommended human daily inhalation dose based on the comparison of the AUCs), salmeterol exhibited fetal toxic effects characteristically resulting from beta-adrenoceptor stimulation. These included precocious eyelid openings, cleft palate, sternebral fusion, limb and paw flexures, and delayed ossification of the frontal cranial bones. No significant effects occurred at an oral dose of 0.6 mg/kg (approximately 10 times the maximum recommended human daily inhalation dose based on comparison of the AUCs).

New Zealand White rabbits were less sensitive since only delayed ossification of the frontal cranial bones was seen at an oral dose of 10 mg/kg (approximately 1,900 times the maximum recommended human daily inhalation dose on a mg/m² basis). Extensive use of other

beta-agonists has provided no evidence that these class effects in animals are relevant to their use in humans.

Salmeterol xinafoate crossed the placenta following oral administration of 10 mg/kg to mice and rats (approximately 480 and 970 times, respectively, the maximum recommended human daily inhalation dose on a mg/m² basis).

There are no adequate and well-controlled studies with salmeterol in pregnant women. Salmeterol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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

Nursing Mothers: Plasma levels of salmeterol, a component of ADVAIR HFA, after inhaled therapeutic doses are very low. In rats, salmeterol xinafoate is excreted in the milk. There are no data from controlled trials on the use of salmeterol by nursing mothers. It is not known whether fluticasone propionate, a component of ADVAIR HFA, is excreted in human breast milk. However, other corticosteroids have been detected in human milk. Subcutaneous administration to lactating rats of 10 mcg/kg tritiated fluticasone propionate (less than the maximum recommended human daily inhalation dose on a mcg/m² basis) resulted in measurable radioactivity in milk.

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

Caution should be exercised when ADVAIR HFA is administered to a nursing woman.

Pediatric Use: Thirty-eight (38) patients 12 to 17 years of age were treated with ADVAIR HFA in US pivotal clinical trials. Patients in this age-group demonstrated efficacy results similar to those observed in patients 18 years of age 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 safety and effectiveness of ADVAIR HFA in children under 12 years have not been established.

Controlled clinical studies have shown that inhaled corticosteroids may cause a reduction in growth in pediatric patients. In these studies, the mean reduction in growth velocity was approximately 1 cm/year (range, 0.3 to 1.8 cm/year) and appears to depend upon dose and duration of exposure. This effect was 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 effects of this reduction in growth velocity associated with orally inhaled corticosteroids, including the impact on final adult height, are unknown. The potential

for “catch-up” growth following discontinuation of treatment with orally inhaled corticosteroids has not been adequately studied. The effects on growth velocity of treatment with orally inhaled corticosteroids for over 1 year, including the impact on final adult height, are unknown. The growth of children and adolescents receiving orally inhaled corticosteroids, including ADVAIR HFA, 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 of corticosteroids should be considered. The potential growth effects of prolonged treatment should be weighed against the clinical benefits obtained and the risks associated with alternative therapies. To minimize the systemic effects of orally inhaled corticosteroids, including ADVAIR HFA, each patient should be titrated to the lowest strength that effectively controls his/her asthma (see DOSAGE AND ADMINISTRATION).

Geriatric Use: Of the total number of patients in clinical studies treated with ADVAIR HFA, 41 were 65 years of age or older and 21 were 75 years of age or older. No overall differences in safety were observed between these patients and younger patients, and other reported clinical experience, including studies of the individual components, has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. As with other products containing beta₂-agonists, special caution should be observed when using ADVAIR HFA in geriatric patients who have concomitant cardiovascular disease that could be adversely affected by beta₂-agonists. Based on available data for ADVAIR HFA or its active components, no adjustment of dosage of ADVAIR HFA in geriatric patients is warranted.

ADVERSE REACTIONS

Long-acting beta₂-adrenergic agonists, such as salmeterol, may increase the risk of asthma-related death. Data from a large, placebo-controlled US study that compared the safety of salmeterol (SEREVENT Inhalation Aerosol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol (see WARNINGS). Salmeterol is a component of ADVAIR HFA. However, the data from this study are not adequate to determine whether concurrent use of inhaled corticosteroids, such as fluticasone propionate, the other component of ADVAIR HFA, or other asthma controller therapy modifies the risk of asthma-related death.

The incidence of common adverse events in Table 4 is based upon 2 placebo-controlled, 12-week, US clinical studies (Studies 1 and 3) and 1 active-controlled, 12-week, US clinical study (Study 2). A total of 1,008 adolescent and adult patients with asthma (556 females and 452 males) previously treated with albuterol alone, salmeterol, or inhaled corticosteroids were treated twice daily with 2 inhalations of ADVAIR HFA 45/21 or ADVAIR HFA 115/21, fluticasone propionate CFC inhalation aerosol (44- or 110-mcg doses), salmeterol CFC inhalation aerosol 21 mcg, or placebo HFA inhalation aerosol.

1111 **Table 4. Overall Adverse Events With $\geq 3\%$ Incidence in US Controlled Clinical Trials**
1112 **With ADVAIR HFA Inhalation Aerosol in Patients With Asthma**

Adverse Events	ADVAIR HFA		Fluticasone Propionate CFC Inhalation Aerosol		Salmeterol CFC Inhalation Aerosol	Placebo HFA Inhalation Aerosol
	45/21 (n = 187) %	115/21 (n = 94) %	44 mcg (n = 186) %	110 mcg (n = 91) %	21 mcg (n = 274) %	(n = 176) %
Ear, nose, & throat						
Upper respiratory tract infection	16	24	13	15	17	13
Throat irritation	9	7	12	13	9	7
Upper respiratory inflammation	4	4	3	7	5	3
Hoarseness/dysphonia	3	1	2	0	1	0
Lower respiratory						
Viral respiratory infections	3	5	4	5	3	4
Neurology						
Headaches	21	15	24	16	20	11
Dizziness	4	1	1	0	<1	0
Gastrointestinal						
Nausea & vomiting	5	3	4	2	2	3
Viral gastrointestinal infections	4	2	2	0	1	2
Gastrointestinal signs & symptoms	3	2	2	1	1	1
Non-site specific						
Pain	3	1	2	1	2	2
Musculoskeletal						
Musculoskeletal pain	5	7	8	2	4	4
Muscle pain	4	1	1	1	3	<1
Drug interaction, overdose, & trauma						
Muscle injuries	3	0	2	1	3	2
Reproduction						
Menstruation symptoms	5	3	1	0	<1	<1

Psychiatry Intoxication & hangover	3	0	0	0	0	0
Average duration of exposure (days)	81.3	78.6	79.9	74.6	71.4	56.3

Table 4 includes all events (whether considered drug-related or nondrug-related by the investigator) that occurred at a rate of 3% or greater in any of the groups receiving ADVAIR HFA and were more common than in the placebo group. In considering these data, differences in average duration of exposure should be taken into account. These adverse reactions were mostly mild to moderate in severity.

Other adverse events that occurred in the groups receiving ADVAIR HFA in these studies with an incidence of 1% to 3% and that occurred at a greater incidence than with placebo were:

Cardiovascular: Tachycardia, arrhythmias, myocardial infarction.

Drug Interaction, Overdose, and Trauma: Postoperative complications, wounds and lacerations, soft tissue injuries, poisoning and toxicity, pressure-induced disorder.

Ear, Nose, and Throat: Ear, nose, and throat infection; ear signs and symptoms; rhinorrhea/postnasal drip; epistaxis; nasal congestion/blockage; laryngitis; unspecified oropharyngeal plaques; dryness of nose.

Endocrine and Metabolic: Weight gain.

Eye: Allergic eye disorders, eye edema and swelling.

Gastrointestinal: Gastrointestinal discomfort and pain, dental discomfort and pain, candidiasis mouth/throat, hyposalivation, gastrointestinal infections, disorders of hard tissue of teeth, hemorrhoids, gastrointestinal gaseous symptoms, abdominal discomfort and pain, constipation, oral abnormalities.

Musculoskeletal: Arthralgia and articular rheumatism, muscle cramps and spasms, musculoskeletal inflammation, bone and skeletal pain.

Neurology: Sleep disorders, migraines.

Non-Site Specific: Allergies and allergic reactions, viral infections, bacterial infections, candidiasis unspecified site, congestion, inflammation.

Reproduction: Bacterial reproductive infections.

Respiratory: Lower respiratory signs and symptoms, lower respiratory infections, lower respiratory hemorrhage.

Skin: Eczema, dermatitis and dermatosis.

Urology: Urinary infections.

Rare cases of immediate and delayed hypersensitivity reactions, including rash and other rare events of angioedema and bronchospasm, have been reported.

The incidence of common adverse events reported in Study 4, a 12-week, non-US clinical study of 509 patients previously treated with inhaled corticosteroids who were treated twice daily with 2 inhalations of ADVAIR HFA 230/21, fluticasone propionate CFC inhalation aerosol

220 mcg, or 1 inhalation of ADVAIR DISKUS 500/50 was similar to the incidences reported in Table 4.

Observed During Clinical Practice: In addition to adverse events reported from clinical trials, the following events have been identified during worldwide use of any formulation of ADVAIR, fluticasone propionate, and/or salmeterol regardless of indication. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, or causal connection to ADVAIR, fluticasone propionate, and/or salmeterol or a combination of these factors.

In extensive US and worldwide postmarketing experience with salmeterol, a component of ADVAIR HFA, serious exacerbations of asthma, including some that have been fatal, have been reported. In most cases, these have occurred in patients with severe asthma and/or in some patients in whom asthma has been acutely deteriorating (see WARNINGS), but they have also occurred in a few patients with less severe asthma. It was not possible from these reports to determine whether salmeterol contributed to these events.

Cardiovascular: Arrhythmias (including atrial fibrillation, extrasystoles, supraventricular tachycardia), hypertension, ventricular tachycardia.

Ear, Nose, and Throat: Aphonia, earache, facial and oropharyngeal edema, paranasal sinus pain, rhinitis, throat soreness and irritation, tonsillitis.

Endocrine and Metabolic: Cushing syndrome, Cushingoid features, growth velocity reduction in children/adolescents, hypercorticism, hyperglycemia, osteoporosis.

Eye: Cataracts, glaucoma.

Gastrointestinal: Dyspepsia, xerostomia.

Hepatobiliary Tract and Pancreas: Abnormal liver function tests.

Musculoskeletal: Back pain, myositis.

Neurology: Paresthesia, restlessness.

Non-Site Specific: Fever, immediate and delayed hypersensitivity reaction, pallor.

Psychiatry: Agitation, aggression, anxiety, depression. Behavioral changes, including hyperactivity and irritability, have been reported very rarely and primarily in children.

Respiratory: Asthma; asthma exacerbation; chest congestion; chest tightness; cough; dyspnea; immediate bronchospasm; influenza; paradoxical bronchospasm; tracheitis; wheezing; pneumonia; reports of upper respiratory symptoms of laryngeal spasm, irritation, or swelling; stridor; choking.

Skin: Contact dermatitis, contusions, ecchymoses, photodermatitis, pruritus.

Urogenital: Dysmenorrhea, irregular menstrual cycle, pelvic inflammatory disease, vaginal candidiasis, vaginitis, vulvovaginitis.

Eosinophilic Conditions: In rare cases, patients on inhaled fluticasone propionate, a component of ADVAIR HFA, may present with systemic eosinophilic conditions, with some patients presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. These events usually, but not

always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of fluticasone propionate. Cases of serious eosinophilic conditions have also been reported with other inhaled corticosteroids in this clinical setting. While ADVAIR HFA should not be used for transferring patients from systemic corticosteroid therapy, physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal relationship between fluticasone propionate and these underlying conditions has not been established (see PRECAUTIONS: General: *Eosinophilic Conditions*).

OVERDOSAGE

ADVAIR HFA Inhalation Aerosol: No deaths occurred in rats given a single-dose combination of salmeterol 3.6 mg/kg and fluticasone propionate 1.9 mg/kg given as the inhalation powder (approximately 290 and 15 times, respectively, the maximum recommended human daily inhalation dose on a mg/m² basis).

Fluticasone Propionate: Chronic overdosage with fluticasone propionate may result in signs/symptoms of hypercorticism (see PRECAUTIONS: General: *Metabolic and Other Effects*). Inhalation by healthy volunteers of a single dose of 4,000 mcg of fluticasone propionate inhalation powder or single doses of 1,760 or 3,520 mcg of fluticasone propionate CFC inhalation aerosol were well tolerated. Fluticasone propionate given by inhalation aerosol at dosages of 1,320 mcg twice daily for 7 to 15 days to healthy human volunteers was also well tolerated. Repeat oral doses up to 80 mg daily for 10 days in healthy volunteers and repeat oral doses up to 20 mg daily for 42 days in patients were well tolerated. Adverse reactions were of mild or moderate severity, and incidences were similar in active and placebo treatment groups. In mice the oral median lethal dose was >1,000 mg/kg (>4,400 times the maximum recommended human daily inhalation dose on a mg/m² basis). In rats the subcutaneous median lethal dose was >1,000 mg/kg (>8,800 times the maximum recommended human daily inhalation dose on a mg/m² basis).

Salmeterol: The expected signs and symptoms with overdosage of salmeterol are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and symptoms listed under ADVERSE REACTIONS, e.g., seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, and insomnia. Overdosage with salmeterol may be expected to result in exaggeration of the pharmacologic adverse effects associated with beta-adrenoceptor agonists, including tachycardia and/or arrhythmia, tremor, headache, and muscle cramps. Overdosage with salmeterol can lead to clinically significant prolongation of the QTc interval, which can produce ventricular arrhythmias. Other signs of overdosage may include hypokalemia and hyperglycemia.

As with all sympathomimetic medications, cardiac arrest and even death may be associated with abuse of salmeterol.

Treatment consists of discontinuation of salmeterol together with appropriate symptomatic 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 salmeterol. Cardiac monitoring is recommended in cases of overdosage.

No deaths were seen in rats given salmeterol at an inhalation dose of 2.9 mg/kg (approximately 280 times the maximum recommended human daily inhalation dose on a mg/m² basis) and in dogs at an inhalation dose of 0.7 mg/kg (approximately 230 times the maximum recommended human daily inhalation dose on a mg/m² basis). By the oral route, no deaths occurred in mice at 150 mg/kg (approximately 7,200 times the maximum recommended human daily inhalation dose on a mg/m² basis) and in rats at 1,000 mg/kg (approximately 97,000 times the maximum recommended human daily inhalation dose on a mg/m² basis).

DOSAGE AND ADMINISTRATION

ADVAIR HFA should be administered by the orally inhaled route only in patients 12 years of age and older. ADVAIR HFA should not be used for transferring patients from systemic corticosteroid therapy. ADVAIR HFA has not been studied in patients under 12 years of age or in patients with COPD.

Long-acting beta₂-adrenergic agonists, such as salmeterol, one of the active ingredients in ADVAIR HFA, may increase the risk of asthma-related death (see WARNINGS). Therefore, when treating patients with asthma, physicians should only prescribe ADVAIR HFA 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 2 maintenance therapies. ADVAIR HFA is not indicated in patients whose asthma can be successfully managed by inhaled corticosteroids along with occasional use of inhaled, short-acting beta₂-agonists.

ADVAIR HFA is available in 3 strengths, ADVAIR HFA 45/21 Inhalation Aerosol, ADVAIR HFA 115/21 Inhalation Aerosol, and ADVAIR HFA 230/21 Inhalation Aerosol, containing 45, 115, and 230 mcg of fluticasone propionate, respectively, and 21 mcg of salmeterol per inhalation.

ADVAIR HFA should be administered as 2 inhalations twice daily every day. More frequent administration (more than twice daily) or a higher number of inhalations (more than 2 inhalations twice daily) of the prescribed strength of ADVAIR HFA is not recommended as some patients are more likely to experience adverse effects with higher doses of salmeterol. The safety and efficacy of ADVAIR HFA when administered in excess of recommended doses have not been established.

If symptoms arise in the period between doses, an inhaled, short-acting beta₂-agonist should be taken for immediate relief.

Patients who are receiving ADVAIR HFA twice daily should not use additional salmeterol or other inhaled, long-acting beta₂-agonists (e.g., formoterol) for prevention of EIB or for any other reason.

For patients 12 years of age and older, the dosage is 2 inhalations twice daily (morning and evening, approximately 12 hours apart).

The recommended starting dosages for ADVAIR HFA are based upon patients' current asthma therapy.

- For patients not adequately controlled on an inhaled corticosteroid, Table 5 provides the recommended starting dosage.
- For patients not currently on inhaled corticosteroids, whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies, the recommended starting dosage is 2 inhalations of ADVAIR HFA 45/21 or ADVAIR HFA 115/21 twice daily (see INDICATIONS AND USAGE).

The maximum recommended dosage is 2 inhalations of ADVAIR HFA 230/21 twice daily.

For all patients it is desirable to titrate to the lowest effective strength after adequate asthma stability is achieved.

Table 5. Recommended Dosages of ADVAIR HFA Inhalation Aerosol for Patients Not Adequately Controlled on Inhaled Corticosteroids

Current Daily Dose of Inhaled Corticosteroid		Recommended Strength of ADVAIR HFA (2 inhalations twice daily)
Beclomethasone dipropionate HFA inhalation aerosol	≤160 mcg	45/21
	320 mcg	115/21
	640 mcg	230/21
Budesonide inhalation powder	≤400 mcg	45/21
	800-1,200 mcg	115/21
	1,600 mcg [*]	230/21
Flunisolide CFC inhalation aerosol	≤1,000 mcg	45/21
	1,250-2,000 mcg	115/21
Flunisolide HFA inhalation aerosol	≤320 mcg	45/21
	640 mcg	115/21
Fluticasone propionate HFA inhalation aerosol	≤176 mcg	45/21
	440 mcg	115/21
	660-880 mcg [*]	230/21
Fluticasone propionate inhalation powder	≤200 mcg	45/21
	500 mcg	115/21
	1,000 mcg [*]	230/21
Mometasone furoate inhalation powder	220 mcg	45/21
	440 mcg	115/21
	880 mcg	230/21
Triamcinolone acetonide inhalation aerosol	≤1,000 mcg	45/21
	1,100-1,600 mcg	115/21

^{*} ADVAIR HFA should not be used for transferring patients from systemic corticosteroid therapy.

Improvement in asthma control following inhaled administration of ADVAIR HFA can occur within 30 minutes of beginning treatment, although maximum benefit may not be achieved for 1 week or longer after starting treatment. Individual patients will experience a variable time to onset and degree of symptom relief.

For patients who do not respond adequately to the starting dosage after 2 weeks of therapy, replacing the current strength of ADVAIR HFA with a higher strength may provide additional improvement in asthma control.

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

ADVAIR HFA should be primed before using for the first time by releasing 4 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 4 weeks or when it has been dropped, prime the inhaler again by releasing 2 test sprays into the air away from the face, shaking well for 5 seconds before each spray.

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

HOW SUPPLIED

Each strength of ADVAIR HFA Inhalation Aerosol is supplied in a 12-g pressurized aluminum canister containing 120 metered actuations in a box of 1.* Each canister is fitted with a counter, supplied with a purple actuator with a light purple strapcap, and sealed in a plastic-coated, moisture-protective foil pouch with a desiccant that should be discarded when the pouch is opened. Each canister is packaged with a Medication Guide leaflet.

*NDC 0173-0715-20 ADVAIR HFA 45/21 Inhalation Aerosol

*NDC 0173-0716-20 ADVAIR HFA 115/21 Inhalation Aerosol

*NDC 0173-0717-20 ADVAIR HFA 230/21 Inhalation Aerosol

The purple actuator supplied with ADVAIR HFA Inhalation Aerosol should not be used with any other product canisters, and actuators from other products should not be used with an ADVAIR HFA Inhalation Aerosol canister.

The correct amount of medication in each actuation cannot be assured after the counter reads 000, even though the canister is not completely empty and will continue to operate.

The inhaler should be discarded when the counter reads 000.

Keep out of reach of children. Avoid spraying in eyes.

Contents Under Pressure: Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 120°F may cause bursting. Never throw container into fire or incinerator.

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). Store the inhaler with the mouthpiece down. For best results, the inhaler should be at room temperature before use. SHAKE WELL FOR 5 SECONDS BEFORE USING.

ADVAIR HFA Inhalation Aerosol does not contain chlorofluorocarbons (CFCs) as the propellant.

PATIENT INFORMATION

MEDICATION GUIDE

**ADVAIR[®] HFA [*ad' vair*] 45/21 Inhalation Aerosol
(fluticasone propionate 45 mcg and salmeterol 21 mcg)**

1335 **ADVAIR® HFA 115/21 Inhalation Aerosol**
1336 **(fluticasone propionate 115 mcg and salmeterol 21 mcg)**
1337

1338 **ADVAIR® HFA 230/21 Inhalation Aerosol**
1339 **(fluticasone propionate 230 mcg and salmeterol 21 mcg)**
1340

1341 Read this Medication Guide carefully before you start to use ADVAIR HFA Inhalation
1342 Aerosol.

1343 Keep this Medication Guide because it has important summary information about ADVAIR
1344 HFA. This Medication Guide does not contain all the information about your medicine. If you
1345 have any questions or are not sure about something, you should ask your doctor or pharmacist.

1346 Read the new Medication Guide that comes with each refill of your prescription because there
1347 may be new information.
1348

1349 **What is the most important information I should know about ADVAIR HFA?**

1350 • **ADVAIR HFA contains 2 medicines:**

- 1351 • **fluticasone propionate (the same medicine found in FLOVENT®)**, an inhaled
1352 corticosteroid medicine. Inhaled corticosteroids help to decrease inflammation in the
1353 lungs. Inflammation in the lungs can lead to asthma symptoms.
- 1354 • **salmeterol (the same medicine found in SEREVENT®)**, a long-acting beta₂-agonist
1355 (LABA) medicine. LABA medicines are used in patients with asthma. LABA medicines
1356 help the muscles around the airways in your lungs stay relaxed to prevent symptoms,
1357 such as wheezing and shortness of breath. These symptoms can happen when the muscles
1358 around the airways tighten. This makes it hard to breathe. In severe cases, wheezing can
1359 stop your breathing and cause death if not treated right away.

- 1360 • **In patients with asthma, LABA medicines, such as salmeterol (one of the medicines in**
1361 **ADVAIR HFA), may increase the chance of death from asthma problems.** In a large
1362 asthma study, more patients who used salmeterol died from asthma problems compared with
1363 patients who did not use salmeterol. It is not known whether fluticasone propionate, the other
1364 medicine in ADVAIR HFA, changes your chance of death from asthma problems seen with
1365 salmeterol. Talk with your healthcare provider about this risk and the benefits of treating your
1366 asthma with ADVAIR HFA.

- 1367 • **ADVAIR HFA does not relieve sudden symptoms. Always have a short-acting**
1368 **beta₂-agonist medicine with you to treat sudden symptoms. If you do not have an**
1369 **inhaled, short-acting bronchodilator, contact your healthcare provider to have one**
1370 **prescribed for you.**

- 1371 • **Do not stop using ADVAIR HFA unless told to do so by your healthcare provider**
1372 **because your symptoms might get worse.**

- **ADVAIR HFA 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 ADVAIR HFA. 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 ADVAIR HFA?

ADVAIR HFA combines an inhaled corticosteroid medicine, fluticasone propionate (the same medicine found in FLOVENT) and a LABA medicine, salmeterol (the same medicine found in SEREVENT).

ADVAIR HFA is used long term, twice a day to control symptoms of asthma, and prevent symptoms such as wheezing in adults and adolescents 12 years of age and older.

ADVAIR HFA contains salmeterol (the same medicine found in SEREVENT). Because LABA medicines, such as salmeterol, may increase the chance of death from asthma problems, ADVAIR HFA is not for adults and children 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

Who should not use ADVAIR HFA?

Do not use ADVAIR HFA:

- to treat sudden severe symptoms of asthma
- if you are allergic to any of the ingredients in ADVAIR HFA. See the end of this Medication Guide for a list of ingredients in ADVAIR HFA.

What should I tell my healthcare provider before using ADVAIR HFA?

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**

1412 • **are pregnant or planning to become pregnant.** It is not known if ADVAIR HFA may harm
1413 your unborn baby.

1414 • **are breastfeeding.** It is not known if ADVAIR HFA passes into your milk and if it can harm
1415 your baby.

1416 • **are allergic to ADVAIR HFA or any other medicines**

1417 • **are exposed to chickenpox or measles**

1418 Tell your healthcare provider about all the medicines you take including prescription and
1419 non-prescription medicines, vitamins, and herbal supplements. ADVAIR HFA and certain other
1420 medicines may interact with each other. This may cause serious side effects. Especially, tell your
1421 healthcare provider if you take ritonavir. The anti-HIV medicines NORVIR[®] (ritonavir capsules)
1422 Soft Gelatin, NORVIR (ritonavir oral solution), and KALETRA[®] (lopinavir/ritonavir) Tablets
1423 contain ritonavir.

1424 Know the medicines you take. Keep a list and show it to your healthcare provider and
1425 pharmacist each time you get a new medicine.
1426

1427 **How do I use ADVAIR HFA?**

1428 **See the step-by-step instructions for using ADVAIR HFA at the end of this Medication**
1429 **Guide.** Do not use ADVAIR HFA unless your healthcare provider has taught you and you
1430 understand everything. Ask your healthcare provider or pharmacist if you have any questions.

1431 • Use ADVAIR HFA exactly as prescribed. **Do not use ADVAIR HFA more often than**
1432 **prescribed.** ADVAIR HFA comes in 3 strengths. Your healthcare provider has prescribed the
1433 one that is best for your condition.

1434 • The usual dose of ADVAIR HFA is 2 inhalations twice a day (morning and evening). The 2
1435 doses should be about 12 hours apart. Rinse your mouth with water after using ADVAIR
1436 HFA.

1437 • If you miss a dose of ADVAIR HFA, just skip that dose. Take your next dose at your usual
1438 time. Do not take 2 doses at one time.

1439 • **While you are using ADVAIR HFA twice a day, do not use other medicines that contain**
1440 **a LABA for any reason. Other LABA-containing medicines include ADVAIR DISKUS[®]**
1441 **(fluticasone propionate and salmeterol inhalation powder), SEREVENT[®] DISKUS[®]**
1442 **(salmeterol xinafoate inhalation powder), FORADIL[®] AEROLIZER[®] (formoterol**
1443 **fumarate inhalation powder), SYMBICORT[®] (budesonide and formoterol fumarate**
1444 **dihydrate) Inhalation Aerosol, PERFOROMIST[™] (formoterol fumarate) Inhalation**
1445 **Solution, and BROVANA[™] (arformoterol tartrate) Inhalation Solution.**

1446 • Do not change or stop any of your medicines used to control or treat your breathing problems.
1447 Your healthcare provider will adjust your medicines as needed.

- 1448 • Make sure you always have a short-acting beta₂-agonist medicine with you. Use your
1449 short-acting beta₂-agonist medicine if you have breathing problems between doses of
1450 ADVAIR HFA.
- 1451 • **Call your healthcare provider or get medical care right away if:**
- 1452 • your breathing problems worsen with ADVAIR HFA
 - 1453 • you need to use your short-acting beta₂-agonist medicine more often than usual
 - 1454 • your short-acting beta₂-agonist medicine does not work as well for you at relieving
1455 symptoms
 - 1456 • you need to use your short-acting beta₂-agonist medicine more than twice in 1 week
 - 1457 • your peak flow meter results decrease. Your healthcare provider will tell you the numbers
1458 that are right for you.
 - 1459 • you have asthma and your symptoms do not improve after using ADVAIR HFA regularly
1460 for 1 week
- 1461

1462 **What are the possible side effects with ADVAIR HFA?**

1463 **ADVAIR HFA contains salmeterol (the same medicine found in SEREVENT). In**
1464 **patients with asthma, LABA medicines, such as salmeterol, may increase the chance of**
1465 **death from asthma problems.** See “What is the most important information I should know
1466 about ADVAIR HFA?”

1467 **Other possible side effects with ADVAIR HFA include:**

- 1468 • **serious allergic reactions including rash; hives; swelling of the face, mouth, and tongue;**
1469 **and breathing problems.** Call your healthcare provider or get emergency medical care if you
1470 get any symptoms of a serious allergic reaction.
- 1471 • **increased blood pressure**
- 1472 • **a fast and irregular heartbeat**
- 1473 • **chest pain**
- 1474 • **headache**
- 1475 • **tremor**
- 1476 • **nervousness**
- 1477 • **immune system effects and a higher chance for infections**
- 1478 • **lower bone mineral density.** This may be a problem for people who already have a higher
1479 chance for low bone density (osteoporosis).
- 1480 • **eye problems including glaucoma and cataracts.** You should have regular eye exams while
1481 using ADVAIR HFA.
- 1482 • **slowed growth in children.** A child’s growth should be checked often.
- 1483 • **throat irritation**
- 1484 • **pneumonia.** ADVAIR HFA contains the same medicine found in ADVAIR DISKUS.
1485 ADVAIR DISKUS is used to treat people with asthma and people with chronic obstructive
1486 pulmonary disease (COPD). People with COPD have a higher chance of getting pneumonia.

ADVAIR DISKUS may increase the chance of getting pneumonia. ADVAIR HFA has not been studied in people with COPD.

Common side effects of ADVAIR HFA include upper respiratory tract infection and headache.

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 ADVAIR HFA. Ask your healthcare provider or pharmacist for more information.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ADVAIR HFA?

Store at room temperature with the mouthpiece down.

Contents Under Pressure: Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 120°F may cause bursting.

Do not throw into fire or an incinerator.

Keep ADVAIR HFA and all medicines out of the reach of children.

General information about ADVAIR HFA

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ADVAIR HFA for a condition for which it was not prescribed. Do not give your ADVAIR HFA to other people, even if they have the same condition that you have. It may harm them.

This Medication Guide summarizes the most important information about ADVAIR HFA. If you would like more information, talk with your healthcare provider or pharmacist. You can ask your healthcare provider or pharmacist for information about ADVAIR HFA that was written for healthcare professionals. You can also contact the company that makes ADVAIR HFA (toll free) at 1-888-825-5249 or at www.advair.com.

What are the ingredients in ADVAIR HFA?

Active ingredients: fluticasone propionate, salmeterol xinafoate

Inactive ingredient: propellant HFA-134a

How to use your ADVAIR HFA

The parts of your ADVAIR HFA:

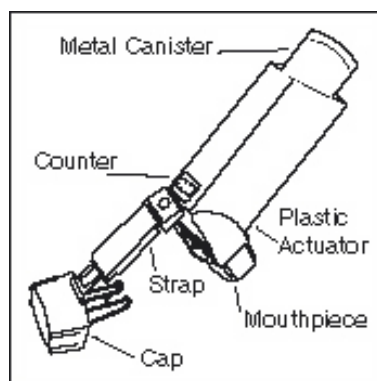


Figure 1

There are 2 main parts to your ADVAIR HFA inhaler—the metal canister that holds the medicine and the purple plastic actuator that sprays the medicine from the canister (see Figure 1).

The inhaler also has a cap that covers the mouthpiece of the actuator. The strap on the cap will stay attached to the actuator.

Do not use the actuator with a canister of medicine from any other inhaler. Do not use an ADVAIR HFA canister with an actuator from any other inhaler.

The canister has a counter to show how many sprays of medicine you have left. The number shows through a window in the back of the actuator.

The counter starts at 124, or at 64 if you have a sample canister. The number will count down by 1 each time you spray the inhaler. The counter will stop counting at 000.

Never try to change the numbers or take the counter off the metal canister. The counter cannot be reset, and it is permanently attached to the canister.

Before using your ADVAIR HFA:

Take the inhaler out of the foil pouch. Safely throw away the foil pouch and the drying packet that comes inside the pouch. The counter should read 124, or 64 if you have a sample canister.

The inhaler should be at room temperature before you use it.

Check each time to make sure the canister fits firmly in the plastic actuator. Also look into the mouthpiece to make sure there are no foreign objects there, especially if the strap is no longer attached to the actuator or if the cap is not being used to cover the mouthpiece.

Priming your ADVAIR HFA:

Before you use ADVAIR HFA for the first time, you must prime the inhaler so that you will get the right amount of medicine when you use it. To prime the inhaler, take the cap off the mouthpiece and shake the inhaler well for 5 seconds. Then spray it 1 time into the air away from your face. Shake and spray the inhaler like this 3 more times to finish priming it. **Avoid spraying in eyes.** The counter should now read 120, or 60 if you have a sample canister.

You must prime your inhaler again if you have not used it in more than 4 weeks or if you have dropped it. Take the cap off the mouthpiece, shake the inhaler well for 5 seconds, and spray it into the air away from your face. Shake and spray the inhaler like this 1 more time to finish priming it.

Instructions for taking a dose from your ADVAIR HFA:

Read through the 7 steps below before using ADVAIR HFA. If you have any questions, ask your doctor or pharmacist.

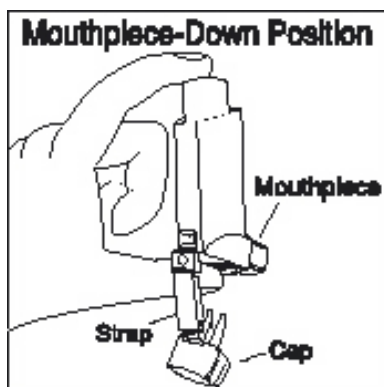


Figure 2

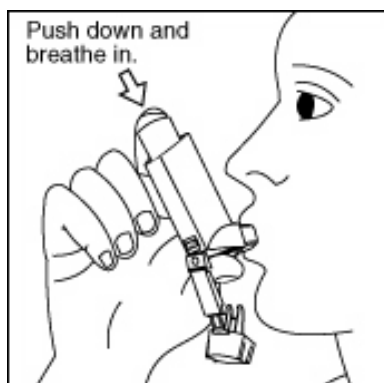


Figure 3

1. Take the cap off the mouthpiece of the actuator. **Shake the inhaler well** for 5 seconds before each spray.
2. Hold the inhaler with the mouthpiece down (see Figure 2). **Breathe out through your mouth** and push as much air from your lungs as you can. Put the mouthpiece in your mouth and close your lips around it.
3. **Push the top of the canister all the way down while you breathe in deeply and slowly through your mouth** (see Figure 3). Right after the spray comes out, take your finger off the canister. After you have breathed in all the way, take the inhaler out of your mouth and close your mouth.
4. **Hold your breath as long as you can**, up to 10 seconds, then breathe normally.
5. Wait about 30 seconds and **shake** the inhaler again for 5 seconds. Repeat steps 2 through 4.
6. After you finish taking this medicine, rinse your mouth with water. Spit out the water. Do not swallow it.
7. Put the cap back on the mouthpiece after every time you use the inhaler, and make sure it snaps firmly into place.

When to replace your ADVAIR HFA:

- **When the counter reads 020**, you should refill your prescription or ask your doctor if you need another prescription for ADVAIR HFA.
- **Throw the inhaler away** when the counter reads 000. You should not keep using the inhaler when the counter reads 000 because you will not receive the right amount of medicine.
- **Do not use the inhaler** after the expiration date, which is on the packaging it comes in.

How to clean your ADVAIR HFA:

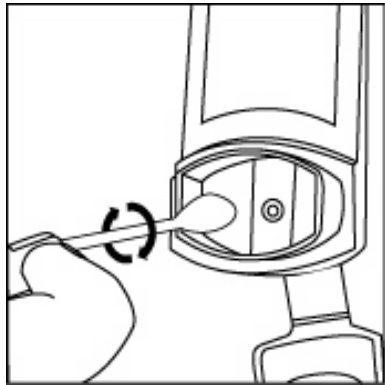


Figure 4

- Clean the inhaler at least once a week after your evening dose. It is important to keep the canister and plastic actuator clean so the medicine will not build-up and block the spray.
1. Take the cap off the mouthpiece. The strap on the cap will stay attached to the actuator. Do not take the canister out of the plastic actuator.
 2. Use a dry cotton swab to clean the small circular opening where the medicine sprays out of the canister. Carefully twist the swab in a circular motion to take off any medicine (see Figure 4).
 3. Wipe the inside of the mouthpiece with a clean tissue dampened with water. Let the actuator air-dry overnight.
 4. Put the cap back on the mouthpiece after the actuator has dried.

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

April 2009

ADH:4MG

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Research Triangle Park, NC 27709

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April 2009

ADH:4PI

PHARMACIST—DETACH HERE AND GIVE MEDICATION GUIDE TO PATIENT

MEDICATION GUIDE

ADVAIR[®] HFA [*ad' vair*] 45/21 Inhalation Aerosol
(fluticasone propionate 45 mcg and salmeterol 21 mcg)

ADVAIR[®] HFA 115/21 Inhalation Aerosol
(fluticasone propionate 115 mcg and salmeterol 21 mcg)

ADVAIR[®] HFA 230/21 Inhalation Aerosol
(fluticasone propionate 230 mcg and salmeterol 21 mcg)

Read this Medication Guide carefully before you start to use ADVAIR HFA Inhalation Aerosol.

Keep this Medication Guide because it has important summary information about ADVAIR HFA. This Medication Guide does not contain all the information about your medicine. If you have any questions or are not sure about something, you should ask your doctor or pharmacist.

Read the new Medication Guide that comes with each refill of your prescription because there may be new information.

What is the most important information I should know about ADVAIR HFA?

- **ADVAIR HFA contains 2 medicines:**
 - **fluticasone propionate (the same medicine found in FLOVENT[®]),** an inhaled corticosteroid medicine. Inhaled corticosteroids help to decrease inflammation in the lungs. Inflammation in the lungs can lead to asthma symptoms.
 - **salmeterol (the same medicine found in SEREVENT[®]),** a long-acting beta₂-agonist (LABA) medicine. LABA medicines are used in patients with asthma. LABA medicines help the muscles around the airways in your lungs stay relaxed to prevent 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 cause death if not treated right away.
- **In patients with asthma, LABA medicines, such as salmeterol (one of the medicines in ADVAIR HFA), may increase the chance of death from asthma problems.** In a large asthma study, more patients who used salmeterol died from asthma problems compared with patients who did not use salmeterol. It is not known whether fluticasone propionate, the other medicine in ADVAIR HFA, changes your chance of death from asthma problems seen with salmeterol. Talk with your healthcare provider about this risk and the benefits of treating your asthma with ADVAIR HFA.
- **ADVAIR HFA does not relieve sudden symptoms. Always have a short-acting beta₂-agonist medicine with you to treat sudden symptoms. If you do not have an**

inhaled, short-acting bronchodilator, contact your healthcare provider to have one prescribed for you.

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

ADVAIR HFA combines an inhaled corticosteroid medicine, fluticasone propionate (the same medicine found in FLOVENT) and a LABA medicine, salmeterol (the same medicine found in SEREVENT).

ADVAIR HFA is used long term, twice a day to control symptoms of asthma, and prevent symptoms such as wheezing in adults and adolescents 12 years of age and older.

ADVAIR HFA contains salmeterol (the same medicine found in SEREVENT). Because LABA medicines, such as salmeterol, may increase the chance of death from asthma problems, ADVAIR HFA is not for adults and children 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

Who should not use ADVAIR HFA?

Do not use ADVAIR HFA:

- to treat sudden severe symptoms of asthma
- if you are allergic to any of the ingredients in ADVAIR HFA. See the end of this Medication Guide for a list of ingredients in ADVAIR HFA.

What should I tell my healthcare provider before using ADVAIR HFA?

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

- 1706 • **have diabetes**
- 1707 • **have liver problems**
- 1708 • **have osteoporosis**
- 1709 • **have an immune system problem**
- 1710 • **are pregnant or planning to become pregnant.** It is not known if ADVAIR HFA may harm
- 1711 your unborn baby.
- 1712 • **are breastfeeding.** It is not known if ADVAIR HFA passes into your milk and if it can harm
- 1713 your baby.
- 1714 • **are allergic to ADVAIR HFA or any other medicines**
- 1715 • **are exposed to chickenpox or measles**
- 1716 Tell your healthcare provider about all the medicines you take including prescription and
- 1717 non-prescription medicines, vitamins, and herbal supplements. ADVAIR HFA and certain other
- 1718 medicines may interact with each other. This may cause serious side effects. Especially, tell your
- 1719 healthcare provider if you take ritonavir. The anti-HIV medicines NORVIR[®] (ritonavir capsules)
- 1720 Soft Gelatin, NORVIR (ritonavir oral solution), and KALETRA[®] (lopinavir/ritonavir) Tablets
- 1721 contain ritonavir.
- 1722 Know the medicines you take. Keep a list and show it to your healthcare provider and
- 1723 pharmacist each time you get a new medicine.
- 1724

1725 **How do I use ADVAIR HFA?**

- 1726 **See the step-by-step instructions for using ADVAIR HFA at the end of this Medication**
- 1727 **Guide.** Do not use ADVAIR HFA unless your healthcare provider has taught you and you
- 1728 understand everything. Ask your healthcare provider or pharmacist if you have any questions.
- 1729 • Use ADVAIR HFA exactly as prescribed. **Do not use ADVAIR HFA more often than**
 - 1730 **prescribed.** ADVAIR HFA comes in 3 strengths. Your healthcare provider has prescribed the
 - 1731 one that is best for your condition.
 - 1732 • The usual dose of ADVAIR HFA is 2 inhalations twice a day (morning and evening). The 2
 - 1733 doses should be about 12 hours apart. Rinse your mouth with water after using ADVAIR
 - 1734 HFA.
 - 1735 • If you miss a dose of ADVAIR HFA, just skip that dose. Take your next dose at your usual
 - 1736 time. Do not take 2 doses at one time.
 - 1737 • **While you are using ADVAIR HFA twice a day, do not use other medicines that contain**
 - 1738 **a LABA for any reason. Other LABA-containing medicines include ADVAIR DISKUS[®]**
 - 1739 **(fluticasone propionate and salmeterol inhalation powder), SEREVENT[®] DISKUS[®]**
 - 1740 **(salmeterol xinafoate inhalation powder), FORADIL[®] AEROLIZER[®] (formoterol**
 - 1741 **fumarate inhalation powder), SYMBICORT[®] (budesonide and formoterol fumarate**
 - 1742 **dihydrate) Inhalation Aerosol, PERFOROMIST[™] (formoterol fumarate) Inhalation**
 - 1743 **Solution, and BROVANA[™] (arformoterol tartrate) Inhalation Solution.**

- 1744 • Do not change or stop any of your medicines used to control or treat your breathing problems.
1745 Your healthcare provider will adjust your medicines as needed.
- 1746 • Make sure you always have a short-acting beta₂-agonist medicine with you. Use your
1747 short-acting beta₂-agonist medicine if you have breathing problems between doses of
1748 ADVAIR HFA.
- 1749 • **Call your healthcare provider or get medical care right away if:**
- 1750 • your breathing problems worsen with ADVAIR HFA
- 1751 • you need to use your short-acting beta₂-agonist medicine more often than usual
- 1752 • your short-acting beta₂-agonist medicine does not work as well for you at relieving
1753 symptoms
- 1754 • you need to use your short-acting beta₂-agonist medicine more than twice in 1 week
- 1755 • your peak flow meter results decrease. Your healthcare provider will tell you the numbers
1756 that are right for you.
- 1757 • you have asthma and your symptoms do not improve after using ADVAIR HFA regularly
1758 for 1 week
- 1759

What are the possible side effects with ADVAIR HFA?

1761 **ADVAIR HFA contains salmeterol (the same medicine found in SEREVENT). In**
1762 **patients with asthma, LABA medicines, such as salmeterol, may increase the chance of**
1763 **death from asthma problems.** See “What is the most important information I should know
1764 about ADVAIR HFA?”

Other possible side effects with ADVAIR HFA include:

- 1765 • **serious allergic reactions including rash; hives; swelling of the face, mouth, and tongue;**
1766 **and breathing problems.** Call your healthcare provider or get emergency medical care if you
1767 get any symptoms of a serious allergic reaction.
- 1768 • **increased blood pressure**
- 1769 • **a fast and irregular heartbeat**
- 1770 • **chest pain**
- 1771 • **headache**
- 1772 • **tremor**
- 1773 • **nervousness**
- 1774 • **immune system effects and a higher chance for infections**
- 1775 • **lower bone mineral density.** This may be a problem for people who already have a higher
1776 chance for low bone density (osteoporosis).
- 1777 • **eye problems including glaucoma and cataracts.** You should have regular eye exams while
1778 using ADVAIR HFA.
- 1779 • **slowed growth in children.** A child’s growth should be checked often.
- 1780 • **throat irritation**
- 1781

- **pneumonia.** ADVAIR HFA contains the same medicine found in ADVAIR DISKUS. ADVAIR DISKUS is used to treat people with asthma and people with chronic obstructive pulmonary disease (COPD). People with COPD have a higher chance of getting pneumonia. ADVAIR DISKUS may increase the chance of getting pneumonia. ADVAIR HFA has not been studied in people with COPD. Common side effects of ADVAIR HFA include upper respiratory tract infection and headache. 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 ADVAIR HFA. Ask your healthcare provider or pharmacist for more information. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ADVAIR HFA?

- Store at room temperature with the mouthpiece down.
- Contents Under Pressure:** Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 120°F may cause bursting. Do not throw into fire or an incinerator.
- Keep ADVAIR HFA and all medicines out of the reach of children.**

General information about ADVAIR HFA

- Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ADVAIR HFA for a condition for which it was not prescribed. Do not give your ADVAIR HFA to other people, even if they have the same condition that you have. It may harm them.
- This Medication Guide summarizes the most important information about ADVAIR HFA. If you would like more information, talk with your healthcare provider or pharmacist. You can ask your healthcare provider or pharmacist for information about ADVAIR HFA that was written for healthcare professionals. You can also contact the company that makes ADVAIR HFA (toll free) at 1-888-825-5249 or at www.advair.com.

What are the ingredients in ADVAIR HFA?

- Active ingredients: fluticasone propionate, salmeterol xinafoate
- Inactive ingredient: propellant HFA-134a

How to use your ADVAIR HFA

The parts of your ADVAIR HFA:

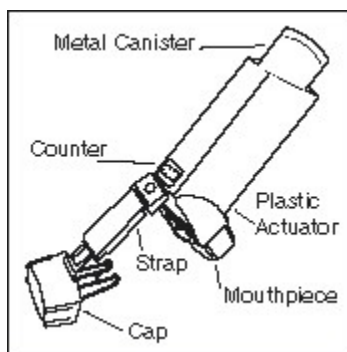


Figure 1

There are 2 main parts to your ADVAIR HFA inhaler—the metal canister that holds the medicine and the purple plastic actuator that sprays the medicine from the canister (see Figure 1).

The inhaler also has a cap that covers the mouthpiece of the actuator. The strap on the cap will stay attached to the actuator.

Do not use the actuator with a canister of medicine from any other inhaler. Do not use an ADVAIR HFA canister with an actuator from any other inhaler.

The canister has a counter to show how many sprays of medicine you have left. The number shows through a window in the back of the actuator.

The counter starts at 124, or at 64 if you have a sample canister. The number will count down by 1 each time you spray the inhaler. The counter will stop counting at 000.

Never try to change the numbers or take the counter off the metal canister. The counter cannot be reset, and it is permanently attached to the canister.

Before using your ADVAIR HFA:

Take the inhaler out of the foil pouch. Safely throw away the foil pouch and the drying packet that comes inside the pouch. The counter should read 124, or 64 if you have a sample canister.

The inhaler should be at room temperature before you use it.

Check each time to make sure the canister fits firmly in the plastic actuator. Also look into the mouthpiece to make sure there are no foreign objects there, especially if the strap is no longer attached to the actuator or if the cap is not being used to cover the mouthpiece.

Priming your ADVAIR HFA:

Before you use ADVAIR HFA for the first time, you must prime the inhaler so that you will get the right amount of medicine when you use it. To prime the inhaler, take the cap off the mouthpiece and shake the inhaler well for 5 seconds. Then spray it 1 time into the air away from your face. Shake and spray the inhaler like this 3 more times to finish priming it. **Avoid spraying in eyes.** The counter should now read 120, or 60 if you have a sample canister.

You must prime your inhaler again if you have not used it in more than 4 weeks or if you have dropped it. Take the cap off the mouthpiece, shake the inhaler well for 5 seconds, and spray it into the air away from your face. Shake and spray the inhaler like this 1 more time to finish priming it.

Instructions for taking a dose from your ADVAIR HFA:

Read through the 7 steps below before using ADVAIR HFA. If you have any questions, ask your doctor or pharmacist.

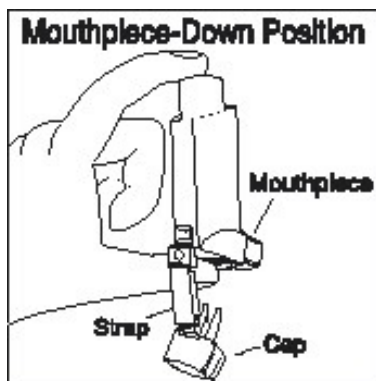


Figure 2

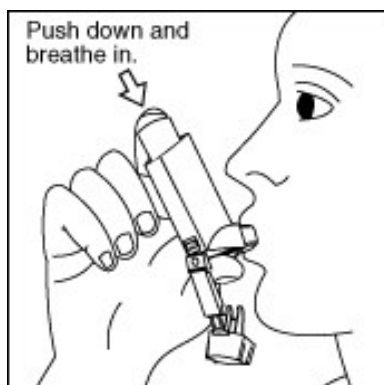


Figure 3

1. Take the cap off the mouthpiece of the actuator. **Shake the inhaler well** for 5 seconds before each spray.
2. Hold the inhaler with the mouthpiece down (see Figure 2). **Breathe out through your mouth** and push as much air from your lungs as you can. Put the mouthpiece in your mouth and close your lips around it.
3. **Push the top of the canister all the way down while you breathe in deeply and slowly through your mouth** (see Figure 3). Right after the spray comes out, take your finger off the canister. After you have breathed in all the way, take the inhaler out of your mouth and close your mouth.
4. **Hold your breath as long as you can**, up to 10 seconds, then breathe normally.
5. Wait about 30 seconds and **shake** the inhaler again for 5 seconds. Repeat steps 2 through 4.
6. After you finish taking this medicine, rinse your mouth with water. Spit out the water. Do not swallow it.
7. Put the cap back on the mouthpiece after every time you use the inhaler, and make sure it snaps firmly into place.

When to replace your ADVAIR HFA:

- **When the counter reads 020**, you should refill your prescription or ask your doctor if you need another prescription for ADVAIR HFA.
- **Throw the inhaler away** when the counter reads 000. You should not keep using the inhaler when the counter reads 000 because you will not receive the right amount of medicine.
- **Do not use the inhaler** after the expiration date, which is on the packaging it comes in.

How to clean your ADVAIR HFA:

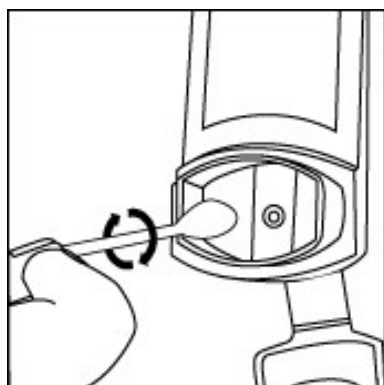


Figure 4

- Clean the inhaler at least once a week after your evening dose. It is important to keep the canister and plastic actuator clean so the medicine will not build-up and block the spray.
1. Take the cap off the mouthpiece. The strap on the cap will stay attached to the actuator. Do not take the canister out of the plastic actuator.
 2. Use a dry cotton swab to clean the small circular opening where the medicine sprays out of the canister. Carefully twist the swab in a circular motion to take off any medicine (see Figure 4).

- 1901 3. Wipe the inside of the mouthpiece with a clean tissue
1902 dampened with water. Let the actuator air-dry overnight.
1903 4. Put the cap back on the mouthpiece after the actuator has
1904 dried.

1905
1906 **This Medication Guide has been approved by the U.S. Food and Drug Administration.**
1907
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1921 April 2009

ADH:4MG

**PROPOSED RISK EVALUATION AND MITIGATION STRATEGY (REMS)
FOR SYMBICORT**

I. GOAL

The goal of this REMS is to communicate the risks of SYMBICORT.

II. REMS ELEMENTS

A. Medication Guide

A Medication Guide will be dispensed with each SYMBICORT prescription. SYMBICORT is packaged as a single unit of use. The Medication Guide is inserted inside the carton during insertion of the overwrapped MDI unit. Each Medication Guide is barcode scanned to ensure that the correct version is being used and that the component is available for insertion into each carton.

Because the Medication Guide is included as part of the secondary package for SYMBICORT, AstraZeneca has met the requirements of 21 CFR 208.24 for distribution and dispensing of the Medication Guide.

B. Communication Plan

The REMS for SYMBICORT does not include a communication plan.

C. Element To Assure Safe Use

The REMS for SYMBICORT does not include elements to assure safe use.

D. Implementation System

Because the REMS for SYMBICORT does not include elements to assure safe use, an implementation system is not required.

III. ASSESSMENT OF REMS

Because the Medication Guide is included as part of the secondary package for SYMBICORT, AstraZeneca has met the requirements of 21 CFR 208.24 for distribution and dispensing of the Medication Guide. Accordingly, AstraZeneca will not be required to assess the distribution and dispensing of the Medication Guide or failures to adhere to distribution and dispensing requirements. However, AstraZeneca will be required to assess patients' understanding of the serious risks of SYMBICORT.

NDA 21-929/S-012 -- SYMBICORT (budesonide/formoterol fumarate dihydrate)

The Timetable for Assessments is as follows:

1st FDAAA assessment: August 2010 (18 months from approval)

2nd FDAAA assessment: February 2012 (3 years from approval)

3rd FDAAA assessment: February 2016 (7 years from approval)

AstraZeneca will submit the assessment within 60 days of the close of the intervals as noted above.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SYMBICORT safely and effectively. See full prescribing information for SYMBICORT.

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

FOR ORAL INHALATION

Initial US Approval: 2006

WARNING: RISK OF ASTHMA-RELATED DEATH (See full prescribing information for complete boxed warning.)

- Long-acting beta₂-adrenergic agonists (LABA) may increase the risk of asthma-related death. A placebo-controlled study with another LABA (salmeterol) showed an increase in asthma-related deaths in patients receiving salmeterol. The finding of an increase in the risk of asthma-related deaths with salmeterol may apply to formoterol. (5.1)
- When treating patients with asthma, prescribe SYMBICORT only for patients not adequately controlled on other asthma-controller medications or whose disease severity clearly warrants initiation of treatment with two maintenance therapies (1.1, 5.1)

RECENT MAJOR CHANGES

Indications and Usage, Maintenance Treatment of Chronic Obstructive Pulmonary Disease (1.2) February 2009

Dosage and Administration, Chronic Obstructive Pulmonary Disease (2.2) February 2009

Warnings and Precautions, Pneumonia (5.5) February 2009

INDICATIONS AND USAGE

SYMBICORT is a combination product containing a corticosteroid and a long-acting beta₂-adrenergic agonist indicated for:

- Maintenance treatment of asthma in patients 12 years of age and older. (1.1)
- Maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema. (1.2)

Important limitations:

- Not indicated for patients whose asthma can be managed by inhaled corticosteroids with occasional use of inhaled short-acting beta₂-agonists. (1.1)
- Not indicated for the relief of acute bronchospasm. (1.1, 1.2)

DOSAGE AND ADMINISTRATION

For oral inhalation only.

- Maintenance treatment of asthma in patients >12 years: 2 inhalations twice daily of SYMBICORT 80/4.5 or 160/4.5. Starting dosage is based on asthma severity. (2.1)
- Maintenance treatment of airflow obstruction in COPD: 2 inhalations of SYMBICORT 160/4.5 twice daily (2.2)

DOSAGE FORMS AND STRENGTHS

Metered-dose inhaler containing a combination of budesonide (80 or 160 mcg) and formoterol (4.5 mcg) as an inhalation aerosol (3)

CONTRAINDICATIONS

- Primary treatment of status asthmaticus or acute episodes of asthma or COPD requiring intensive measures. (4)
- Hypersensitivity to any of the ingredients in SYMBICORT (4)

WARNINGS AND PRECAUTIONS

- Asthma-related death: Long-acting beta₂-adrenergic agonists may increase the risk. Prescribe only for recommended patient populations. (5.1)
- Deterioration of disease and acute episodes: Do not initiate in acutely deteriorating asthma or to treat acute symptoms. (5.2)
- Use with additional long-acting beta₂-agonist: Do not use in combination because of risk of overdose. (5.3)

- Localized infections: *Candida albicans* infection of the mouth and throat may occur. Monitor patients periodically for signs of adverse effects on the oral cavity. Advise patients to rinse the mouth following inhalation. (5.4)
- Pneumonia: Increased risk in patients with COPD. Monitor patients for signs and symptoms of pneumonia and other potential lung infections. (5.5)
- Immunosuppression: Potential worsening of infections (e.g., existing tuberculosis, fungal, bacterial, viral, or parasitic infection; or ocular herpes simplex). Use with caution in patients with these infections. More serious or even fatal course of chickenpox or measles can occur in susceptible patients. (5.6)
- Transferring patients from systemic corticosteroids: Risk of impaired adrenal function when transferring from oral steroids. Taper patients slowly from systemic corticosteroids if transferring to SYMBICORT. (5.7)
- Hypercorticism and adrenal suppression: May occur with very high dosages or at the regular dosage in susceptible individuals. If such changes occur, discontinue SYMBICORT slowly. (5.8)
- Strong cytochrome P450 3A4 inhibitors (e.g., ritonavir): Risk of increased systemic corticosteroid effects. Exercise caution when used with SYMBICORT. (5.9)
- Paradoxical bronchospasm: Discontinue SYMBICORT and institute alternative therapy if paradoxical bronchospasm occurs. (5.10)
- Patients with cardiovascular or central nervous system disorders: Use with caution because of beta-adrenergic stimulation. (5.12)
- Decreases in bone mineral density: Assess bone mineral density initially and periodically thereafter. (5.13)
- Effects on growth: Monitor growth of pediatric patients. (5.14)
- Glaucoma and cataracts: Close monitoring is warranted. (5.15)
- Metabolic effects: Be alert to eosinophilic conditions, hypokalemia, and hyperglycemia. (5.16, 5.18)
- Coexisting conditions: Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis. (5.17)

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥ 3%) are:

- Asthma: nasopharyngitis, headache, upper respiratory tract infection, pharyngolaryngeal pain, sinusitis, influenza, back pain, nasal congestion, stomach discomfort, vomiting, and oral candidiasis. (6.3)
- COPD: nasopharyngitis, oral candidiasis, bronchitis, sinusitis, upper respiratory tract infections. (6.3).

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Strong cytochrome P450 3A4 inhibitors (e.g., ritonavir): Use with caution. May cause increased systemic corticosteroid effects.
- Monoamine oxidase inhibitors and tricyclic antidepressants: Use with extreme caution. May potentiate effect of formoterol on vascular system. (7.2)
- Beta-blockers: Use with caution. May block bronchodilatory effects of beta-agonists and produce severe bronchospasm. (7.3)
- Diuretics: Use with caution. Electrocardiographic changes and/or hypokalemia associated with nonpotassium-sparing diuretics may worsen with concomitant beta-agonists. (7.4)

USE IN SPECIFIC POPULATIONS

Hepatic impairment: Monitor patients for signs of increased drug exposure. (8)

SEE 17 FOR PATIENT COUNSELING INFORMATION AND MEDICATION GUIDE

Revised FEBRUARY, 2009

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- 2.1 Asthma
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†Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: RISK OF ASTHMA RELATED DEATH

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 U.S. 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 and Precautions (5.1)*].

1 INDICATIONS AND USAGE

1.1 Maintenance Treatment of Asthma

SYMBICORT is indicated for the long-term, twice-daily, 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 and Precautions (5.1)*]. One of the active ingredients of SYMBICORT is formoterol, a long-acting beta₂-agonist, 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 2 maintenance therapies.

Important Limitations of Use:

- SYMBICORT is NOT indicated for the relief of acute bronchospasm.
- 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.

1.2 Maintenance Treatment of Chronic Obstructive Pulmonary Disease (COPD)

SYMBICORT 160/4.5 is indicated for the twice daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema. SYMBICORT 160/4.5 is the only approved dosage for the treatment of airflow obstruction in COPD.

Important Limitations of Use: SYMBICORT is not indicated for the relief of acute bronchospasm.

2 DOSAGE AND ADMINISTRATION

SYMBICORT should be administered twice daily every day by the orally inhaled route only. After inhalation, the patient should rinse the mouth with water without swallowing. *[see Patient Counseling Information (17.4)]*

Prime SYMBICORT before using for the first time by releasing two 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 two test sprays into the air away from the face.

More frequent administration or a higher number of inhalations (more than 2 inhalations twice daily) of the prescribed strength of SYMBICORT is not recommended as some patients are more likely to experience adverse effects with higher doses of formoterol. Patients using SYMBICORT should not use additional long-acting beta₂-agonists for any reason. *[See Warnings and Precautions (5.3, 5.12)]*

2.1 Asthma

If asthma symptoms arise in the period between doses, an inhaled, short-acting beta₂-agonist should be taken for immediate relief.

Adult and Adolescent Patients 12 Years of Age and Older: For patients 12 years of age and older, the dosage is 2 inhalations twice daily (morning and evening, approximately 12 hours apart).

The recommended starting dosages for SYMBICORT for patients 12 years of age and older are based upon patients' asthma severity.

For patients who are not currently receiving inhaled corticosteroid therapy, but whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies,

the recommended starting dose is SYMBICORT 80/4.5 or 160/4.5, two inhalations twice daily depending upon asthma severity.

The maximum recommended dosage is SYMBICORT 160/4.5 mg twice daily.

For all patients it is desirable to titrate to the lowest effective strength after adequate asthma stability is achieved.

Improvement in asthma control following inhaled administration of SYMBICORT can occur within 15 minutes of beginning treatment, although maximum benefit may not be achieved for 2 weeks or longer after beginning treatment. Individual patients will experience a variable time to onset and degree of symptom relief.

For patients who do not respond adequately to the starting dose after 1-2 weeks of therapy with SYMBICORT 80/4.5, replacement with SYMBICORT 160/4.5 may provide additional asthma control.

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

2.2 Chronic Obstructive Pulmonary Disease (COPD)

For patients with COPD the recommended dose is SYMBICORT 160/4.5, two inhalations twice daily.

If shortness of breath occurs in the period between doses, an inhaled, short-acting beta₂-agonist should be taken for immediate relief.

3 DOSAGE FORMS AND STRENGTHS

SYMBICORT is available as a metered-dose inhaler containing a combination of budesonide (80 or 160 mcg) and formoterol (4.5 mcg) as an inhalation aerosol in the following two strengths: 80/4.5 and 160/4.5. Each dosage strength contains 60 or 120 actuations per/canister. Each strength of SYMBICORT is supplied with a red plastic actuator with a gray dust cap.

4 CONTRAINDICATIONS

The use of SYMBICORT is contraindicated in the following conditions:

- Primary treatment of status asthmaticus or other acute episodes of asthma or COPD where intensive measures are required.
- Hypersensitivity to any of the ingredients in SYMBICORT.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Asthma-related Death with Long-Acting Beta₂-Adrenergic Agonists

Long-acting beta₂-adrenergic agonists may increase the risk of asthma-related death [*see Warnings and Precautions (5.1)*]. One of the active ingredients of SYMBICORT is formoterol, a long-acting beta₂-agonist, 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 2 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 beta₂-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.

5.2 Deterioration of Disease and Acute Episodes

SYMBICORT should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of asthma or COPD. SYMBICORT has not been studied in patients with acutely deteriorating asthma or COPD. The initiation of SYMBICORT in this setting is not appropriate.

Increasing use of inhaled, short-acting beta₂-agonists is a marker of deteriorating asthma. In this situation, the patient requires immediate re-evaluation with 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 2 inhalations twice daily (morning and evening) of SYMBICORT.

SYMBICORT should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. An inhaled, short-acting beta₂-agonist, not SYMBICORT, should be used to relieve acute symptoms such as shortness of breath. When prescribing SYMBICORT, the physician must also provide the patient with an inhaled, short-acting beta₂-agonist (e.g., albuterol) for treatment of acute symptoms, 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.

5.3 Excessive Use of SYMBICORT and Use with Other Long-Acting Beta₂-Agonists

As with other inhaled drugs containing beta₂-adrenergic agents, SYMBICORT should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medications containing long-acting beta₂-agonists, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using SYMBICORT should not use an additional long-acting beta₂-agonist (e.g., salmeterol, formoterol fumarate, arformoterol tartrate) for any reason, including prevention of exercise-induced bronchospasm (EIB) or the maintenance treatment of asthma or COPD.

5.4 Local Effects

In clinical studies, the development of localized infections of the mouth and pharynx with *Candida albicans* has occurred in patients treated with SYMBICORT. When such an infection develops, it should be treated with appropriate local or systemic (i.e., oral antifungal) therapy while treatment with SYMBICORT continues, but at times therapy with SYMBICORT may need to be interrupted. Patients should rinse the mouth after inhalation of SYMBICORT.

5.5 Pneumonia and Other Lower Respiratory Tract infections

Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of pneumonia and exacerbations frequently overlap. Lower respiratory tract infections, including pneumonia, have been reported following the inhaled administration of corticosteroids.

In a 6 month study of 1,704 patients with COPD, there was a higher incidence of lung infections other than pneumonia (e.g., bronchitis, viral lower respiratory tract infections, etc.) in patients receiving SYMBICORT 160/4.5 (7.6%) than in those receiving SYMBICORT 80/4.5 (3.2%), formoterol 4.5 mcg (4.6%) or placebo (3.3%). Pneumonia did not occur with greater incidence in the SYMBICORT 160/4.5 group (1.1 %) compared with placebo (1.3%). In a 12-month study of 1,964 patients with COPD, there was also a higher incidence of lung infections other than pneumonia in patients receiving SYMBICORT 160/4.5 (8.1%) than in those receiving SYMBICORT 80/4.5 (6.9%), formoterol 4.5 mcg (7.1%) or placebo (6.2%). Similar to the 6 month study, pneumonia did not occur with greater incidence in the SYMBICORT 160/4.5 group (4.0%) compared with placebo (5.0%).

5.6 Immunosuppression

Patients who are on drugs that suppress the immune system are more susceptible to infection than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in susceptible children or adults using corticosteroids. In such children or adults who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chicken pox develops, treatment with antiviral agents may be considered. The immune responsiveness to varicella vaccine was evaluated in pediatric patients with asthma ages 12 months to 8 years with budesonide inhalation suspension.

An open-label, nonrandomized 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 noncorticosteroid 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 noncorticosteroid asthma therapy (90%). No patient treated with budesonide inhalation suspension developed chicken pox as a result of vaccination.

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

5.7 Transferring Patients From Systemic Corticosteroid Therapy

Particular care is needed for patients who have been transferred from systemically active corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function.

Patients who have been previously maintained on 20 mg or more per day of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although SYMBICORT 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

warning card indicating that they may need supplementary systemic corticosteroids during periods of stress or a severe asthma attack.

Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to SYMBICORT. Prednisone reduction can be accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during therapy with SYMBICORT. Lung function (mean forced expiratory volume in 1 second [FEV₁] or morning peak expiratory flow [PEF], beta-agonist use, and asthma symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition to monitoring asthma signs and symptoms, patients should be observed for signs and symptoms of adrenal insufficiency, such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension.

Transfer of patients from systemic corticosteroid therapy to inhaled corticosteroids or SYMBICORT may unmask conditions previously suppressed by the systemic corticosteroid therapy (e.g., rhinitis, conjunctivitis, eczema, arthritis, eosinophilic conditions). Some patients may experience symptoms of systemically active corticosteroid withdrawal (e.g., joint and/or muscular pain, lassitude, depression) despite maintenance or even improvement of respiratory function.

5.8 Hypercorticism and Adrenal Suppression

Budesonide, a component of SYMBICORT, will often help control 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 at higher doses, the beneficial effects of SYMBICORT in minimizing HPA dysfunction may be expected only when recommended dosages are not exceeded and individual patients are titrated to the lowest effective dose.

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

It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression (including adrenal crisis) may appear in a small number of patients, particularly when budesonide is administered at higher than recommended

doses over prolonged periods of time. If such effects occur, the dosage of SYMBICORT should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids and for management of asthma symptoms.

5.9 Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors

Caution should be exercised when considering the coadministration of SYMBICORT with ketoconazole, and other known strong CYP3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) because adverse effects related to increased systemic exposure to budesonide may occur [*see Drug Interactions (7.1), Clinical Pharmacology (12.3)*]

5.10 Paradoxical Bronchospasm and Upper Airway Symptoms

As with other inhaled medications, SYMBICORT can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with SYMBICORT, it should be treated immediately with an inhaled, short-acting bronchodilator, SYMBICORT should be discontinued immediately, and alternative therapy should be instituted.

5.11 Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions may occur after administration of SYMBICORT, as demonstrated by cases of urticaria, angioedema, rash, and bronchospasm.

5.12 Cardiovascular and Central Nervous System Effects

Excessive beta-adrenergic stimulation has been associated with seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, palpitation, nausea, dizziness, fatigue, malaise, and insomnia [*see Overdosage (10)*]. Therefore, 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, can 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 formoterol at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been

reported to produce 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. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

5.13 Reduction in Bone Mineral Density

Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing inhaled corticosteroids. The clinical significance of small changes in BMD with regard to long-term consequences such as fracture is unknown. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, post menopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care. Since patients with COPD often have multiple risk factors for reduced BMD, assessment of BMD is recommended prior to initiating SYMBICORT and periodically thereafter. If significant reductions in BMD are seen and SYMBICORT is still considered medically important for that patient's COPD therapy, use of medication to treat or prevent osteoporosis should be strongly considered.

Effects of treatment with SYMBICORT 160/4.5, SYMBICORT 80/4.5, formoterol 4.5, or placebo on BMD was evaluated in a subset of 326 patients (females and males 41 to 88 years of age) with COPD in the 12-month study. BMD evaluations of the hip and lumbar spine regions were conducted at baseline and 52 weeks using dual energy x-ray absorptiometry (DEXA) scans. Mean changes in BMD from baseline to end of treatment were small (mean changes ranged from -0.01 - 0.01 g/cm²). ANCOVA results for total spine and total hip BMD based on the end of treatment time point showed that all geometric LS Mean ratios for the pairwise treatment group comparisons were dose to 1, indicating that overall, bone mineral density for total hip and total spine regions for the 12 month time point were stable over the entire treatment period.

5.14 Effect on Growth

Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to pediatric patients. Monitor the growth of pediatric patients receiving SYMBICORT routinely (e.g., via stadiometry). To minimize the systemic effects of orally inhaled corticosteroids, including SYMBICORT, titrate each patient's dose to the

lowest dosage that effectively controls his/her symptoms. [See *Dosage and Administration (2.1)*, *Use in Specific Populations (8.4)*.]

5.15 Glaucoma and Cataracts

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

Effects of treatment with SYMBICORT 160/4.5, SYMBICORT 80/4.5, formoterol 4.5, or placebo on development of cataracts or glaucoma were evaluated in a subset of 461 patients with COPD in the 12-month study. Ophthalmic examinations were conducted at baseline, 24 weeks, and 52 weeks. There were 26 subjects (6%) with an increase in posterior subcapsular score from baseline to maximum value (>0.7) during the randomized treatment period. Changes in posterior subcapsular scores of >0.7 from baseline to treatment maximum occurred in 11 patients (9.0%) in the SYMBICORT 160/4.5 group, 4 patients (3.8%) in the SYMBICORT 80/4.5 group, 5 patients (4.2%) in the formoterol group, and 6 patients (5.2%) in the placebo group.

5.16 Eosinophilic Conditions and Churg-Strauss Syndrome

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

5.17 Coexisting Conditions

SYMBICORT, like all medications containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the related beta₂-adrenoceptor agonist

albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

5.18 Hypokalemia and Hyperglycemia

Beta-adrenergic agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects [see *Clinical Pharmacology* (12.2)]. The decrease in serum potassium is usually transient, not requiring supplementation. Clinically significant changes in blood glucose and/or serum potassium were seen infrequently during clinical studies with SYMBICORT at recommended doses.

6 ADVERSE REACTIONS

Long-acting beta₂-adrenergic agonists may increase the risk of asthma-related death. One of the active ingredients of SYMBICORT is formoterol, a long-acting beta₂-agonist. 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. [see *Warnings and Precautions* (5.1)].

Systemic and inhaled corticosteroid use may result in the following:

- Candida albicans infection [see *Warnings and Precautions* (5.4)]
- Pneumonia or lower respiratory tract infections in patients with COPD [see *Warnings and Precautions* (5.5)]
- Immunosuppression [see *Warnings and Precautions* (5.6)]
- Hypercorticism and adrenal suppression [see *Warnings and Precautions* (5.8)]
- Growth effects in pediatric patients [see *Warnings and Precautions* (5.14)]
- Glaucoma and cataracts [see *Warnings and Precautions* (5.15)]

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.1 Clinical Trials Experience in Asthma Patients 12 years and older

The overall safety data in adults and adolescents are based upon 10 active- and placebo-controlled clinical trials in which 3393 patients ages 12 years and older (2052 females and 1341 males) with asthma of varying severity were treated with SYMBICORT 80/4.5 or 160/4.5 mcg taken two inhalations once or twice daily for 12 to 52 weeks. In these trials, the patients on SYMBICORT had a mean age of 38 years and were predominantly Caucasian (82%).

The incidence of common adverse events in Table 1 below is based upon pooled data from three 12-week, double-blind, placebo-controlled clinical studies in which 401 adult and adolescent patients (148 males and 253 females) age 12 years and older were treated with two inhalations of SYMBICORT 80/4.5 or SYMBICORT 160/4.5 twice daily. The SYMBICORT group was composed of mostly Caucasian (84%) patients with a mean age of 38 years, and a mean percent predicted FEV₁ at baseline of 76 and 68 for the 80/4.5 mcg and 160/4.5 mcg treatment groups, respectively. Control arms for comparison included two inhalations of budesonide HFA metered dose inhaler (MDI) 80 or 160 mcg, formoterol dry powder inhaler (DPI) 4.5 mcg, or placebo (MDI and DPI) twice daily. Table 1 includes all adverse events that occurred at an incidence of $\geq 3\%$ in any one SYMBICORT group and more commonly than in the placebo group with twice-daily dosing. In considering these data, the increased average duration of patient exposure for SYMBICORT patients should be taken into account, as incidences are not adjusted for an imbalance of treatment duration.

Table 1 Adverse-reactions occurring at an incidence of $\geq 3\%$ and more commonly than placebo in the SYMBICORT groups: pooled data from three 12-week, double-blind, placebo-controlled clinical asthma trials in patients 12 years and older

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

*All treatments were administered as two inhalations twice daily.

Long-term safety - asthma clinical trials in patients 12 years and older

Long-term safety studies in adolescent and adult patients 12 years of age and older, treated for up to 1 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 1 year in safety measures including chemistry, hematology, ECG, Holter monitor, and HPA-axis assessments.

6.2 Clinical Trials Experience in Chronic Obstructive Pulmonary Disease

The incidence of common adverse events in Table 2 below is based upon pooled data from two double-blind, placebo-controlled clinical studies (6 and 12 months in duration) in which 771 adult COPD patients (496 males and 275 females) 40 years of age and older were treated with SYMBICORT 160/4.5, two inhalations twice daily. Of these patients 651

were treated for 6 months and 366 were treated for 12 months. The SYMBICORT group was composed of mostly Caucasian (93%) patients with a mean age of 63 years, and a mean percent predicted FEV₁ at baseline of 33%. Control arms for comparison included two inhalations of budesonide HFA (MDI) 160 mcg, formoterol (DPI) 4.5 mcg or placebo (MDI and DPI) twice daily. Table 2 includes all adverse events that occurred at an incidence of $\geq 3\%$ in the SYMBICORT group and more commonly than in the placebo group. In considering these data, the increased average duration of patient exposure to SYMBICORT should be taken into account, as incidences are not adjusted for an imbalance of treatment duration.

Table 2 Adverse reactions occurring at an incidence of $\geq 3\%$ and more commonly than placebo in the SYMBICORT group: pooled data from two double-blind, placebo-controlled clinical COPD trials

Treatment*	SYMBICORT	Budesonide	Formoterol	Placebo
	160/4.5 mcg	160 mcg	4.5 mcg	
	N = 771	N = 275	N = 779	N = 781
Adverse Event	%	%	%	%
Nasopharyngitis	7.3	3.3	5.8	4.9
Oral candidiasis	6.0	4.4	1.2	1.8
Bronchitis	5.4	4.7	4.5	3.5
Sinusitis	3.5	1.5	3.1	1.8
Upper respiratory tract infection viral	3.5	1.8	3.6	2.7
Average Duration of Exposure (days)	255.2	157.1	240.3	223.7

* All treatments were administered as two inhalations twice daily.

Lung infections other than pneumonia (mostly bronchitis) occurred in a greater percentage of subjects treated with SYMBICORT 160/4.5 compared with placebo (7.9% vs. 5.1%, respectively). There were no clinically important or unexpected patterns of abnormalities observed for up to 1 year in chemistry, haematology, ECG, ECG (Holter) monitoring, HPA-axis, bone mineral density and ophthalmology assessments.

6.3 Postmarketing Experience

The following adverse reactions have been reported during post-approval use of SYMBICORT. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or

establish a causal relationship to drug exposure. Some of these adverse reactions may also have been observed in clinical studies with SYMBICORT.

Cardiac disorders: angina pectoris, tachycardia, atrial and ventricular tachyarrhythmias, atrial fibrillation, extrasystoles, palpitations

Endocrine disorders: hypercorticism, growth velocity reduction in pediatric patients

Eye disorders: cataract, glaucoma, increased intraocular pressure

Gastrointestinal disorders: oropharyngeal candidiasis, nausea

Immune system disorders: immediate and delayed hypersensitivity reactions, such as anaphylactic reaction, angioedema, bronchospasm, urticaria, exanthema, dermatitis, pruritus

Metabolic and nutrition disorders: hyperglycemia, hypokalemia

Musculoskeletal, connective tissue, and bone disorders: muscle cramps

Nervous system disorders: tremor, dizziness

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

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

Skin and subcutaneous tissue disorders: skin bruising

Vascular disorders: hypotension, hypertension

7 DRUG INTERACTIONS

In clinical studies, concurrent administration of SYMBICORT and other drugs, such as short-acting beta₂-agonists, intranasal corticosteroids, and antihistamines/decongestants has not resulted in an increased frequency of adverse reactions. No formal drug interaction studies have been performed with SYMBICORT.

7.1 Inhibitors of Cytochrome P4503A4

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 strong inhibitor of CYP3A4, the mean plasma concentration of orally administered budesonide increased. Concomitant administration of CYP3A4 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 strong CYP3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir,

saquinavir, telithromycin) [*see Warnings and Precautions (5.9)*].

7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

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

7.3 Beta-Adrenergic Receptor Blocking Agents

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

7.4 Diuretics

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C.

There are no adequate and well-controlled studies of SYMBICORT in pregnant women. SYMBICORT was teratogenic and embryocidal in rats. Budesonide alone was teratogenic and embryocidal in rats and rabbits, but not in humans at therapeutic doses. Formoterol fumarate alone was teratogenic in rats and rabbits. Formoterol fumarate was also embryocidal, increased pup loss at birth and during lactation, and decreased pup weight in rats. SYMBICORT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

SYMBICORT

In a reproduction study in rats, budesonide combined with formoterol fumarate by the inhalation route at doses approximately 1/7 and 1/3, respectively, the maximum recommended human daily inhalation dose on a mg/m² basis produced umbilical hernia. No teratogenic or embryocidal effects were detected with budesonide combined with formoterol fumarate by the inhalation route at doses approximately 1/32 and 1/16, respectively, the maximum recommended human daily inhalation dose on a mg/m² basis.

Budesonide

Studies of pregnant women 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%).

Budesonide produced fetal loss, decreased pup weight, and skeletal abnormalities at subcutaneous doses in rabbits less than the maximum recommended human daily inhalation dose on a mcg/m² basis and in rats at doses 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 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.

Formoterol

Formoterol fumarate has been shown to be teratogenic, embryocidal, to increase pup loss at birth and during lactation, and to decrease pup weights in rats when given at oral doses 1400 times and greater the maximum recommended human daily inhalation dose on a mcg/m² basis. Umbilical hernia was observed in rat fetuses at oral doses 1400 times and greater the maximum recommended human daily inhalation dose on a mcg/m² basis. Brachygnathia was observed in rat fetuses at an oral dose 7000 times the maximum recommended human daily inhalation dose on a mcg/m² basis. Pregnancy was prolonged at an oral dose 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 500 times the maximum recommended human daily inhalation dose on a mcg/m² basis.

Subcapsular cysts on the liver were observed in rabbit fetuses at an oral dose 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 3200 times the maximum recommended human daily inhalation dose on a mcg/m² basis.

Nonteratogenic Effects

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

8.2 Labor and Delivery

There are no well-controlled human studies that have investigated the 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.

8.3 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.

Budesonide, like other corticosteroids, is secreted in human milk. Data with budesonide delivered via dry powder inhaler indicates that the total daily oral dose of budesonide available in breast milk to the infant is approximately 0.3% to 1% of the dose inhaled by the mother [*see Clinical Pharmacology, Pharmacokinetics (12.3)*]. For SYMBICORT, the dose of budesonide available to the infant in breast milk, as a percentage of the maternal dose, would be expected to be similar.

In reproductive studies in rats, formoterol was excreted in the milk. It is not known whether formoterol is excreted in human milk.

8.4 Pediatric Use

Safety and effectiveness of SYMBICORT in asthma 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 [*see Clinical Studies (14.1)*]. 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 safety and effectiveness of SYMBICORT in asthma patients 6 to <12 years of age has not been established.

Overall 1447 asthma 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 4 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 (2)*].

8.5 Geriatric Use

Of the total number of patients in asthma 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.

In the COPD studies of 6 to 12 months duration, 349 patients treated with SYMBICORT 160/4.5 twice daily were 65 years old and above and of those, 73 patients were 75 years of age and older. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly 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.

8.6 Hepatic Impairment

Formal pharmacokinetic studies using SYMBICORT have not been conducted in patients with hepatic impairment. However, since both budesonide and formoterol fumarate are predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of budesonide and formoterol fumarate in plasma. Therefore, patients with hepatic disease should be closely monitored.

8.7 Renal Impairment

Formal pharmacokinetic studies using SYMBICORT have not been conducted in patients with renal impairment.

10 OVERDOSAGE

SYMBICORT

SYMBICORT contains both budesonide and formoterol; therefore, the risks associated with overdosage for the individual components described below apply to SYMBICORT. In pharmacokinetic studies, single doses of 960/54 mcg (12 actuations of SYMBICORT 80/4.5) and 1280/36 mcg (8 actuations of 160/4.5), were administered to patients with COPD. 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. In a long-term active-controlled safety study in asthma patients, SYMBICORT 160/4.5 was administered for up to 12 months at doses up to twice the highest recommended daily dose. There were no clinically significant adverse reactions observed in any of these studies.

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 doses 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 doses 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 Warnings and Precautions (5)*]. 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: seizures, angina, hypertension, hypotension, tachycardia, atrial and ventricular tachyarrhythmias, nervousness, headache, tremor, palpitations, muscle cramps, nausea, dizziness, sleep disturbances, metabolic acidosis, hyperglycemia, hypokalemia. As with all sympathomimetic medications, cardiac arrest and even death may be associated with abuse of formoterol. No clinically significant adverse reactions were seen when formoterol was delivered to adult patients with acute bronchoconstriction at a dose of 90 mcg/day over 3 hours or to stable asthmatics 3 times a day at a total dose of 54 mcg/day for 3 days.

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/m² 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/m² 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/m² basis). Maximum nonlethal 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/m² basis).

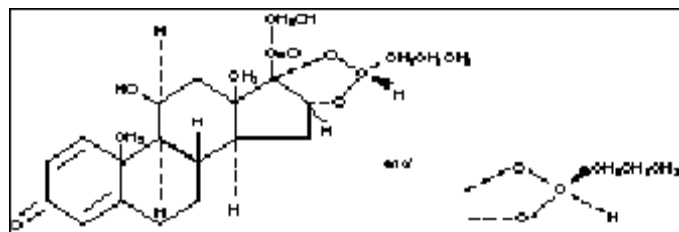
11 DESCRIPTION

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

Each 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 either 60 or 120 actuations [*see Dosage Forms and Strengths (3) and How Supplied/Storage and Handling (16)*]. 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.

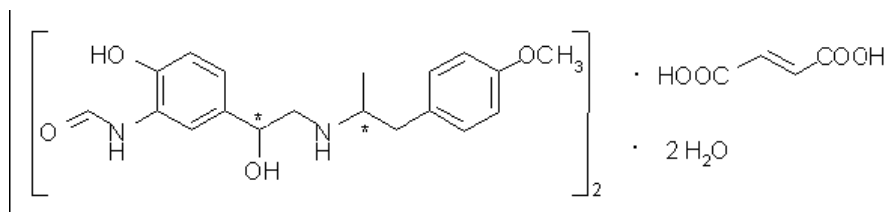
SYMBICORT should be primed before using for the first time by releasing two test sprays into the air away from the face, shaking well for 5 seconds before each spray. In cases where the inhaler has not been used for more than 7 days or when it has been dropped, prime the inhaler again by shaking well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

One active component of SYMBICORT is budesonide, a corticosteroid designated chemically as (RS)-11 β , 16 α , 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 C₂₅H₃₄O₆ and its molecular weight is 430.5. Its structural formula is:



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

The other active component of SYMBICORT is formoterol fumarate dihydrate, a selective β_2 -agonist designated chemically as (R*,R*)-(\pm)-N-[2-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]formamide, (E)-2-butendioate(2:1), dihydrate. The empirical formula of formoterol is C₂₂H₂₆N₂O₅ and its molecular weight is 398.4. Its structural formula is:



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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

SYMBICORT

SYMBICORT contains both budesonide and formoterol; therefore, the mechanisms of action described below for the individual components apply to SYMBICORT. These drugs represent two classes of medications (a synthetic corticosteroid and a long-acting selective beta₂-adrenoceptor agonist) that have different effects on clinical, physiological, and inflammatory indices of Chronic Obstructive Pulmonary Disease (COPD) and 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 COPD and asthma. Corticosteroids have a wide range of inhibitory activities against multiple cell types (eg, mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (eg, 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 COPD and 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 beta₂-adrenergic agonist (beta₂-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 beta₂-receptors than at beta₁-receptors. The *in vitro* binding selectivity to beta₂- over beta₁-adrenoceptors is higher for formoterol than for albuterol (5 times), whereas salmeterol has a higher (3 times) beta₂-selectivity ratio than formoterol.

Although beta₂-receptors are the predominant adrenergic receptors in bronchial smooth muscle and beta₁-receptors are the predominant receptors in the heart, there are also beta₂-receptors in the human heart comprising 10% to 50% of the total beta-adrenergic receptors. The precise function of these receptors has not been established, but they raise the possibility that even highly selective beta₂-agonists may have cardiac effects.

The pharmacologic effects of beta₂-adrenoceptor agonist drugs, including formoterol, are at least in part attributable to stimulation of intracellular adenylyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3', 5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

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

12.2 Pharmacodynamics

Asthma

Cardiovascular effects: In a single-dose cross-over study involving 201 patients with persistent asthma, single-dose treatments of 4.5, 9, and 18 mcg of formoterol in combination with 320 mcg of budesonide delivered via SYMBICORT were compared to budesonide 320 mcg alone. Dose-ordered improvements in FEV₁ were demonstrated when compared with budesonide. ECGs and blood samples for glucose and potassium were obtained postdose. For SYMBICORT, small mean increases in serum glucose and decreases in serum potassium (+0.44 mmol/L and -0.18 mmol/L at the highest dose, respectively) were observed with increasing doses of formoterol, compared to budesonide. In ECGs, SYMBICORT produced small dose-related mean increases in heart rate

(approximately 3 bpm at the highest dose), and QTc intervals (3-6 msec) compared to budesonide alone. No subject had a QT or QTc value ≥ 500 msec.

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

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

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

Chronic Obstructive Pulmonary Disease:

Cardiovascular effects: In 2 clinical studies, 6 months and 12 months in duration including 3668 COPD patients, no clinically important differences were seen in pulse rate, blood pressure, potassium, and glucose between SYMBICORT, the individual components of SYMBICORT, and placebo. [see *Clinical Studies (14.2)*].

ECGs recorded at multiple clinic visits on treatment in both studies showed no clinically important differences for heart rate, PR interval, QRS duration, heart rate, signs of cardiac ischemia or arrhythmias between SYMBICORT 160/4.5 the monoproducts and placebo, all administered as two inhalations twice daily. Based on ECGs, 6 patients treated with SYMBICORT 160/4.5, 6 patients treated with formoterol 4.5, and 6 patients in the placebo group experienced atrial fibrillation or flutter that was not present at baseline. There were no cases of nonsustained ventricular tachycardia in the SYMBICORT 160/4.5, formoterol 4.5, or placebo groups.

In the 12-month study, 520 patients had evaluable continuous 24-hour ECG (Holter) monitoring prior to the first dose and after approximately 1 and 4 months on treatment. No clinically important differences in ventricular or supraventricular arrhythmias, ventricular or supraventricular ectopic beats, or heart rate were observed among the groups treated with SYMBICORT 160/4.5, formoterol or placebo taken as two inhalations twice daily. Based on ECG (Holter) monitoring, one patient on SYMBICORT 160/4.5, no patients on formoterol 4.5, and three patients in the placebo group experienced atrial fibrillation or flutter that was not present at baseline.

HPA axis effects: Twenty-four hour urinary cortisol measurements were collected in a pooled subset (n=616) of patients from two COPD studies. The data indicated approximately 30% lower mean 24-hour urinary free cortisol values following chronic administration (> 6 months) of SYMBICORT relative to placebo. SYMBICORT appeared to exhibit comparable cortisol suppression to budesonide 160 mcg alone or coadministration of budesonide 160 mcg and formoterol 4.5 mcg. For patients treated with SYMBICORT or placebo for up to 12 months, the percentage of patients who shifted from normal to low for this measure were generally comparable.

Other Budesonide Products

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 SYMBICORT compared with inhaled budesonide administered at the same delivered dose via a dry powder inhaler [see *Clinical Pharmacology, Pharmacokinetics, SYMBICORT (12.3)*]. Therefore, the systemic effects (HPA axis and growth) of budesonide delivered from SYMBICORT would be expected to be no greater than what is reported for inhaled budesonide when administered at comparable doses via the dry powder inhaler [see *Use in Specific Populations, Pediatric Use (8.4)*].

HPA Axis Effects: 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.

Other Formoterol Products

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 beta₂-adrenergic agonist drugs, can produce dose-related cardiovascular effects and effects on blood glucose and/or serum potassium [see *Warnings and Precautions* (5)]. For SYMBICORT, these effects are detailed in the *Clinical Pharmacology, Pharmacodynamics, SYMBICORT* (12.2) section.

Use of long-acting beta₂-adrenergic agonist drugs can result in tolerance to bronchoprotective and bronchodilatory effects.

Rebound bronchial hyperresponsiveness after cessation of chronic long-acting beta-agonist therapy has not been observed.

12.3 Pharmacokinetics SYMBICORT

Absorption: Budesonide: Healthy Subjects: 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.

Following administration of SYMBICORT 160/4.5 mcg, two or four inhalations twice daily) for 5 days in healthy subjects, plasma concentration of budesonide generally increased in proportion to dose. The accumulation index for the group that received two inhalations twice daily was 1.32 for budesonide.

Asthma Patients: 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 budesonide plasma concentration of 4.5 nmol/L occurred at 20 minutes following dosing. This study 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.

In a repeat dose study, the highest recommended dose of SYMBICORT (160/4.5 mcg, two inhalations twice daily) was administered to patients with moderate asthma and healthy subjects for 1 week. Peak budesonide plasma concentration of 1.2 nmol/L occurred at 21 minutes in asthma patients. Peak budesonide plasma concentration was 27% lower in asthma patients compared to that in healthy subjects. However, the total systemic exposure of budesonide was comparable to that in asthma patients.

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 single and repeated dosing of inhaled budesonide.

COPD Patients: In a single-dose study, 12 inhalations of SYMBICORT 80/4.5 mcg (total dose 960/54 mcg) were administered to patients with COPD. Mean budesonide peak plasma concentration of 3.3 nmol/L occurred at 30 minutes following dosing. Budesonide systemic exposure was comparable between SYMBICORT pMDI and coadministration of budesonide via a metered-dose inhaler and formoterol via a dry powder inhaler (budesonide 960 mcg and formoterol 54 mcg). In the same study, an open-label group of moderate asthma patients also received the same higher dose of SYMBICORT. For budesonide, COPD patients exhibited 12% greater AUC and 10% lower C_{\max} compared to asthma patients.

In the 6 month pivotal clinical study, steady-state pharmacokinetic data of budesonide was obtained in a subset of COPD patients with treatment arms of SYMBICORT pMDI 160/4.5 mcg, SYMBICORT pMDI 80/4.5 mcg, budesonide 160 mcg, budesonide 160 mcg and formoterol 4.5 mcg given together, all administered as two inhalations twice daily. Budesonide systemic exposure (AUC and C_{\max}) increased proportionally with doses from 80 mcg to 160 mcg and was generally similar between the 3 treatment groups receiving the same dose of budesonide (SYMBICORT pMDI 160/4.5 mcg, budesonide 160 mcg, budesonide 160 mcg and formoterol 4.5 mcg administered together).

Formoterol:

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.

Healthy Subjects: Following administration of SYMBICORT (160/4.5 mcg, two or four inhalations twice daily) for 5 days in healthy subjects, plasma concentration of formoterol generally increased in proportion to dose. The accumulation index for the group that received two inhalations twice daily was 1.77 for formoterol.

Asthma patients: 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 concentration 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.

In a repeat dose study, the highest recommended dose of SYMBICORT (160/4.5 mcg, two inhalations twice daily) was administered to patients with moderate asthma and healthy subjects for 1 week. Peak formoterol plasma concentration of 28 pmol/L occurred at 10 minutes in asthma patients. Peak formoterol plasma concentration was about 42% lower in asthma patients compared to that in healthy subjects. However, the total systemic exposure of formoterol was comparable to that in asthma patients.

COPD patients: Following single-dose administration of 12 inhalations of SYMBICORT 80/4.5, mean peak formoterol plasma concentration of 167 pmol/L was rapidly achieved at 15 minutes after dosing. Formoterol exposure was slightly greater (~16-18%) from SYMBICORT pMDI compared to coadministration of budesonide via a metered-dose inhaler and formoterol via a dry powder inhaler (total dose of budesonide 960 mcg and formoterol 54 mcg). In the same study, an open label group of moderate asthma patients received the same dose of SYMBICORT. COPD patients exhibited 12-15% greater AUC and C_{max} for formoterol compared to asthma patients.

In the 6 month pivotal clinical study, steady-state pharmacokinetic data of formoterol was obtained in a subset of COPD patients with treatment arms of SYMBICORT pMDI 160/4.5 mcg, SYMBICORT pMDI 80/4.5 mcg, formoterol 4.5 mcg, budesonide 160 mcg and formoterol 4.5 mcg given together, all administered as two inhalations twice daily. The systemic exposure of formoterol as evidenced by AUC, was about 30% and 16% higher from SYMBICORT pMDI compared to formoterol alone treatment arm and

coadministration of individual components of budesonide and formoterol treatment arm, respectively.

Distribution: *Budesonide:* 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.

Formoterol: 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: *Budesonide:* *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 16 α -hydroxyprednisolone and 6 β -hydroxybudesonide. The corticosteroid activity of each of these two metabolites was less than 1% of that of the parent compound. No qualitative differences between the *in vitro* and *in vivo* metabolic patterns were detected. Negligible metabolic inactivation was observed in human lung and serum preparations.

Formoterol: 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.

Elimination: *Budesonide:* 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: The excretion of formoterol was studied in four 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.

Special Populations

Geriatric

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

Pediatric

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

Gender/Race

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

Nursing Mothers

The disposition of budesonide when delivered by inhalation from a dry powder inhaler at doses of 200 or 400 mcg twice daily for at least 3 months was studied in eight lactating women with asthma from 1 to 6 months postpartum. Systemic exposure to budesonide in these women appears to be comparable to that in non-lactating women with asthma from other studies. Breast milk obtained over eight hours post-dose revealed that the maximum concentration of budesonide for the 400 and 800 mcg total daily doses was 0.39 and 0.78 nmol/L, respectively, and occurred within 45 minutes after dosing. The estimated oral daily dose of budesonide from breast milk to the infant is approximately 0.007 and 0.014 mcg/kg/day for the two dose regimens used in this study, which represents approximately 0.3% to 1% of the dose

inhaled by the mother. Budesonide levels in plasma samples obtained from five infants at about 90 minutes after breastfeeding (and about 140 minutes after drug administration to the mother) were below quantifiable levels (<0.02 nmol/L in four infants and <0.04 nmol/L in one infant) [see *Use in Specific Populations, Nursing Mothers* (8.3)].

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 because 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.

Inhibitors of cytochrome P450 enzymes

Ketoconazole: Ketoconazole, a strong inhibitor of cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4), the main metabolic enzyme for corticosteroids, increased plasma levels of orally ingested budesonide.

Cimetidine: At recommended doses, cimetidine, a non-specific inhibitor of CYP enzymes, had a slight but clinically insignificant effect on the pharmacokinetics of oral budesonide.

Specific drug-drug interaction studies with formoterol have not been performed.

13 NONCLINICAL TOXICOLOGY

13.1 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 2-year study in Sprague-Dawley rats, budesonide caused a statistically significant increase in the incidence of gliomas in male rats at an oral dose of 50 mcg/kg (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 2-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 inhalation dose on a mcg/m² basis). However, it caused a decrease in prenatal viability and viability in the pups at birth and during lactation, along with a decrease in maternal body-weight gain, at subcutaneous doses of 20 mcg/kg and above (less than the maximum recommended human daily inhalation dose on a mcg/m² basis). No such effects were noted at 5 mcg/kg (less than the maximum recommended human daily inhalation dose on a mcg/m² basis).

Formoterol

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

In a 24-month carcinogenicity study in CD-1 mice, formoterol at oral doses of 0.1 mg/kg and above (approximately 20 times

the maximum recommended human daily inhalation dose on a mcg/m² basis) caused a dose-related increase in the incidence of uterine leiomyomas.

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

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

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

A reduction in fertility and/or reproductive performance was identified in male rats treated with formoterol at an oral dose of 15 mg/kg (approximately 7000 times the maximum recommended human daily inhalation dose on a mcg/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 spermatid 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).

13.2 Animal Toxicology and/or Pharmacology

Preclinical: 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.

Reproductive Toxicology Studies: SYMBICORT

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 inhalation 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 inhalation 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 inhalation dose on a mcg/m² basis).

Budesonide

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).

Formoterol

Formoterol fumarate has been shown to be teratogenic, embryocidal, to increase pup loss at birth and during lactation, and to decrease 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 in 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 in 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).

14 CLINICAL STUDIES

14.1 Asthma

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 end points 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 two 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 two inhalations twice daily. The study included a 2-week run-in period with budesonide 80 mcg, two 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 coprimary efficacy end points were 12-hour-average postdose

FEV₁ at week 2, and predose FEV₁ averaged over the course of the study. The study also required that patients who satisfied a predefined asthma worsening criterion be withdrawn. The predefined 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 3.

Table 3 **The number and percentage of patients withdrawing due to or meeting predefined criteria for worsening asthma (Study 1)**

	SYMBICORT 160/4.5 mcg n=124	Budesonide 160 mcg plus Formoterol 4.5 mcg n=115	Budesonide 160 mcg n=109	Formoterol 4.5 mcg n=123	Placebo n=125
Patients withdrawn due to predefined asthma event*	13 (10.5)	13 (11.3)	22 (20.2)	44 (35.8)	62 (49.6)
Patients with a predefined asthma event* [†]	37 (29.8)	24 (20.9)	48 (44.0)	68 (55.3)	84 (67.2)
Decrease in FEV ₁	4 (3.2)	8 (7.0)	7 (6.4)	15 (12.2)	14 (11.2)
Rescue medication use	2 (1.6)	0	3 (2.8)	3 (2.4)	7 (5.6)
Decrease in AM PEF	2 (1.6)	5 (4.3)	5 (4.6)	17 (13.8)	15 (12.0)
Nighttime awakenings [‡]	24 (19.4)	11 (9.6)	29 (26.6)	32 (26.0)	49 (39.2)
Clinical exacerbation	7 (5.6)	6 (5.2)	5 (4.6)	17 (3.8)	16 (12.8)

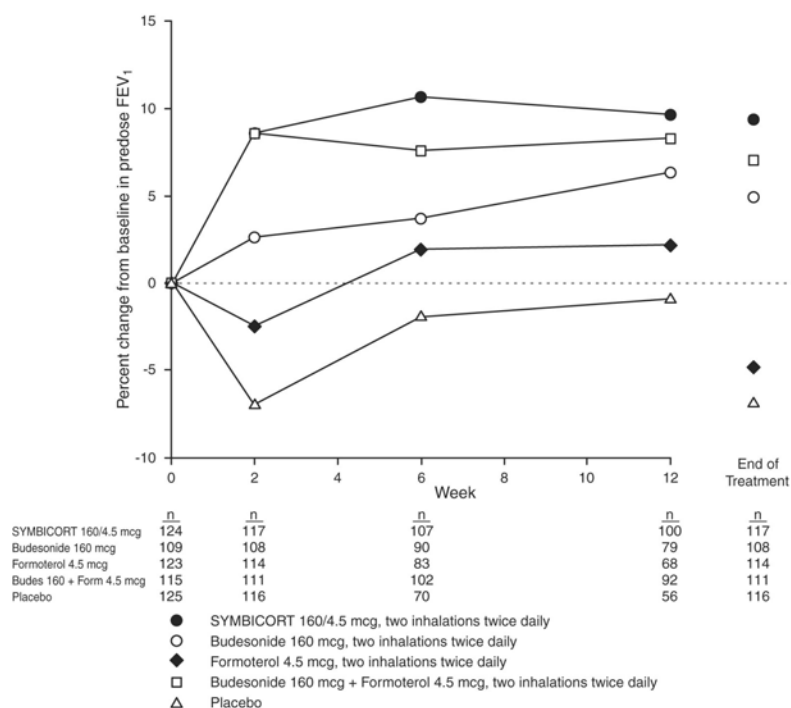
*These criteria were assessed on a daily basis irrespective of the timing of the clinic visit, with the exception of FEV₁, which was assessed at each clinic visit.

*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 SYMBICORT 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 two 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 4.

Table 4 **Mean values for selected secondary efficacy variables
(Study 1)**

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

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

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

>0.5 points in change from baseline in overall AQLQ score (difference in AQLQ score of 0.70 [95% CI 0.47, 0.93], compared to placebo).

Study 2: Clinical Study with SYMBICORT 80/4.5

This 12-week study was similar in design to Study 1, and included 480 patients 12 years of age and older. This study compared SYMBICORT 80/4.5 mcg, budesonide 80 mcg, formoterol 4.5 mcg, and placebo; each administered as two 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 end points 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 5. The method of assessment and criteria used were identical to that in Study 1.

Table 5 **The number and percentage of patients withdrawing due to or meeting predefined criteria for worsening asthma (Study 2)**

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

Table 5 **The number and percentage of patients withdrawing due to or meeting predefined criteria for worsening asthma (Study 2)**

	SYMBICORT 80/4.5 mcg (n=123)	Budesonide 80 mcg (n=121)	Formoterol 4.5 mcg (n=114)	Placebo (n=122)
Clinical exacerbation	1 (0.8)	3 (2.5)	5 (4.4)	20 (16.4)

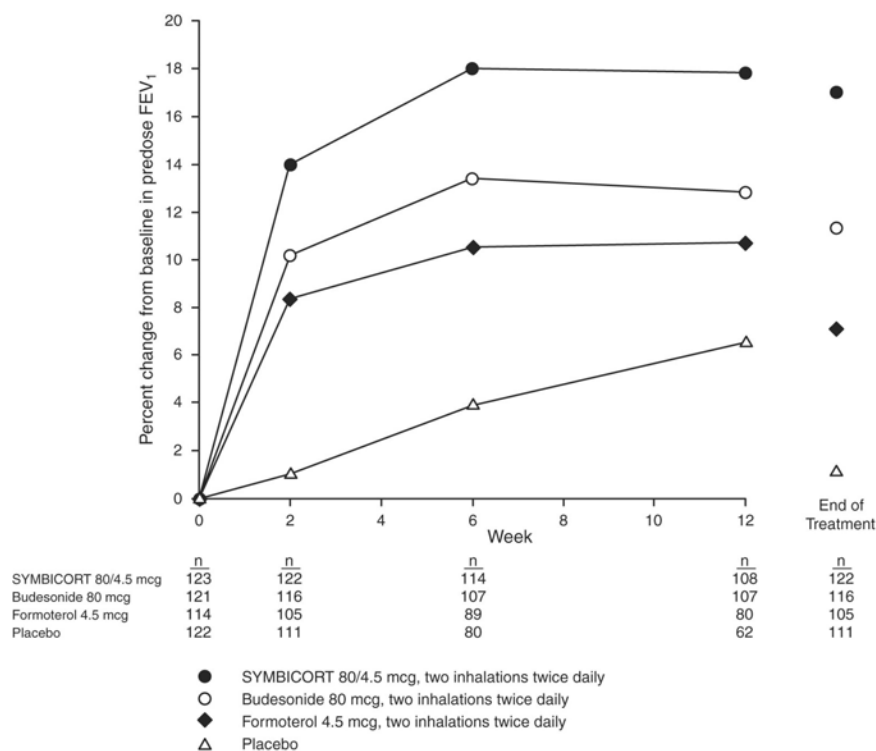
*These criteria were assessed on a daily basis irrespective of the timing of the clinic visit, with the exception of FEV₁, which was assessed at each clinic visit.

†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 predose FEV₁ 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 end points, 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 two 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 was 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)

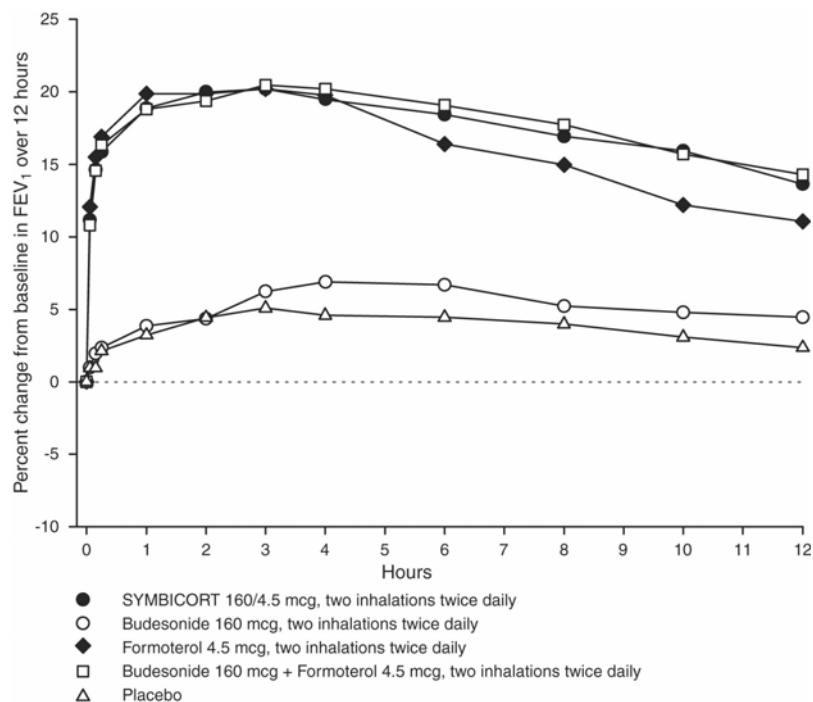
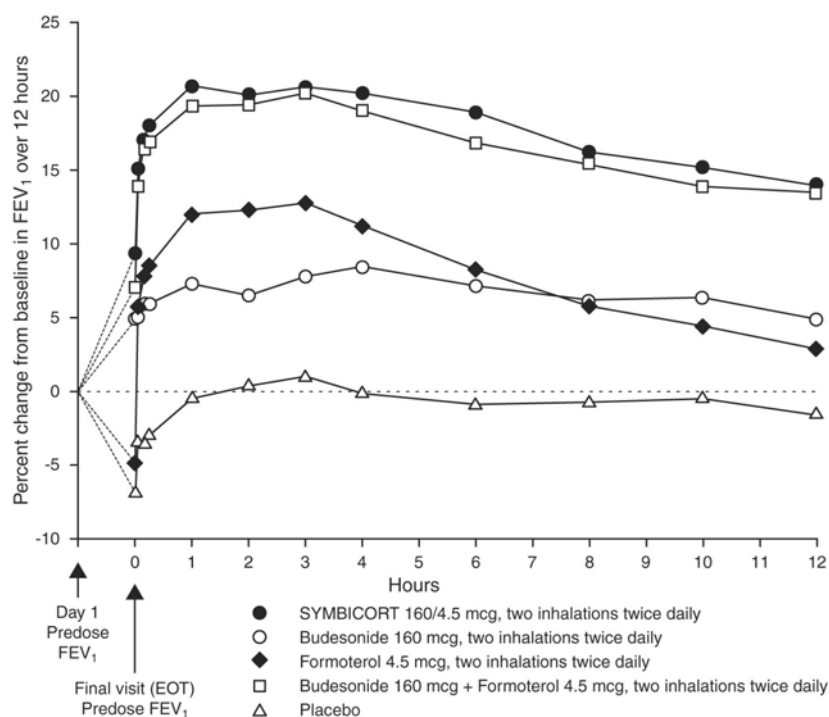


Figure 4 - Mean Percent Change From Baseline in FEV₁ At End of Treatment (Study 1)



14.2 Chronic Obstructive Pulmonary Disease (COPD)

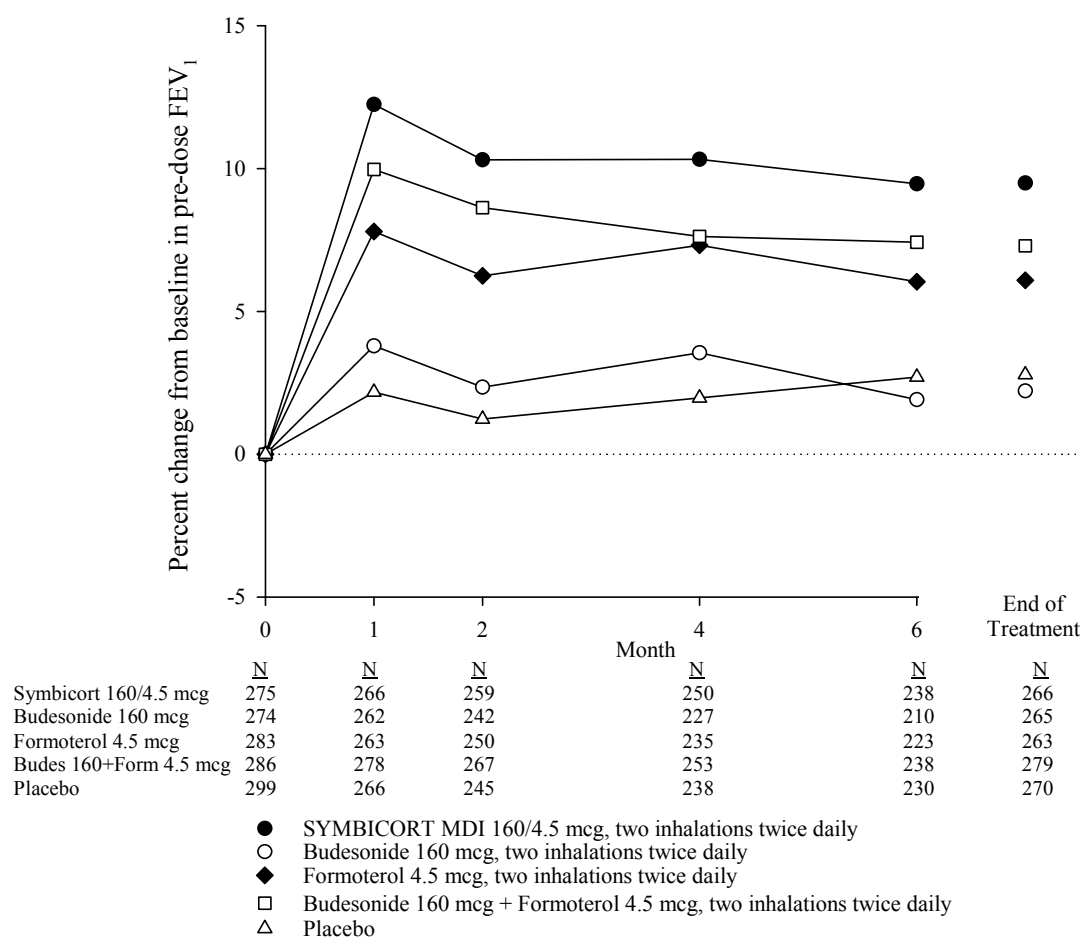
The efficacy of SYMBICORT 80/4.5 and SYMBICORT 160/4.5 in the maintenance treatment of airflow obstruction in COPD patients was evaluated in two randomized, double-blind, placebo-controlled multinational studies, conducted over 6 months (Study 1) and 12 months (Study 2), in a total of

3668 patients (2416 males and 1252 females). The majority of patients (93%) were Caucasian. All patients were required to be at least 40 years of age, with a FEV₁ of less than or equal to 50% predicted, a clinical diagnosis of COPD with symptoms for at least 2 years, and a smoking history of at least 10 pack years, prior to entering the trial. The mean prebronchodilator FEV₁ at baseline of the patients enrolled in the study was 34% predicted. Forty-eight percent of the patients enrolled were on inhaled corticosteroids and 52.7% of patients were on short-acting anticholinergic bronchodilators during run-in. On randomization, inhaled corticosteroids were discontinued, and ipratropium bromide was allowed at a stable dose for those patients previously treated with short-acting anticholinergic bronchodilators. The co-primary efficacy variables in both studies were the change from baseline in average pre-dose and 1-hour post-dose FEV₁ over the treatment period. The results of both studies 1 and 2 are described below.

Study 1

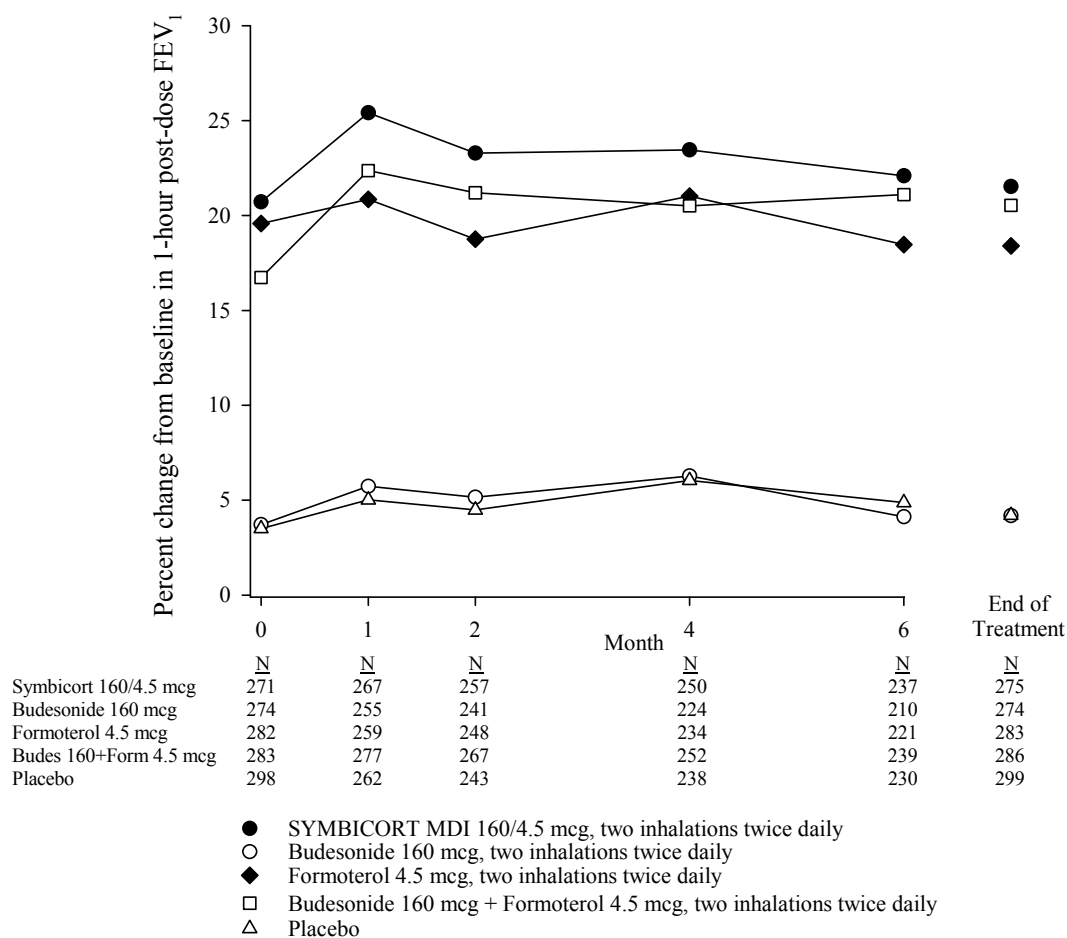
This was a 6-month, placebo-controlled study of 1704 COPD patients (mean % predicted FEV₁ at baseline ranging from 33.5% -34.7%) conducted to demonstrate the efficacy and safety of SYMBICORT in the treatment of airflow obstruction in COPD. The patients were randomized to one of the following treatment groups: SYMBICORT 160/4.5 (n=277), SYMBICORT 80/4.5 (n=281), budesonide 160 mcg + formoterol 4.5 mcg (n=287), budesonide 160 mcg (n=275), formoterol 4.5 mcg (n=284), or placebo (n=300). Patients receiving SYMBICORT 160/4.5 mcg, two inhalations twice daily, had significantly greater mean improvements from baseline in pre-dose FEV₁ averaged over the treatment period [0.08 L, 10.7%] compared with formoterol 4.5 mcg [0.04 L, 6.9%] and placebo [0.01 L, 2.2%] (See Figure 5). Patients receiving SYMBICORT 80/4.5 mcg, two inhalations twice daily, did not have significantly greater improvement from baseline in the pre-dose FEV₁ averaged over the treatment period compared with formoterol 4.5 mcg.

Figure 5 Mean Percent Change From Baseline in Pre-dose FEV₁ Over 6 months (Study 1)



Patients receiving SYMBICORT 160/4.5 mcg, two inhalations twice daily, had significantly greater mean improvements from baseline in 1-hour post-dose FEV₁ averaged over the treatment period [0.20 L, 22.6%], compared with budesonide 160 mcg [0.03 L, 4.9%] and placebo [0.03 L, 4.1%] (See Figure 6)

Figure 6 Mean Percent Change From Baseline in 1-hour Post-dose FEV₁ Over 6 months (Study 1)



Study 2

This was a 12-month, placebo-controlled study of 1964 COPD patients (mean % predicted FEV₁ at baseline ranging from 33.7% -35.5%) conducted to demonstrate the efficacy and safety of SYMBICORT in the treatment of airflow obstruction in COPD. The patients were randomized to one of the following treatment groups: SYMBICORT 160/4.5 (n=494), SYMBICORT 80/4.5 (n=494), formoterol 4.5 mcg (n=495), or placebo (n=481). Patients receiving SYMBICORT 160/4.5 mcg, two inhalations twice daily, had significantly greater improvements from baseline in mean pre-dose FEV₁ averaged over the treatment period [0.10 L, 10.8%] compared with formoterol 4.5 mcg [0.06 L, 7.2%] and placebo [0.01 L, 2.8%]. Patients receiving SYMBICORT 80/4.5 mcg, two inhalations twice daily, did not have significantly greater improvements from baseline in the mean pre-dose FEV₁ averaged over the treatment period compared to formoterol. Patients receiving SYMBICORT 160/4.5 mcg, two inhalations twice daily, also had significantly greater mean improvements from baseline in 1-hour post-dose FEV₁ averaged over the treatment period [0.21 L, 24.0%] compared with placebo [0.02 L, 5.2%].

Serial FEV₁ measures over 12 hours were obtained in a subset of patients in Study 1 (n=99) and Study 2 (n=121). The median time to onset of bronchodilation, defined as an FEV₁ increase of 15% or greater from baseline, occurred at 5 minutes post-dose. Maximum improvement (calculated as the average change from baseline at each timepoint) in FEV₁ occurred at approximately 2 hours post-dose.

In both Studies 1 and 2, improvements in secondary endpoints of morning and evening peak expiratory flow and reduction in rescue medication use were supportive of the efficacy of SYMBICORT 160/4.5.

16 HOW SUPPLIED/STORAGE AND HANDLING

SYMBICORT is available in two strengths and is supplied in the following package sizes:

Dosage Forms and Strengths

Package Size	NDC
SYMBICORT 80/4.5, 120 inhalations	0186-0372-20
SYMBICORT 80/4.5, 60 inhalations (institutional pack)	0186-0372-28
SYMBICORT 160/4.5, 120 inhalations	0186-0370-20
SYMBICORT 160/4.5, 60 inhalations (institutional pack)	0186-0370-28

Each strength is supplied as a pressurized aluminium canister with an attached counting device, a red plastic actuator body with a white mouthpiece, and attached gray dust cap. Each 120 inhalation canister has a net fill weight of 10.2 grams and each 60 inhalation canister has a net fill weight of 6.9 grams (SYMBICORT 80/4.5) or 6 grams (SYMBICORT 160/4.5). Each canister is packaged in a foil overwrap pouch with desiccant sachet and placed into a carton. Each carton contains one canister and a Medication Guide.

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

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

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

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

Keep out of the reach of children.

CONTENTS UNDER PRESSURE.

Do not puncture or incinerate. Do not store near heat or open flame. Exposure to temperatures over 120°F may cause bursting. Never throw container into fire or incinerator.

17 PATIENT COUNSELING INFORMATION

See Medication Guide (17.6)

17.1 Risk of Asthma-Related Death

Patients with asthma should be informed that formoterol fumarate dihydrate, one of the active ingredients in SYMBICORT, may increase the risk of asthma-related death.

They should also be informed that data are not adequate to determine whether the concurrent use of inhaled corticosteroids, the other component of SYMBICORT, or other asthma-controller therapy modifies this risk.

17.2 Not for Acute Symptoms

SYMBICORT is not meant to relieve acute asthma symptoms or exacerbations of COPD and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting beta₂-agonist such as albuterol. (The physician should provide the patient with such medication and instruct the patient in how it should be used.)

Patients should be instructed to notify their physician immediately if they experience any of the following:

- Decreasing effectiveness of inhaled, short-acting beta₂-agonists
- Need for more inhalations than usual of inhaled, short-acting beta₂-agonists

- Significant decrease in lung function as outlined by the physician

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

17.3 Do Not Use Additional Long-Acting Beta₂-Agonists

When patients are prescribed SYMBICORT, other long-acting beta₂-agonists for asthma and COPD should not be used.

17.4 Risks Associated With Corticosteroid Therapy

Local Effects: Patients should be advised that localized infections with *Candida albicans* occurred in the mouth and pharynx in some patients. If oropharyngeal candidiasis develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while still continuing therapy with SYMBICORT, but at times therapy with SYMBICORT may need to be temporarily interrupted under close medical supervision. Rinsing the mouth after inhalation is advised.

Pneumonia: Patients with COPD have a higher risk of pneumonia and should be instructed to contact their healthcare provider if they develop symptoms of pneumonia.

Immunosuppression: Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chicken pox or measles and, if exposed, to consult their physician without delay. Patients should be informed of potential worsening of existing tuberculosis, fungal, bacterial, viral, or parasitic infections, or ocular herpes simplex.

Hypercorticism and Adrenal Suppression: Patients should be advised that SYMBICORT may cause systemic corticosteroid effects of hypercorticism and adrenal suppression. Additionally, patients should be instructed that deaths due to adrenal insufficiency have occurred during and after transfer from systemic corticosteroids. Patients should taper slowly from systemic corticosteroids if transferring to SYMBICORT.

Reduction in Bone Mineral Density: Patients who are at an increased risk for decreased BMD should be advised that the use of corticosteroids may pose an additional risk.

Reduced Growth Velocity: Patients should be informed that orally inhaled corticosteroids, component of SYMBICORT, may cause a reduction in growth velocity when administered to pediatric patients. Physicians should closely follow the

growth of children and adolescents taking corticosteroids by any route.

Ocular Effects: Long-term use of inhaled corticosteroids may increase the risk of some eye problems (cataracts or glaucoma); regular eye examinations should be considered.

17.5 Risks Associated With Beta-Agonist Therapy

Patients should be informed of adverse effects associated with beta₂-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.

17.6 Medication Guide

SYMBICORT is a trademark of the AstraZeneca group of companies.

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Manufactured for: AstraZeneca LP, Wilmington, DE 19850

By: AstraZeneca Dunkerque Production, Dunkerque, France

Product of France

31152-XX

MEDICATION GUIDE

SYMBICORT 80/4.5

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

SYMBICORT 160/4.5

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

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

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

- **SYMBICORT contains 2 medicines:**
 - **Budesonide (the same medicine found in PULMICORT FLEXHALER®)**, an inhaled corticosteroid medicine. Inhaled corticosteroids help to decrease inflammation in the lungs. Inflammation in the lungs can lead to asthma symptoms.
 - **Formoterol (the same medicine found in FORADIL® AEROLIZER®)**, a long-acting beta₂-agonist medicine or LABA. LABA medicines are used in patients with chronic obstructive pulmonary disease (COPD) and 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 two 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 FLEXHALER), and a long-acting beta₂-agonist medicine (LABA), formoterol (the same medicine found in FORADIL AEROLIZER).

Asthma

SYMBICORT is used long-term, two times each day to control symptoms of asthma, and prevent symptoms such as wheezing in patients age 12 year 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

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

Chronic Obstructive Pulmonary Disease (COPD)

COPD is a chronic lung disease that includes chronic bronchitis, emphysema, or both. SYMBICORT 160/4.5 mcg is used long term, two times each day to help improve lung function for better breathing in adults with COPD.

Who should not use SYMBICORT?

Do not use SYMBICORT:

- to treat sudden severe symptoms of asthma or COPD.
- if you are allergic to any of the ingredients in SYMBICORT. See the end of the Medication Guide for a list of ingredients in SYMBICORT.

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**
- **have eye problems such as increased pressure in the eye, glaucoma, or cataracts**
- **are allergic to any medicines**
- **are exposed to chicken pox or measles**
- **are pregnant or planning to become pregnant.** It is not known if SYMBICORT may harm your unborn baby.
- **are breastfeeding.** Budesonide, one of the active ingredients in SYMBICORT, passes into breast milk. You and your healthcare provider should decide if you will take SYMBICORT while breast-feeding.

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. Especially tell your healthcare provider if you take antifungal and anti-HIV medicines.

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 two strengths. Your healthcare provider has prescribed the strength that is best for you. Note the differences between SYMBICORT and your other inhaled medications, including the differences in prescribed use and physical appearance.

- SYMBICORT should be taken every day as two puffs in the morning and two puffs in the evening.
- 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 and spit the water out after each dose (two puffs) of SYMBICORT. Do not swallow the water. This will help to lessen the chance of getting a fungus infection (thrush) in the mouth and throat.
- Do not spray SYMBICORT in your eyes. If you accidentally get SYMBICORT in your eyes, rinse your eyes with water, and if redness or irritation persists, consult your healthcare provider.
- Do not change or stop any medicines used to control or treat your breathing problems. Your healthcare provider will change your medicines as needed.
- **While you are using SYMBICORT 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 formoterol containing products (FORADIL AEROLIZER, Brovana, Performist)**
- 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:**
 - your breathing problems worsen with SYMBICORT
 - you need to use your short-acting beta₂-agonist medicine more often than usual
 - your short-acting beta₂-agonist medicine does not work as well for you at relieving symptoms

- you need to use four or more inhalations of your short-acting beta₂-agonist medicine for 2 or more days in a row
- you use one whole canister of your short-acting beta₂-agonist medicine in 8 weeks' time
- your peak flow meter results decrease. Your healthcare provider will tell you the numbers that are right for you.
- your 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?”
- **Pneumonia and other lower respiratory tract infections.** People with COPD have a higher chance of getting pneumonia and other lung infections. Inhaled corticosteroids may increase the chance of getting pneumonia. Call your healthcare provider if you notice any of these symptoms:
 - increase in mucus (sputum) production
 - change in mucus color
 - fever
 - chills
 - increased cough
 - increased breathing problems.

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.** You should have regular eye exams 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.
- **thrush in the mouth and throat**
- **throat pain**

The most common side effects with SYMBICORT include:

Adults and children with asthma:

- throat irritation
- headache
- upper respiratory tract infection
- throat pain
- inflammation of mucous membranes of the sinuses (sinusitis)
- flu
- back pain

- nasal congestion
- stomach discomfort
- vomiting
- thrush in the mouth and throat

Patients with COPD:

- throat irritation
- thrush in the mouth and throat
- lower respiratory tract infections, mostly infections and/or inflammation of the mucous membranes of the bronchial tubes (bronchitis)
- inflammation of mucous membranes in the sinuses (sinusitis)
- upper respiratory tract infection

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

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

Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088 and/or ASTRAZENECA at 1-800-236-9933.

How do I store SYMBICORT?

- Store SYMBICORT at room temperature between 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.
- Throw away SYMBICORT when the counter reaches zero ("0") or 3 months after you take SYMBICORT out of its foil pouch, whichever comes first.
- **Keep SYMBICORT and all medicines out of the reach of children.**

General Information about SYMBICORT

Medicines are sometimes prescribed for purposes other than those listed 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. For more information, call 1-800-236-9933 or go to www.MySymbicort.com.

What are the ingredients in SYMBICORT?

Active ingredient: micronized budesonide and micronized formoterol fumarate dihydrate

Inactive ingredients: hydrofluroalkane (HFA 227), povidone K25 USP, and polyethylene glycol 1000 NF

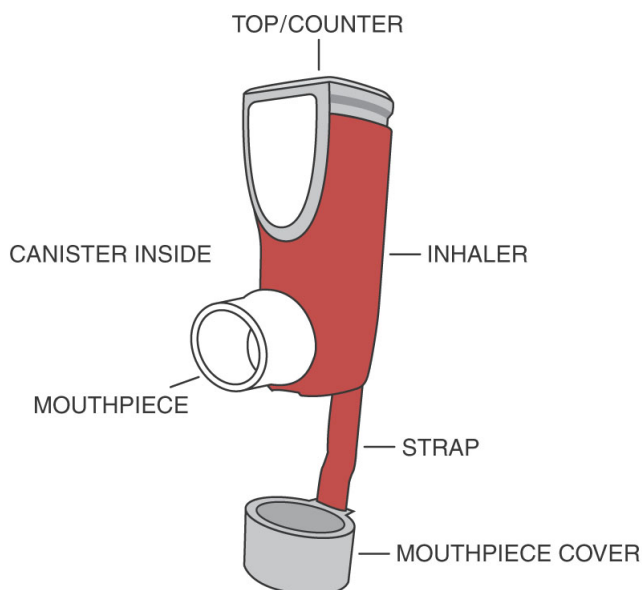


Figure 1
Upright Position

How to Use SYMBICORT

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

Preparing your inhaler for use

1. Take your SYMBICORT out of the moisture-protective foil pouch before you use it for the first time and throw the foil away. Write the date that you open the foil pouch on the box.
2. A counter is attached to the top of the metal canister. The counter will count down each time you release a puff of SYMBICORT. The arrow points to the number of inhalations (puffs) left in the canister. The counter will stop counting at zero ("0").
3. Use the SYMBICORT canister only with the red SYMBICORT inhaler supplied with the product. Parts of the SYMBICORT inhaler should not be used with parts from any other inhalation product.
4. Shake your SYMBICORT inhaler well for 5 seconds right before each use. Remove the mouthpiece cover. Check the mouthpiece for foreign objects before use.
5. **Priming** Before you use SYMBICORT for the first time, you will need to prime it. To prime SYMBICORT, hold it in the upright position. See figure 1 above. Shake the SYMBICORT inhaler well for 5 seconds. Hold your SYMBICORT inhaler facing away from you and then release a test spray. Then shake it again for 5 seconds and release a second test spray. Your SYMBICORT inhaler is now primed and ready for use. After you have primed the SYMBICORT inhaler for the first time, the counter will read either 120 or 60, depending on which size was provided to you.

If you do not use your SYMBICORT inhaler for more than 7 days or if you drop it, you will need to prime again.

Ways to hold the SYMBICORT inhaler for use

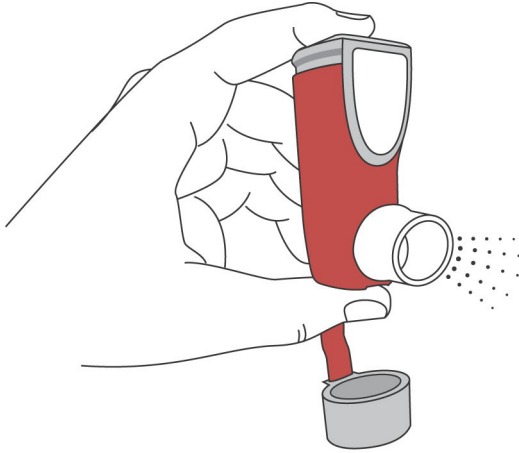


Figure 2

OR

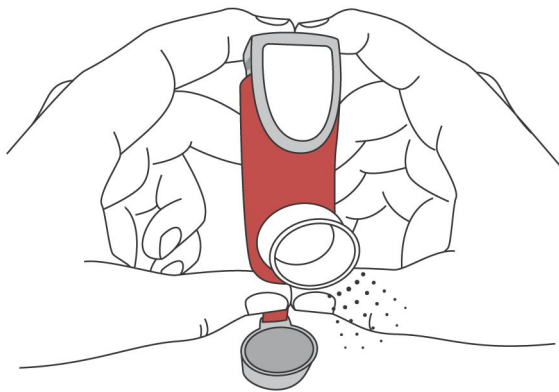


Figure 3

Using your SYMBICORT inhaler

6. Shake your SYMBICORT inhaler well for 5 seconds. Remove the mouthpiece cover. Check the mouthpiece for foreign objects.

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

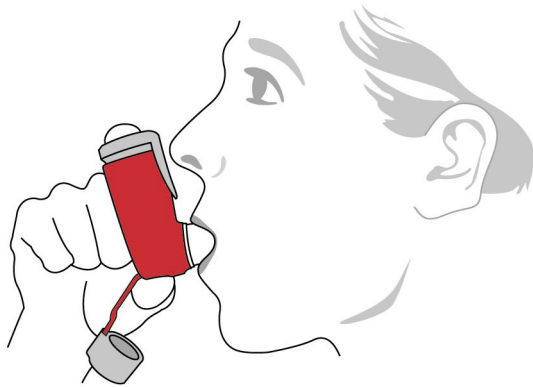


Figure 4

8. Breathe in (inhale) deeply and slowly through your mouth. Press down firmly and fully on the top of the counter on the SYMBICORT inhaler to release the medicine (see Figures 2 and 3).
9. Continue to breathe in (inhale) and hold your breath for about 10 seconds, or for as long as is comfortable. Before you breathe out (exhale), release your finger from the top of the counter. Keep the SYMBICORT inhaler upright and remove from your mouth.
10. Shake the SYMBICORT inhaler again for 5 seconds and repeat steps 7 to 9.

After using your SYMBICORT inhaler

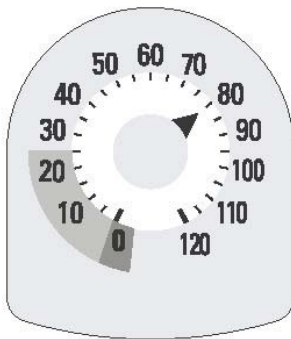
11. Replace the mouthpiece cover after use.

12. After you finish taking SYMBICORT (two puffs),
rinse your mouth with water. Spit out the water.
Do not swallow it.

Reading the counter

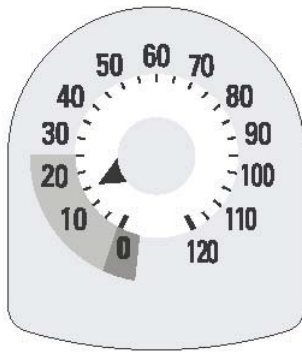
- The arrow on the counter on the top of the SYMBICORT inhaler points to the number of inhalations (puffs) left in your inhaler.

COUNTER



- The counter will count down each time you release a puff of medicine (either when preparing your SYMBICORT inhaler for use or when taking the medicine).
- When the arrow on the counter approaches 20, you will notice the beginning of a yellow area letting you know that it is time to call your healthcare provider for a refill.

COUNTER



- It is important that you pay attention to the number of inhalations (puffs) left in your SYMBICORT inhaler by reading the counter. Throw away SYMBICORT when the counter shows zero ("0"). Your SYMBICORT inhaler may not feel empty and it may continue to operate, but you will not get the right amount of medicine if you keep using it. Use a new SYMBICORT inhaler and follow the instructions for priming (instruction 5 above).

How to clean your SYMBICORT inhaler

Clean the white mouthpiece of your SYMBICORT 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 SYMBICORT inhaler into water**
- Do not try to take apart your **SYMBICORT** inhaler

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19850

By: AstraZeneca Dunkerque Production, Dunkerque,
France

Product of France

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PREScribing INFORMATION

SEREVENT[®] DISKUS[®] (salmeterol xinafoate inhalation powder)

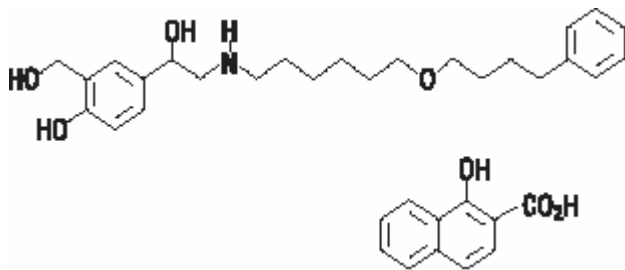
For Oral Inhalation Only

WARNING

Long-acting beta₂-adrenergic agonists, such as salmeterol, the active ingredient in SEREVENT DISKUS, may increase the risk of asthma-related death. Therefore, when treating patients with asthma, SEREVENT DISKUS should only be used as additional therapy 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 2 maintenance therapies, including SEREVENT DISKUS. Data from a large placebo-controlled US study that compared the safety of salmeterol (SEREVENT[®] Inhalation Aerosol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176 patients treated for 28 weeks on salmeterol versus 3 deaths out of 13,179 patients on placebo) (see WARNINGS and CLINICAL TRIALS: Asthma: *Salmeterol Multi-center Asthma Research Trial*).

DESCRIPTION

SEREVENT DISKUS (salmeterol xinafoate inhalation powder) contains salmeterol xinafoate as the racemic form of the 1-hydroxy-2-naphthoic acid salt of salmeterol. The active component of the formulation is salmeterol base, a highly selective beta₂-adrenergic bronchodilator. The chemical name of salmeterol xinafoate is 4-hydroxy- α^1 -[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol, 1-hydroxy-2-naphthalenecarboxylate. Salmeterol xinafoate has the following chemical structure:



Salmeterol xinafoate is a white powder with a molecular weight of 603.8, and the empirical formula is C₂₅H₃₇NO₄•C₁₁H₈O₃. It is freely soluble in methanol; slightly soluble in ethanol, chloroform, and isopropanol; and sparingly soluble in water.

SEREVENT DISKUS is a specially designed plastic inhalation delivery system containing a double-foil blister strip of a powder formulation of salmeterol xinafoate intended for oral inhalation only. The DISKUS[®], which is the delivery component, is an integral part of the drug

product. Each blister on the double-foil strip within the unit contains 50 mcg of salmeterol administered as the salmeterol xinafoate salt in 12.5 mg of formulation containing lactose (which contains milk proteins). After a blister containing medication is opened by activating the DISKUS, the medication is dispersed into the airstream created by the patient inhaling through the mouthpiece.

Under standardized in vitro test conditions, SEREVENT DISKUS delivers 47 mcg when tested at a flow rate of 60 L/min for 2 seconds. In adult patients with obstructive lung disease and severely compromised lung function (mean forced expiratory volume in 1 second [FEV₁] 20% to 30% of predicted), mean peak inspiratory flow (PIF) through a DISKUS was 82.4 L/min (range, 46.1 to 115.3 L/min).

The actual amount of drug delivered to the lung will depend on patient factors, such as inspiratory flow profile.

CLINICAL PHARMACOLOGY

Mechanism of Action: Salmeterol is a long-acting beta₂-adrenergic agonist. In vitro studies and in vivo pharmacologic studies demonstrate that salmeterol is selective for beta₂-adrenoceptors compared with isoproterenol, which has approximately equal agonist activity on beta₁- and beta₂-adrenoceptors. In vitro studies show salmeterol to be at least 50 times more selective for beta₂-adrenoceptors than albuterol. Although beta₂-adrenoceptors are the predominant adrenergic receptors in bronchial smooth muscle and beta₁-adrenoceptors are the predominant receptors in the heart, there are also beta₂-adrenoceptors in the human heart comprising 10% to 50% of the total beta-adrenoceptors. The precise function of these receptors has not been established, but they raise the possibility that even highly selective beta₂-agonists may have cardiac effects.

The pharmacologic effects of beta₂-adrenoceptor agonist drugs, including salmeterol, are at least in part attributable to stimulation of intracellular adenylyl 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 salmeterol is a potent and long-lasting inhibitor of the release of mast cell mediators, such as histamine, leukotrienes, and prostaglandin D₂, from human lung. Salmeterol inhibits histamine-induced plasma protein extravasation and inhibits platelet-activating factor-induced eosinophil accumulation in the lungs of guinea pigs when administered by the inhaled route. In humans, single doses of salmeterol administered via inhalation aerosol attenuate allergen-induced bronchial hyper-responsiveness.

Pharmacokinetics: Salmeterol xinafoate, an ionic salt, dissociates in solution so that the salmeterol and 1-hydroxy-2-naphthoic acid (xinafoate) moieties are absorbed, distributed, metabolized, and eliminated independently. Salmeterol acts locally in the lung; therefore, plasma levels do not predict therapeutic effect.

Absorption: Because of the small therapeutic dose, systemic levels of salmeterol are low or

undetectable after inhalation of recommended doses (50 mcg of salmeterol inhalation powder twice daily). Following chronic administration of an inhaled dose of 50 mcg of salmeterol inhalation powder twice daily, salmeterol was detected in plasma within 5 to 45 minutes in 7 patients with asthma; plasma concentrations were very low, with mean peak concentrations of 167 pg/mL at 20 minutes and no accumulation with repeated doses.

Distribution: The percentage of salmeterol bound to human plasma proteins averages 96% in vitro over the concentration range of 8 to 7,722 ng of salmeterol base per milliliter, much higher concentrations than those achieved following therapeutic doses of salmeterol.

Metabolism: Salmeterol base is extensively metabolized by hydroxylation, with subsequent elimination predominantly in the feces. No significant amount of unchanged salmeterol base has been detected in either urine or feces.

An in vitro study using human liver microsomes showed that salmeterol is extensively metabolized to α -hydroxysalmeterol (aliphatic oxidation) by cytochrome P450 3A4 (CYP3A4). Ketoconazole, a strong inhibitor of CYP3A4, essentially completely inhibited the formation of α -hydroxysalmeterol in vitro.

Elimination: In 2 healthy subjects who received 1 mg of radiolabeled salmeterol (as salmeterol xinafoate) orally, approximately 25% and 60% of the radiolabeled salmeterol was eliminated in urine and feces, respectively, over a period of 7 days. The terminal elimination half-life was about 5.5 hours (1 volunteer only).

The xinafoate moiety has no apparent pharmacologic activity. The xinafoate moiety is highly protein bound (>99%) and has a long elimination half-life of 11 days.

Special Populations: The pharmacokinetics of salmeterol base has not been studied in elderly patients nor in patients with hepatic or renal impairment. Since salmeterol is predominantly cleared by hepatic metabolism, liver function impairment may lead to accumulation of salmeterol in plasma. Therefore, patients with hepatic disease should be closely monitored.

Drug Interactions: Salmeterol is a substrate of CYP3A4.

Inhibitors of Cytochrome P450 3A4: Ketoconazole: In a placebo-controlled, crossover drug interaction study in 20 healthy male and female subjects, coadministration of salmeterol (50 mcg twice daily) and the strong CYP3A4 inhibitor ketoconazole (400 mg once daily) for 7 days resulted in a significant increase in plasma salmeterol exposure as determined by a 16-fold increase in AUC (ratio with and without ketoconazole 15.76; 90% CI: 10.66, 23.31) mainly due to increased bioavailability of the swallowed portion of the dose. Peak plasma salmeterol concentrations were increased by 1.4-fold (90% CI: 1.23, 1.68). Three (3) out of 20 subjects (15%) were withdrawn from salmeterol and ketoconazole coadministration due to beta-agonist-mediated systemic effects (2 with QTc prolongation and 1 with palpitations and sinus tachycardia). Coadministration of salmeterol and ketoconazole did not result in a clinically significant effect on mean heart rate, mean blood potassium, or mean blood glucose. Although there was no statistical effect on the mean QTc, coadministration of salmeterol and ketoconazole was associated with more frequent increases in QTc duration compared with salmeterol and

placebo administration. Due to the potential increased risk of cardiovascular adverse events, the concomitant use of salmeterol with strong CYP3A4 inhibitors (e.g., ketoconazole, ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) is not recommended.

Erythromycin: In a repeat-dose study in 13 healthy subjects, concomitant administration of erythromycin (a moderate CYP3A4 inhibitor) and salmeterol inhalation aerosol resulted in a 40% increase in salmeterol C_{max} at steady state (ratio with and without erythromycin 1.4; 90% CI: 0.96, 2.03; $p = 0.12$), a 3.6-beat/min increase in heart rate (95% CI: 0.19, 7.03; $p < 0.04$), a 5.8-msec increase in QTc interval (95% CI: -6.14, 17.77; $p = 0.34$), and no change in plasma potassium.

Pharmacodynamics: Inhaled salmeterol, like other beta-adrenergic agonist drugs, can in some patients produce dose-related cardiovascular effects and effects on blood glucose and/or serum potassium (see PRECAUTIONS: General). The cardiovascular effects (heart rate, blood pressure) associated with salmeterol inhalation aerosol occur with similar frequency, and are of similar type and severity, as those noted following albuterol administration.

The effects of rising doses of salmeterol and standard inhaled doses of albuterol were studied in volunteers and in patients with asthma. Salmeterol doses up to 84 mcg administered as inhalation aerosol resulted in heart rate increases of 3 to 16 beats/min, about the same as albuterol dosed at 180 mcg by inhalation aerosol (4 to 10 beats/min). Adolescent and adult patients receiving 50-mcg doses of salmeterol inhalation powder ($N = 60$) underwent continuous electrocardiographic monitoring during two 12-hour periods after the first dose and after 1 month of therapy, and no clinically significant dysrhythmias were noted. Also, pediatric patients receiving 50-mcg doses of salmeterol inhalation powder ($N = 67$) underwent continuous electrocardiographic monitoring during two 12-hour periods after the first dose and after 3 months of therapy, and no clinically significant dysrhythmias were noted.

In 24-week clinical studies in patients with chronic obstructive pulmonary disease (COPD), the incidence of clinically significant abnormalities on the predose electrocardiograms (ECGs) at Weeks 12 and 24 in patients who received salmeterol 50 mcg was not different compared with placebo.

No effect of treatment with salmeterol 50 mcg was observed on pulse rate and systolic and diastolic blood pressure in a subset of patients with COPD who underwent 12-hour serial vital sign measurements after the first dose ($N = 91$) and after 12 weeks of therapy ($N = 74$). Median changes from baseline in pulse rate and systolic and diastolic blood pressure were similar for patients receiving either salmeterol or placebo (see ADVERSE REACTIONS).

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.

CLINICAL TRIALS

Asthma: During the initial treatment day in several multiple-dose clinical trials with SEREVENT DISKUS in patients with asthma, the median time to onset of clinically significant bronchodilatation ($\geq 15\%$ improvement in FEV₁) ranged from 30 to 48 minutes after a 50-mcg dose.

One hour after a single dose of 50 mcg of SEREVENT DISKUS, the majority of patients had $\geq 15\%$ improvement in FEV₁. Maximum improvement in FEV₁ generally occurred within 180 minutes, and clinically significant improvement continued for 12 hours in most patients.

In 2 randomized, double-blind studies, SEREVENT DISKUS was compared with albuterol inhalation aerosol and placebo in adolescent and adult patients with mild-to-moderate asthma (protocol defined as 50% to 80% predicted FEV₁, actual mean of 67.7% at baseline), including patients who did and who did not receive concurrent inhaled corticosteroids. The efficacy of SEREVENT DISKUS was demonstrated over the 12-week period with no change in effectiveness over this time period (see Figure 1). There were no gender- or age-related differences in safety or efficacy. No development of tachyphylaxis to the bronchodilator effect was noted in these studies. FEV₁ measurements (mean change from baseline) from these two 12-week studies are shown in Figure 1 for both the first and last treatment days.

Figure 1. Serial 12-Hour FEV₁ From Two 12-Week Clinical Trials in Patients With Asthma

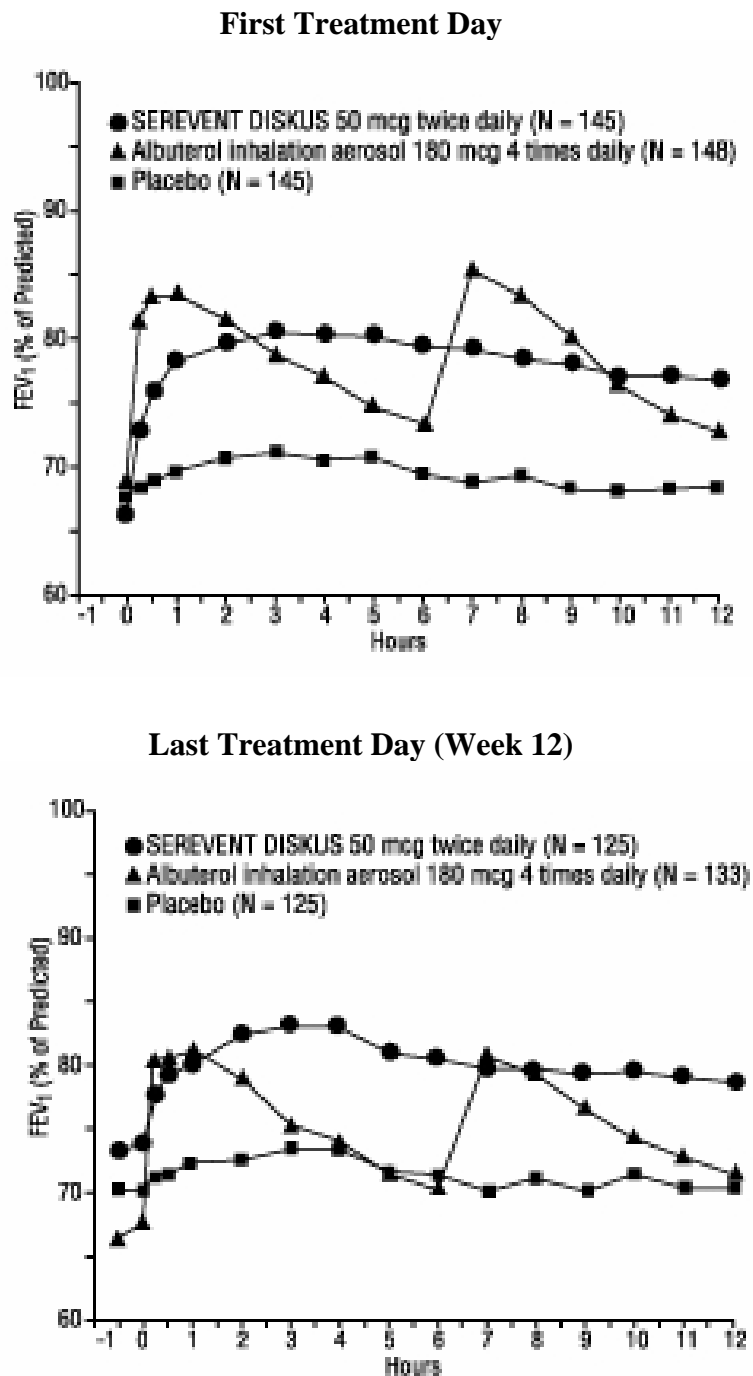


Table 1 shows the treatment effects seen during daily treatment with SEREVENT DISKUS for 12 weeks in adolescent and adult patients with mild-to-moderate asthma.

Table 1. Daily Efficacy Measurements in Two 12-Week Clinical Trials (Combined Data)

Parameter	Time	Placebo	SEREVENT DISKUS	Albuterol Inhalation Aerosol
No. of randomized subjects		152	149	148
Mean AM peak expiratory flow (L/min)	baseline	394	395	394
	12 weeks	396	427*	394
Mean % days with no asthma symptoms	baseline	14	13	12
	12 weeks	20	33	21
Mean % nights with no awakenings	baseline	70	63	68
	12 weeks	73	85*	71
Rescue medications (mean no. of inhalations per day)	baseline	4.2	4.3	4.3
	12 weeks	3.3	1.6†	2.2
Asthma exacerbations		14%	15%	16%

*Statistically superior to placebo and albuterol ($p < 0.001$).

†Statistically superior to placebo ($p < 0.001$).

Maintenance of efficacy for periods up to 1 year has been documented.

SEREVENT DISKUS and SEREVENT[®] (salmeterol xinafoate) Inhalation Aerosol were compared to placebo in 2 additional randomized, double-blind clinical trials in adolescent and adult patients with mild-to-moderate asthma. SEREVENT DISKUS 50 mcg and SEREVENT Inhalation Aerosol 42 mcg, both administered twice daily, produced significant improvements in pulmonary function compared with placebo over the 12-week period. While no statistically significant differences were observed between the active treatments for any of the efficacy assessments or safety evaluations performed, there were some efficacy measures on which the metered-dose inhaler appeared to provide better results. Similar findings were noted in 2 randomized, single-dose, crossover comparisons of SEREVENT DISKUS and SEREVENT Inhalation Aerosol for the prevention of exercise-induced bronchospasm (EIB). Therefore, while SEREVENT DISKUS was comparable to SEREVENT Inhalation Aerosol in clinical trials in mild-to-moderate patients with asthma, it should not be assumed that they will produce clinically equivalent outcomes in all patients.

In a randomized, double-blind, controlled study (N = 449), 50 mcg of SEREVENT DISKUS was administered twice daily to pediatric patients with asthma who did and who did not receive concurrent inhaled corticosteroids. The efficacy of salmeterol inhalation powder was demonstrated over the 12-week treatment period with respect to periodic serial peak expiratory flow (PEF) (36% to 39% postdose increase from baseline) and FEV₁ (32% to 33% postdose increase from baseline). Salmeterol was effective in demographic subgroup analyses (gender and age) and was effective when coadministered with other inhaled asthma medications such as short-acting bronchodilators and inhaled corticosteroids. A second randomized, double-blind,

placebo-controlled study (N = 207) with 50 mcg of salmeterol inhalation powder via an alternate device supported the findings of the trial with the DISKUS.

Effects in Patients With Asthma on Concomitant Inhaled Corticosteroids: In 4 clinical trials in adult and adolescent patients with asthma (N = 1,922), the effect of adding salmeterol to inhaled corticosteroid therapy was evaluated. The studies utilized the inhalation aerosol formulation of salmeterol xinafoate for a treatment period of 6 months. They compared the addition of salmeterol therapy to an increase (at least doubling) of the inhaled corticosteroid dose.

Two randomized, double-blind, controlled, parallel-group clinical trials (N = 997) enrolled patients (ages 18 to 82 years) with persistent asthma who were previously maintained but not adequately controlled on inhaled corticosteroid therapy. During the 2-week run-in period, all patients were switched to beclomethasone dipropionate 168 mcg twice daily. Patients still not adequately controlled were randomized to either the addition of SEREVENT Inhalation Aerosol 42 mcg twice daily or an increase of beclomethasone dipropionate to 336 mcg twice daily. As compared to the doubled dose of beclomethasone dipropionate, the addition of SEREVENT Inhalation Aerosol resulted in statistically significantly greater improvements in pulmonary function and asthma symptoms, and statistically significantly greater reduction in supplemental albuterol use. The percent of patients who experienced asthma exacerbations overall was not different between groups (i.e., 16.2% in the group receiving SEREVENT Inhalation Aerosol versus 17.9% in the higher-dose beclomethasone dipropionate group).

Two randomized, double-blind, parallel-group clinical trials (N = 925) enrolled patients (ages 12 to 78 years) with persistent asthma who were previously maintained but not adequately controlled on prior therapy. During the 2- to 4-week run-in period, all patients were switched to fluticasone propionate 88 mcg twice daily. Patients still not adequately controlled were randomized to either the addition of SEREVENT Inhalation Aerosol 42 mcg twice daily or an increase of fluticasone propionate to 220 mcg twice daily. As compared to the increased (2.5 times) dose of fluticasone propionate, the addition of SEREVENT Inhalation Aerosol resulted in statistically significantly greater improvements in pulmonary function and asthma symptoms, and statistically significantly greater reductions in supplemental albuterol use. Fewer patients receiving SEREVENT Inhalation Aerosol experienced asthma exacerbations than those receiving the higher dose of fluticasone propionate (8.8% versus 13.8%).

Exercise-Induced Bronchospasm: In 2 randomized, single-dose, crossover studies in adolescents and adults with EIB (N = 53), 50 mcg of SEREVENT DISKUS prevented EIB when dosed 30 minutes prior to exercise. For many patients, this protective effect against EIB was still apparent up to 8.5 hours following a single dose.

Table 2. Results of 2 Exercise-Induced Bronchospasm Studies in Adolescents and Adults

		Placebo (N = 52)		SEREVENT DISKUS (N = 52)	
		n	% Total	n	% Total
0.5-Hour postdose exercise challenge	<u>% Fall in FEV₁</u>				
	<10%	15	29	31	60
	≥10%, <20%	3	6	11	21
	≥20%	34	65	10	19
Mean maximal % fall in FEV ₁ (SE)		-25% (1.8)		-11% (1.9)	
8.5-Hour postdose exercise challenge	<u>% Fall in FEV₁</u>				
	<10%	12	23	26	50
	≥10%, <20%	7	13	12	23
	≥20%	33	63	14	27
Mean maximal % fall in FEV ₁ (SE)		-27% (1.5)		-16% (2.0)	

In 2 randomized studies in children 4 to 11 years old with asthma and EIB (N = 50), a single 50-mcg dose of SEREVENT DISKUS prevented EIB when dosed 30 minutes prior to exercise, with protection lasting up to 11.5 hours in repeat testing following this single dose in many patients.

Salmeterol Multi-center Asthma Research Trial: The Salmeterol Multi-center Asthma Research Trial (SMART) was a randomized, double-blind study that enrolled long-acting beta₂-agonist-naïve patients with asthma (average age of 39 years, 71% Caucasian, 18% African American, 8% Hispanic) to assess the safety of salmeterol (SEREVENT Inhalation Aerosol) 42 mcg twice daily over 28 weeks compared to placebo when added to usual asthma therapy.

A planned interim analysis was conducted when approximately half of the intended number of patients had been enrolled (N = 26,355), which led to premature termination of the study. The results of the interim analysis showed that patients receiving salmeterol were at increased risk for fatal asthma events (see Table 3 and Figure 2). In the total population, a higher rate of asthma-related death occurred in patients treated with salmeterol than those treated with placebo (0.10% vs. 0.02%; relative risk 4.37 [95% CI 1.25, 15.34]).

Post-hoc subpopulation analyses were performed. In Caucasians, asthma-related death occurred at a higher rate in patients treated with salmeterol than in patients treated with placebo (0.07% vs. 0.01%; relative risk 5.82 [95% CI 0.70, 48.37]). In African Americans also, asthma-related death occurred at a higher rate in patients treated with salmeterol than those treated with placebo (0.31% vs. 0.04%; relative risk 7.26 [95% CI 0.89, 58.94]). Although the relative risks of asthma-related death were similar in Caucasians and African Americans, the estimate of excess deaths in patients treated with salmeterol was greater in African Americans because there was a higher overall rate of asthma-related death in African American patients (see

Table 3).

The data from the SMART study are not adequate to determine whether concurrent use of inhaled corticosteroids or other asthma-controller therapy modifies the risk of asthma-related death.

Table 3: Asthma-Related Deaths in the 28-Week Salmeterol Multi-center Asthma Research Trial (SMART)

	Salmeterol n (% [*])	Placebo n (% [*])	Relative Risk [†] (95% Confidence Interval)	Excess Deaths Expressed per 10,000 Patients [‡] (95% Confidence Interval)
Total Population[§] Salmeterol: N = 1,3176 Placebo: N = 1,3179	13 (0.10%)	3 (0.02%)	4.37 (1.25, 15.34)	8 (3, 13)
Caucasian Salmeterol: N = 9,281 Placebo: N = 9,361	6 (0.07%)	1 (0.01%)	5.82 (0.70, 48.37)	6 (1, 10)
African American Salmeterol: N = 2,366 Placebo: N = 2,319	7 (0.31%)	1 (0.04%)	7.26 (0.89, 58.94)	27 (8, 46)

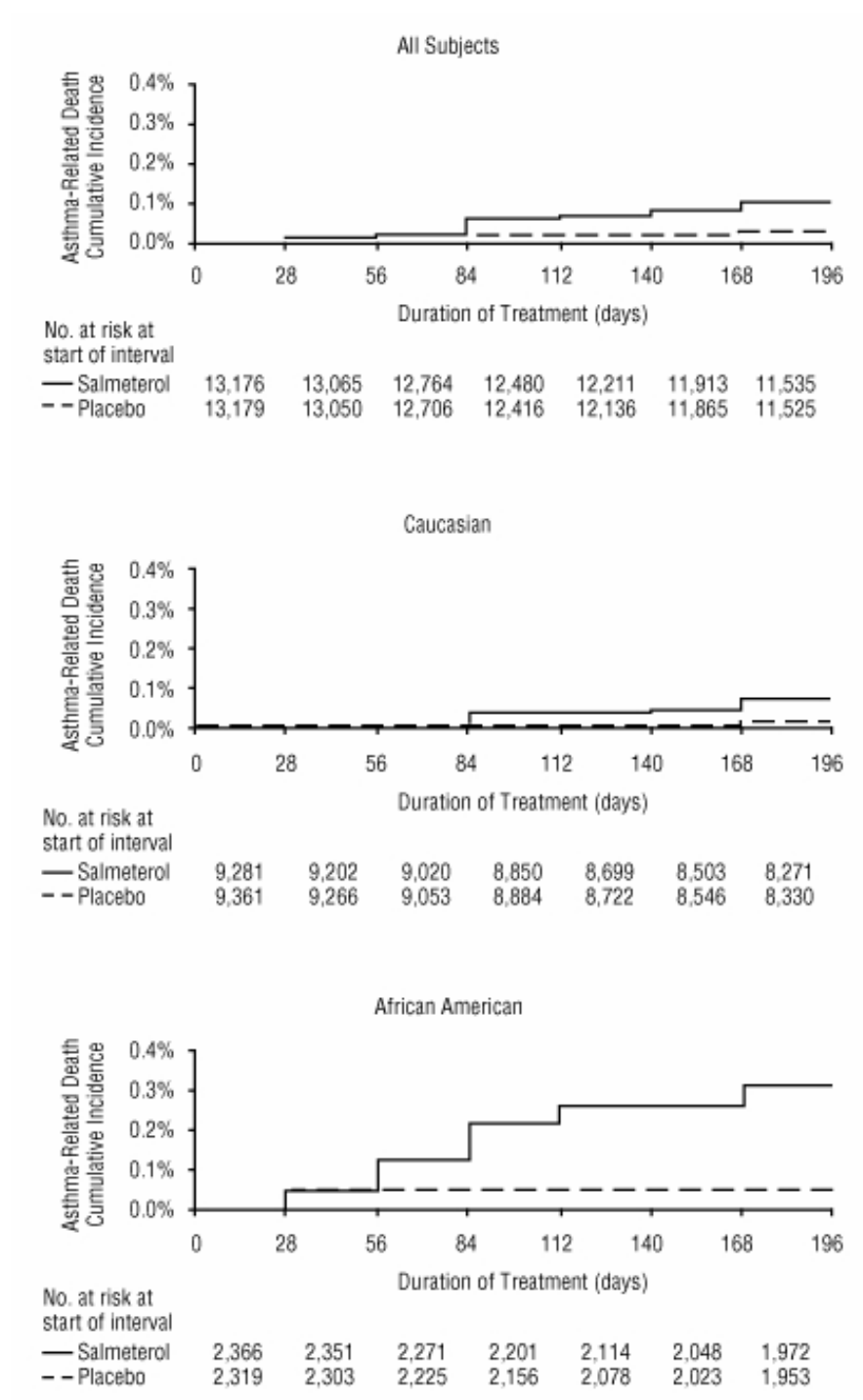
^{*} Life-table 28-week estimate, adjusted according to the patients' actual lengths of exposure to study treatment to account for early withdrawal of patients from the study.

[†] Relative risk is the ratio of the rate of asthma-related death in the salmeterol group and the rate in the placebo group. The relative risk indicates how many more times likely an asthma-related death occurred in the salmeterol group than in the placebo group in a 28-week treatment period.

[‡] Estimate of the number of additional asthma-related deaths in patients treated with salmeterol in SMART, assuming 10,000 patients received salmeterol for a 28-week treatment period. Estimate calculated as the difference between the salmeterol and placebo groups in the rates of asthma-related death multiplied by 10,000.

[§] The Total Population includes the following ethnic origins listed on the case report form: Caucasian, African American, Hispanic, Asian, and "Other." In addition, the Total Population includes those patients whose ethnic origin was not reported. The results for Caucasian and African American subpopulations are shown above. No asthma-related deaths occurred in the Hispanic (salmeterol n = 996, placebo n = 999), Asian (salmeterol n = 173, placebo n = 149), or "Other" (salmeterol n = 230, placebo n = 224) subpopulations. One asthma-related death occurred in the placebo group in the subpopulation whose ethnic origin was not reported (salmeterol n = 130, placebo n = 127).

Figure 2. Cumulative Incidence of Asthma-Related Deaths in the 28-Week Salmeterol Multi-center Asthma Research Trial (SMART), by Duration of Treatment

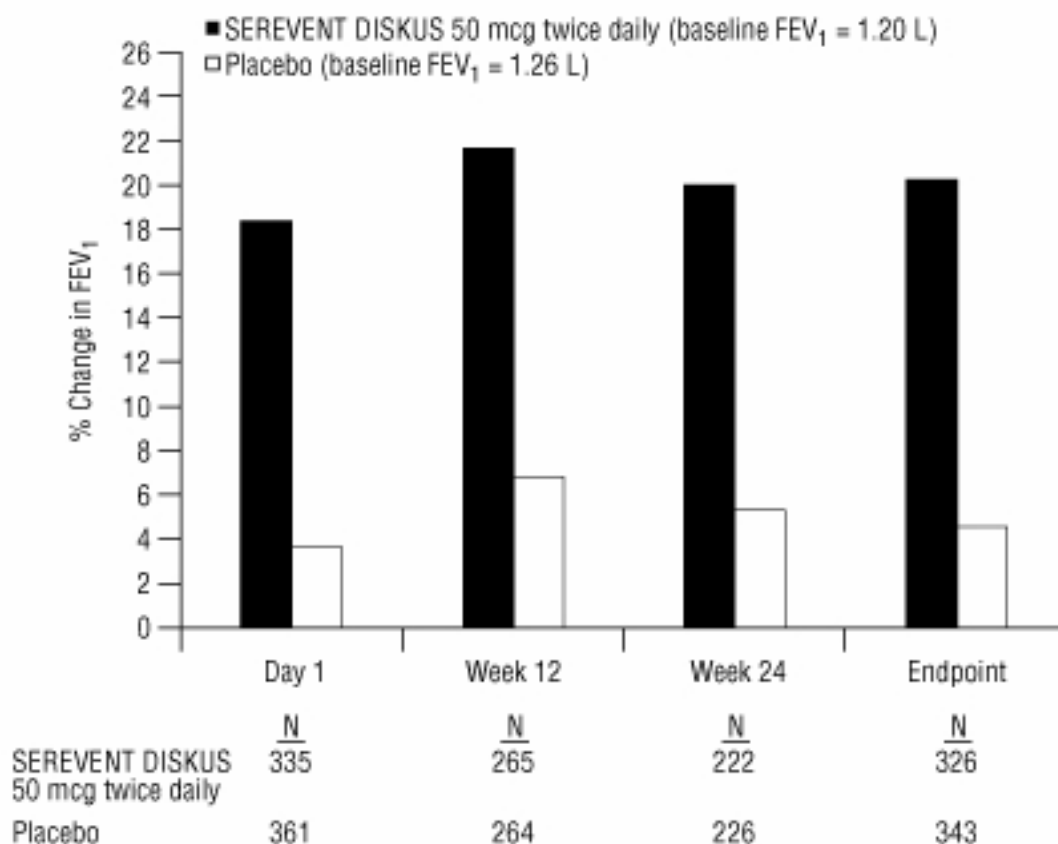


Chronic Obstructive Pulmonary Disease: In 2 clinical trials evaluating twice-daily

treatment with SEREVENT DISKUS 50 mcg (N = 336) compared to placebo (N = 366) in patients with chronic bronchitis with airflow limitation, with or without emphysema, improvements in pulmonary function endpoints were greater with salmeterol 50 mcg than with placebo. Treatment with SEREVENT DISKUS did not result in significant improvements in secondary endpoints assessing COPD symptoms in either clinical trial. Both trials were randomized, double-blind, parallel-group studies of 24 weeks' duration and were identical in design, patient entrance criteria, and overall conduct.

Figure 3 displays the integrated 2-hour postdose FEV₁ results from the 2 clinical trials. The percent change in FEV₁ refers to the change from baseline, defined as the predose value on Treatment Day 1. To account for patient withdrawals during the study, Endpoint (last evaluable FEV₁) data are provided. Patients receiving SEREVENT DISKUS 50 mcg had significantly greater improvements in 2-hour postdose FEV₁ at Endpoint (216 mL, 20%) compared to placebo (43 mL, 5%). Improvement was apparent on the first day of treatment and maintained throughout the 24 weeks of treatment.

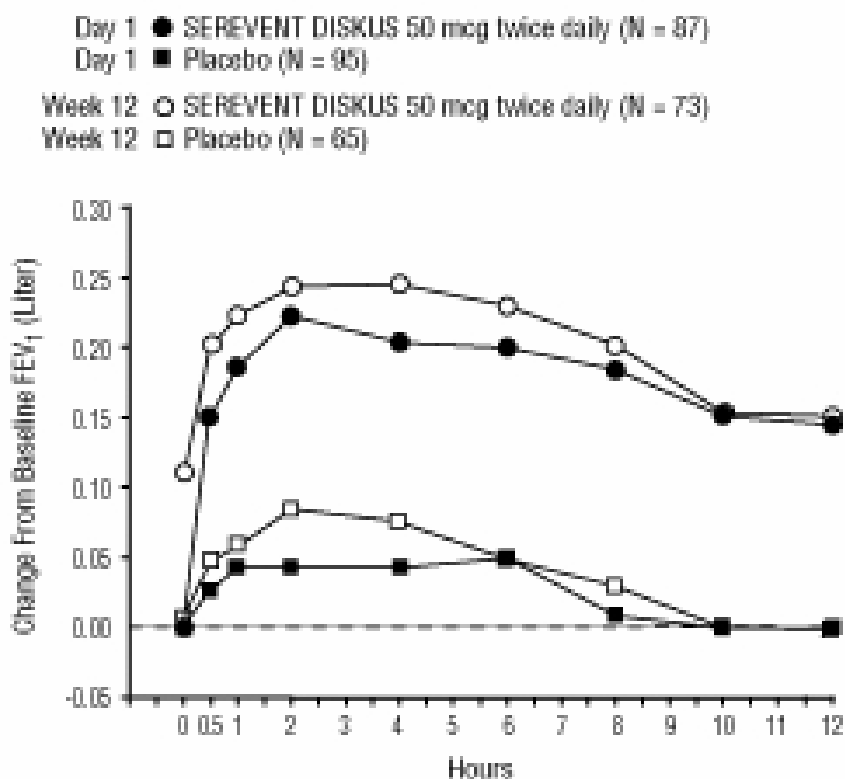
Figure 3. Mean Percent Change From Baseline in Postdose FEV₁ Integrated Data From 2 Trials of Patients With Chronic Bronchitis and Airflow Limitation



Onset of Action and Duration of Effect: The onset of action and duration of effect of

SEREVENT DISKUS were evaluated in a subset of patients (n = 87) from 1 of the 2 clinical trials discussed above. Following the first 50-mcg dose, significant improvement in pulmonary function (mean FEV₁ increase of 12% or more and at least 200 mL) occurred at 2 hours. The mean time to peak bronchodilator effect was 4.75 hours. As seen in Figure 4, evidence of bronchodilatation was seen throughout the 12-hour period. Figure 4 also demonstrates that the bronchodilating effect after 12 weeks of treatment was similar to that observed after the first dose. The mean time to peak bronchodilator effect after 12 weeks of treatment was 3.27 hours.

Figure 4. Serial 12-Hour FEV₁ on the First Day and at Week 12 of Treatment



INDICATIONS AND USAGE

Asthma: SEREVENT DISKUS is indicated for long-term, twice-daily (morning and evening) administration in the maintenance treatment of asthma and in the prevention of bronchospasm in patients 4 years of age and older with reversible obstructive airway disease, including patients with symptoms of nocturnal asthma.

Long-acting beta₂-adrenergic agonists, such as salmeterol, the active ingredient in SEREVENT DISKUS, may increase the risk of asthma-related death (see WARNINGS). Therefore, when treating patients with asthma, SEREVENT DISKUS should only be used as additional therapy 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 2 maintenance therapies, including SEREVENT DISKUS. It is not indicated for patients whose asthma can be managed by occasional use of inhaled, short-acting beta₂-agonists or 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.

SEREVENT DISKUS is also indicated for prevention of exercise-induced bronchospasm in patients 4 years of age and older.

Chronic Obstructive Pulmonary Disease: SEREVENT DISKUS is indicated for the long-term, twice-daily (morning and evening) administration in the maintenance treatment of bronchospasm associated with COPD (including emphysema and chronic bronchitis).

CONTRAINDICATIONS

SEREVENT DISKUS is contraindicated in patients with a history of hypersensitivity to salmeterol or any other component of the drug product (see DESCRIPTION and ADVERSE REACTIONS: Observed During Clinical Practice: *Non-Site Specific*).

WARNINGS

- **Long-acting beta₂-adrenergic agonists, such as salmeterol, the active ingredient in SEREVENT DISKUS, may increase the risk of asthma-related death. Therefore, when treating patients with asthma, SEREVENT DISKUS should only be used as additional therapy 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 2 maintenance therapies, including SEREVENT DISKUS.**
 - A large 28-week, placebo-controlled US study comparing the safety of salmeterol (SEREVENT Inhalation Aerosol) with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in patients receiving salmeterol (see CLINICAL TRIALS: Asthma: *Salmeterol Multi-center Asthma Research Trial*). Given the similar basic mechanisms of action of beta₂-agonists, it is possible that the findings seen in the SMART study represent a class effect.
 - A 16-week clinical study performed in the United Kingdom, the Salmeterol Nationwide Surveillance (SNS) study, showed results similar to the SMART study. In the SNS study, the rate of asthma-related death was numerically, though not statistically significantly, greater in patients with asthma treated with salmeterol (42 mcg twice daily) than those treated with albuterol (180 mcg 4 times daily) added to usual asthma therapy.
- **The SNS and SMART studies enrolled patients with asthma. No studies have been conducted that were adequate to determine whether the rate of death in patients with COPD is increased by long-acting beta₂-adrenergic agonists.**
- **It is important to watch for signs of worsening asthma, such as increasing use of inhaled, short-acting beta₂-agonists or a significant decrease in PEF or lung function.**

Such findings require immediate evaluation. Patients should be advised to seek immediate medical attention should their condition deteriorate.

- **SEREVENT DISKUS should not be used to treat acute symptoms.** It is crucial to inform patients of this and prescribe an inhaled, short-acting beta₂-agonist for this purpose and to warn them that increasing inhaled beta₂-agonist use is a signal of deteriorating asthma that requires prompt consultation with a physician.
- **SEREVENT DISKUS should not be initiated in patients with significantly worsening or acutely deteriorating asthma, which may be a life-threatening condition.** Serious acute respiratory events, including fatalities, have been reported both in the United States and worldwide when SEREVENT has been initiated in this situation. Although it is not possible from these reports to determine whether SEREVENT contributed to these adverse events or simply failed to relieve the deteriorating asthma, the use of SEREVENT DISKUS in this setting is inappropriate.
- **SEREVENT DISKUS is not a substitute for inhaled or oral corticosteroids.** Corticosteroids should not be stopped or reduced when SEREVENT DISKUS is initiated.

See **PRECAUTIONS: Information for Patients and the Medication Guide** accompanying the product.

The following additional WARNINGS about SEREVENT DISKUS should be noted.

1. **SEREVENT DISKUS should not be used as a treatment for acutely deteriorating asthma.**

SEREVENT DISKUS is intended for the maintenance treatment of asthma (see INDICATIONS AND USAGE) and should not be introduced in acutely deteriorating asthma, which is a potentially life-threatening condition. There are no data demonstrating that SEREVENT DISKUS provides greater efficacy than or additional efficacy to inhaled, short-acting beta₂-agonists in patients with worsening asthma. Serious acute respiratory events, including fatalities, have been reported both in the United States and worldwide in patients receiving SEREVENT. In most cases, these have occurred in patients with severe asthma (e.g., patients with a history of corticosteroid dependence, low pulmonary function, intubation, mechanical ventilation, frequent hospitalizations, or previous life-threatening acute asthma exacerbations) and/or in some patients in whom asthma has been acutely deteriorating (e.g., unresponsive to usual medications; increasing need for inhaled, short-acting beta₂-agonists; increasing need for systemic corticosteroids; significant increase in symptoms; recent emergency room visits; sudden or progressive deterioration in pulmonary function). However, they have occurred in a few patients with less severe asthma as well. It was not possible from these reports to determine whether SEREVENT contributed to these events.

2. **SEREVENT DISKUS should not be used to treat acute symptoms.** An inhaled, short-acting beta₂-agonist, not SEREVENT DISKUS, should be used to relieve acute asthma or COPD symptoms. When prescribing SEREVENT DISKUS, the physician must also provide the patient with an inhaled, short-acting beta₂-agonist (e.g., albuterol) for treatment of symptoms that occur acutely, despite regular twice-daily (morning and evening) use of SEREVENT DISKUS.

When beginning treatment with SEREVENT DISKUS, patients who have been taking 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 and use them only for symptomatic relief of acute asthma or COPD symptoms (see PRECAUTIONS: Information for Patients).

3. Increasing use of inhaled, short-acting beta₂-agonists is a marker of deteriorating asthma or COPD. The physician and patient should be alert to such changes. The patient's condition 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 PEF or lung function, these may be markers of destabilization of their disease. In this setting, the patient requires immediate reevaluation with reassessment of the treatment regimen, giving special consideration to the possible need for corticosteroids. If the patient uses 4 or more inhalations per day of an inhaled, short-acting beta₂-agonist for 2 or more consecutive days, or if more than 1 canister (200 inhalations per canister) of inhaled, short-acting beta₂-agonist is used in an 8-week period in conjunction with SEREVENT DISKUS, then the patient should consult the physician for reevaluation. **Increasing the daily dosage of SEREVENT DISKUS in this situation is not appropriate. SEREVENT DISKUS should not be used more frequently than twice daily (morning and evening) at the recommended dose of 1 inhalation.**

4. SEREVENT DISKUS should not be used in conjunction with an inhaled, long-acting beta₂-agonist. SEREVENT DISKUS should not be used with other medications containing long-acting beta₂-agonists.

5. SEREVENT DISKUS is not a substitute for oral or inhaled corticosteroids. There are no data demonstrating that SEREVENT DISKUS has a clinical anti-inflammatory effect and could be expected to take the place of corticosteroids. When initiating SEREVENT DISKUS in patients receiving oral or inhaled corticosteroids for treatment of asthma, patients should be continued on a suitable dose of corticosteroids to maintain clinical stability even if they feel better as a result of initiating SEREVENT DISKUS. Any change in corticosteroid dosage should be made ONLY after clinical evaluation (see PRECAUTIONS: Information for Patients).

6. The recommended dosage should not be exceeded. As with other inhaled beta₂-adrenergic drugs, SEREVENT DISKUS 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. Large doses of inhaled or oral salmeterol (12 to 20 times the recommended dose) have been associated with clinically significant prolongation of the QTc interval, which has the potential for producing ventricular arrhythmias.

7. Paradoxical bronchospasm. As with other inhaled asthma and COPD medications, SEREVENT DISKUS can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with SEREVENT DISKUS, it should be treated immediately with a short-acting, inhaled bronchodilator; SEREVENT DISKUS should be discontinued immediately; and alternative therapy should be instituted.

8. Immediate hypersensitivity reactions. Immediate hypersensitivity reactions may occur after

administration of SEREVENT DISKUS, as demonstrated by cases of urticaria, angioedema, rash, and bronchospasm.

9. Upper airway symptoms. Symptoms of laryngeal spasm, irritation, or swelling, such as stridor and choking, have been reported in patients receiving SEREVENT DISKUS.

10. Cardiovascular disorders. SEREVENT DISKUS, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension. SEREVENT DISKUS, like all other beta-adrenergic agonists, can 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 SEREVENT DISKUS at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce 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.

11. Potential drug interactions. Because of the potential for drug interactions and the potential for increased risk of cardiovascular adverse events, the concomitant use of SEREVENT DISKUS with strong CYP 3A4 inhibitors (e.g., ketoconazole, ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) is not recommended (see CLINICAL PHARMACOLOGY: Pharmacokinetics: *Drug Interactions*).

PRECAUTIONS

General: Cardiovascular Effects: No effect on the cardiovascular system is usually seen after the administration of inhaled salmeterol at recommended doses, but the cardiovascular and central nervous system effects seen with all sympathomimetic drugs (e.g., increased blood pressure, heart rate, excitement) can occur after use of salmeterol and may require discontinuation of SEREVENT DISKUS. SEREVENT DISKUS, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive disorders or thyrotoxicosis; and in patients who are unusually responsive to sympathomimetic amines.

As has been described with other beta-adrenergic agonist bronchodilators, clinically significant changes in systolic and/or diastolic blood pressure, pulse rate, and ECGs have been seen infrequently in individual patients in controlled clinical studies with salmeterol.

Metabolic Effects: Doses of the related beta₂-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis. Beta-adrenergic agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation.

Clinically significant changes in blood glucose and/or serum potassium were seen rarely during clinical studies with long-term administration of SEREVENT DISKUS at recommended

doses.

Information for Patients: Patients should be instructed to read the accompanying Medication Guide with each new prescription and refill. The complete text of the Medication Guide is reprinted at the end of this document.

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

It is important that patients understand how to use the DISKUS appropriately and how to use SEREVENT DISKUS in relation to other asthma or COPD medications they are taking. Patients should be given the following information:

- 1. Patients should be informed that salmeterol may increase the risk of asthma-related death.**
2. SEREVENT DISKUS is not meant to relieve acute asthma or COPD symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting bronchodilator (the physician should provide the patient with such medication and instruct the patient in how it should be used).
3. The physician should be notified immediately if any of the following signs of seriously worsening asthma or COPD occur:
 - decreasing effectiveness of inhaled, short-acting beta₂-agonists;
 - need for more inhalations than usual of inhaled, short-acting beta₂-agonists;
 - significant decrease in PEF or lung function as outlined by the physician;
 - use of 4 or more inhalations per day of a short-acting beta₂-agonist for 2 or more days consecutively;
 - use of more than 1 canister (200 inhalations per canister) of an inhaled, short-acting beta₂-agonist in an 8-week period.
4. Patients should not stop therapy with SEREVENT DISKUS for asthma or COPD without physician/provider guidance since symptoms may worsen after discontinuation.
5. SEREVENT DISKUS should not be used as a substitute for oral or inhaled corticosteroids. The dosage of these medications should not be changed and they should not be stopped without consulting the physician, even if the patient feels better after initiating treatment with SEREVENT DISKUS.
6. Patients should be cautioned regarding adverse effects associated with beta₂-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.
7. When patients are prescribed SEREVENT DISKUS, other medications for asthma and COPD should be used only as directed by the physician.
8. SEREVENT DISKUS should not be used with a spacer device.
9. Patients who are pregnant or nursing should contact the physician about the use of SEREVENT DISKUS.
10. The action of SEREVENT DISKUS may last up to 12 hours or longer. The recommended dosage (1 inhalation twice daily, morning and evening) should not be exceeded.

11. When used for the treatment of EIB, 1 inhalation of SEREVENT DISKUS should be taken 30 minutes before exercise.
 - Additional doses of SEREVENT should not be used for 12 hours.
 - Patients who are receiving SEREVENT DISKUS twice daily should not use additional SEREVENT for prevention of EIB.
12. Effective and safe use of SEREVENT DISKUS includes an understanding of the way that it should be used:
 - Never exhale into the DISKUS.
 - Never attempt to take the DISKUS apart.
 - Always activate and use the DISKUS in a level, horizontal position.
 - Never wash the mouthpiece or any part of the DISKUS. KEEP IT DRY.
 - Always keep the DISKUS in a dry place.
 - Discard **6 weeks** after removal from the moisture-protective foil overwrap pouch or after all blisters have been used (when the dose indicator reads “0”), whichever comes first.
13. For the proper use of SEREVENT DISKUS and to attain maximum benefit, the patient should read and follow carefully the Instructions for Using SEREVENT DISKUS in the Medication Guide accompanying the product.
14. Most patients are able to taste or feel a dose delivered from SEREVENT DISKUS. However, whether or not patients are able to sense delivery of a dose, they should not exceed the recommended dose of 1 inhalation twice daily, morning and evening. Patients should contact a physician or pharmacist if they have questions.

Drug Interactions: *Inhibitors of Cytochrome P450 3A4*: In a drug interaction study in 20 healthy subjects, coadministration of salmeterol (50 mcg twice daily) and ketoconazole (400 mg once daily) for 7 days resulted in greater systemic exposure to salmeterol (AUC increased 16-fold and C_{max} increased 1.4-fold). Three (3) subjects were withdrawn due to beta₂-agonist side effects (2 with prolonged QTc and 1 with palpitations and sinus tachycardia). Although there was no statistical effect on the mean QTc, coadministration of salmeterol and ketoconazole was associated with more frequent increases in QTc duration compared with salmeterol and placebo administration. Due to the potential increased risk of cardiovascular adverse events, the concomitant use of salmeterol with strong CYP3A4 inhibitors (e.g., ketoconazole, ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) is not recommended.

Short-Acting Beta₂-Agonists: In two 12-week, repetitive-dose adolescent and adult clinical trials in patients with asthma (N = 149), the mean daily need for additional beta₂-agonist in patients using SEREVENT DISKUS was approximately 1½ inhalations/day. Twenty-six percent (26%) of the patients in these trials used between 8 and 24 inhalations of short-acting beta-agonist per day on 1 or more occasions. Nine percent (9%) of the patients in these trials averaged over 4 inhalations/day over the course of the 12-week trials. No increase in frequency of cardiovascular events was observed among the 3 patients who averaged 8 to 11 inhalations/day; however, the safety of concomitant use of more than 8 inhalations/day of

short-acting beta₂-agonist with SEREVENT DISKUS has not been established. In 29 patients who experienced worsening of asthma while receiving SEREVENT DISKUS during these trials, albuterol therapy administered via either nebulizer or inhalation aerosol (1 dose in most cases) led to improvement in FEV₁ and no increase in occurrence of cardiovascular adverse events.

In 2 clinical trials in patients with COPD, the mean daily need for additional beta₂-agonist for patients using SEREVENT DISKUS was approximately 4 inhalations/day. Twenty-four percent (24%) of the patients using SEREVENT DISKUS in these trials averaged 6 or more inhalations of albuterol per day over the course of the 24-week trials. No increase in frequency of cardiovascular events was observed among patients who averaged 6 or more inhalations per day.

Monoamine Oxidase Inhibitors and Tricyclic Antidepressants: Salmeterol should be administered with extreme 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 salmeterol on the vascular system may be potentiated by these agents.

Corticosteroids and Cromoglycate: In clinical trials, inhaled corticosteroids and/or inhaled cromolyn sodium did not alter the safety profile of salmeterol when administered concurrently.

Methylxanthines: The concurrent use of intravenously or orally administered methylxanthines (e.g., aminophylline, theophylline) by patients receiving salmeterol has not been completely evaluated. In 1 clinical asthma trial, 87 patients receiving SEREVENT Inhalation Aerosol 42 mcg twice daily concurrently with a theophylline product had adverse event rates similar to those in 71 patients receiving SEREVENT Inhalation Aerosol without theophylline. Resting heart rates were slightly higher in the patients on theophylline but were little affected by therapy with SEREVENT Inhalation Aerosol.

In 2 clinical trials in patients with COPD, 39 subjects receiving SEREVENT DISKUS concurrently with a theophylline product had adverse event rates similar to those in 302 patients receiving SEREVENT DISKUS without theophylline. Based on the available data, the concomitant administration of methylxanthines with SEREVENT DISKUS did not alter the observed adverse event profile.

Beta-Adrenergic Receptor Blocking Agents: Beta-blockers not only block the pulmonary effect of beta-agonists, such as SEREVENT DISKUS, but may also produce severe bronchospasm in patients with asthma or COPD. Therefore, patients with asthma or COPD should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with asthma or COPD. 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 beta-agonists with nonpotassium-sparing diuretics.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In an 18-month oral carcinogenicity study in CD-mice, salmeterol xinafoate caused a dose-related increase in the incidence of smooth muscle hyperplasia, cystic glandular hyperplasia, leiomyomas of the uterus, and ovarian cysts at doses of 1.4 mg/kg and above (approximately 20 times the maximum recommended daily inhalation dose in adults and children based on comparison of the area under the plasma concentration versus time curves [AUCs]). The incidence of leiomyosarcomas was not statistically significant. No tumors were seen at 0.2 mg/kg (approximately 3 times the maximum recommended daily inhalation doses in adults and children based on comparison of the AUCs).

In a 24-month oral and inhalation carcinogenicity study in Sprague Dawley rats, salmeterol caused a dose-related increase in the incidence of mesovarian leiomyomas and ovarian cysts at doses of 0.68 mg/kg and above (approximately 55 times the maximum recommended daily inhalation dose in adults and approximately 25 times the maximum recommended daily inhalation dose in children on a mg/m² basis). No tumors were seen at 0.21 mg/kg (approximately 15 times the maximum recommended daily inhalation dose in adults and approximately 8 times the maximum recommended daily inhalation dose in children on a mg/m² basis). These findings in rodents are similar to those reported previously for other beta-adrenergic agonist drugs. The relevance of these findings to human use is unknown.

Salmeterol produced no detectable or reproducible increases in microbial and mammalian gene mutation in vitro. No clastogenic activity occurred in vitro in human lymphocytes or in vivo in a rat micronucleus test. No effects on fertility were identified in male and female rats treated with salmeterol at oral doses up to 2 mg/kg (approximately 160 times the maximum recommended daily inhalation dose in adults on a mg/m² basis).

Pregnancy: Teratogenic Effects: Pregnancy Category C. No teratogenic effects occurred in rats at oral doses up to 2 mg/kg (approximately 160 times the maximum recommended daily inhalation dose in adults on a mg/m² basis). In pregnant Dutch rabbits administered oral doses of 1 mg/kg and above (approximately 50 times the maximum recommended daily inhalation dose in adults based on comparison of the AUCs), salmeterol exhibited fetal toxic effects characteristically resulting from beta-adrenoceptor stimulation. These included precocious eyelid openings, cleft palate, sternebral fusion, limb and paw flexures, and delayed ossification of the frontal cranial bones. No significant effects occurred at an oral dose of 0.6 mg/kg (approximately 20 times the maximum recommended daily inhalation dose in adults based on comparison of the AUCs).

New Zealand White rabbits were less sensitive since only delayed ossification of the frontal bones was seen at an oral dose of 10 mg/kg (approximately 1,600 times the maximum recommended daily inhalation dose in adults on a mg/m² basis). Extensive use of other beta-agonists has provided no evidence that these class effects in animals are relevant to their use in humans. There are no adequate and well-controlled studies with SEREVENT DISKUS in pregnant women. SEREVENT DISKUS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Salmeterol xinafoate crossed the placenta following oral administration of 10 mg/kg to mice and rats (approximately 410 and 810 times, respectively, the maximum recommended daily inhalation dose in adults on a mg/m² basis).

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

Nursing Mothers: Plasma levels of salmeterol after inhaled therapeutic doses are very low. In rats, salmeterol xinafoate is excreted in the milk. However, since there are no data from controlled trials on the use of salmeterol by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue SEREVENT DISKUS, taking into account the importance of SEREVENT DISKUS to the mother. Caution should be exercised when SEREVENT DISKUS is administered to a nursing woman.

Pediatric Use: The safety and efficacy of SEREVENT DISKUS has been evaluated in over 2,500 patients aged 4 to 11 years with asthma, 346 of whom were administered SEREVENT DISKUS for 1 year. Based on available data, no adjustment of dosage of SEREVENT DISKUS in pediatric patients is warranted for either asthma or EIB (see DOSAGE AND ADMINISTRATION).

In 2 randomized, double-blind, controlled clinical trials of 12 weeks' duration, SEREVENT DISKUS 50 mcg was administered to 211 pediatric patients with asthma who did and who did not receive concurrent inhaled corticosteroids. The efficacy of SEREVENT DISKUS was demonstrated over the 12-week treatment period with respect to PEF and FEV₁. SEREVENT DISKUS was effective in demographic subgroups (gender and age) of the population. SEREVENT DISKUS was effective when coadministered with other inhaled asthma medications, such as short-acting bronchodilators and inhaled corticosteroids. SEREVENT DISKUS was well tolerated in the pediatric population, and there were no safety issues identified specific to the administration of SEREVENT DISKUS to pediatric patients.

In 2 randomized studies in children 4 to 11 years old with asthma and EIB, a single 50-mcg dose of SEREVENT DISKUS prevented EIB when dosed 30 minutes prior to exercise, with protection lasting up to 11.5 hours in repeat testing following this single dose in many patients.

Geriatric Use: Of the total number of adolescent and adult patients with asthma who received SEREVENT DISKUS in chronic dosing clinical trials, 209 were 65 years of age and older. Of the total number of patients with COPD who received SEREVENT DISKUS in chronic dosing clinical trials, 167 were 65 years of age or older and 45 were 75 years of age or older. No apparent differences in the safety of SEREVENT DISKUS were observed when geriatric patients were compared with younger patients in clinical trials. As with other beta₂-agonists, however, special caution should be observed when using SEREVENT DISKUS in geriatric patients who have concomitant cardiovascular disease that could be adversely affected by this class of drug. Data from the trials in patients with COPD suggested a greater effect on FEV₁ of SEREVENT DISKUS in the <65 years age-group, as compared with the ≥65 years age-group. However,

based on available data, no adjustment of dosage of SEREVENT DISKUS in geriatric patients is warranted.

ADVERSE REACTIONS

Data from a large, 28-week, placebo-controlled US study that compared the safety of salmeterol (SEREVENT Inhalation Aerosol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol (see WARNINGS and CLINICAL TRIALS: Asthma: *Salmeterol Multi-center Asthma Research Trial*).

Asthma: Two multicenter, 12-week, controlled studies have evaluated twice-daily doses of SEREVENT DISKUS in patients 12 years of age and older with asthma. Table 4 reports the incidence of adverse events in these 2 studies.

Table 4. Adverse Event Incidence in Two 12-Week Adolescent and Adult Clinical Trials in Patients With Asthma

Adverse Event	Percent of Patients		
	Placebo (N = 152)	SEREVENT DISKUS 50 mcg Twice Daily (N = 149)	Albuterol Inhalation Aerosol 180 mcg 4 Times Daily (N = 150)
Ear, nose, and throat			
Nasal/sinus congestion, pallor	6	9	8
Rhinitis	4	5	4
Neurological			
Headache	9	13	12
Respiratory			
Asthma	1	3	<1
Tracheitis/bronchitis	4	7	3
Influenza	2	5	5

Table 4 includes all events (whether considered drug-related or nondrug-related by the investigator) that occurred at a rate of 3% or greater in the group receiving SEREVENT DISKUS and were more common than in the placebo group.

Pharyngitis, sinusitis, upper respiratory tract infection, and cough occurred at $\geq 3\%$ but were more common in the placebo group. However, throat irritation has been described at rates exceeding that of placebo in other controlled clinical trials.

Other adverse events that occurred in the group receiving SEREVENT DISKUS in these studies with an incidence of 1% to 3% and that occurred at a greater incidence than with placebo were:

Ear, Nose, and Throat: Sinus headache.

Gastrointestinal: Nausea.

Mouth and Teeth: Oral mucosal abnormality.

Musculoskeletal: Pain in joint.

Neurological: Sleep disturbance, paresthesia.

Skin: Contact dermatitis, eczema.

Miscellaneous: Localized aches and pains, pyrexia of unknown origin.

Two multicenter, 12-week, controlled studies have evaluated twice-daily doses of SEREVENT DISKUS in patients aged 4 to 11 years with asthma. Table 5 includes all events (whether considered drug-related or nondrug-related by the investigator) that occurred at a rate of 3% or greater in the group receiving SEREVENT DISKUS and were more common than in the placebo group.

Table 5. Adverse Event Incidence in Two 12-Week Pediatric Clinical Trials in Patients With Asthma

Adverse Event	Percent of Patients		
	Placebo (N = 215)	SEREVENT DISKUS 50 mcg Twice Daily (N = 211)	Albuterol Inhalation Powder 200 mcg 4 Times Daily (N = 115)
Ear, nose, and throat			
Ear signs and symptoms	3	4	9
Pharyngitis	3	6	3
Neurological			
Headache	14	17	20
Respiratory			
Asthma	2	4	<1
Skin			
Skin rashes	3	4	2
Urticaria	0	3	2

The following events were reported at an incidence of 1% to 2% (3 to 4 patients) in the salmeterol group and with a higher incidence than in the albuterol and placebo groups: gastrointestinal signs and symptoms, lower respiratory signs and symptoms, photodermatitis, and arthralgia and articular rheumatism.

In clinical trials evaluating concurrent therapy of salmeterol with inhaled corticosteroids, adverse events were consistent with those previously reported for salmeterol, or with events that would be expected with the use of inhaled corticosteroids.

Chronic Obstructive Pulmonary Disease: Two multicenter, 24-week, controlled studies

have evaluated twice-daily doses of SEREVENT DISKUS in patients with COPD. For presentation (Table 6), the placebo data from a third trial, identical in design, patient entrance criteria, and overall conduct but comparing fluticasone propionate with placebo, were integrated with the placebo data from these 2 studies (total N = 341 for salmeterol and 576 for placebo).

Table 6. Adverse Events With $\geq 3\%$ Incidence in US Controlled Clinical Trials With SEREVENT DISKUS in Patients With Chronic Obstructive Pulmonary Disease*

Adverse Event	Percent of Patients	
	Placebo (N = 576)	SEREVENT DISKUS 50 mcg Twice Daily (N = 341)
Cardiovascular		
Hypertension	2	4
Ear, nose, and throat		
Throat irritation	6	7
Nasal congestion/blockage	3	4
Sinusitis	2	4
Ear signs and symptoms	1	3
Gastrointestinal		
Nausea and vomiting	3	3
Lower respiratory		
Cough	4	5
Rhinitis	2	4
Viral respiratory infection	4	5
Musculoskeletal		
Musculoskeletal pain	10	12
Muscle cramps and spasms	1	3
Neurological		
Headache	11	14
Dizziness	2	4
Average duration of exposure (days)	128.9	138.5

* Table 6 includes all events (whether considered drug-related or nondrug-related by the investigator) that occurred at a rate of 3% or greater in the group receiving SEREVENT DISKUS and were more common in the group receiving SEREVENT DISKUS than in the placebo group.

Other events occurring in the group receiving SEREVENT DISKUS that occurred at a frequency of 1% to <3% and were more common than in the placebo group were as follows:

Endocrine and Metabolic: Hyperglycemia.

Eye: Keratitis and conjunctivitis.

Gastrointestinal: Candidiasis mouth/throat, dyspeptic symptoms, hyposalivation, dental discomfort and pain, gastrointestinal infections.

Lower Respiratory: Lower respiratory signs and symptoms.

Musculoskeletal: Arthralgia and articular rheumatism; muscle pain; bone and skeletal pain; musculoskeletal inflammation; muscle stiffness, tightness, and rigidity.

Neurology: Migraines.

Non-Site Specific: Pain, edema and swelling.

Psychiatry: Anxiety.

Skin: Skin rashes.

Adverse reactions to salmeterol are similar in nature to those seen with other selective beta₂-adrenoceptor agonists, i.e., tachycardia; palpitations; immediate hypersensitivity reactions, including urticaria, angioedema, rash, bronchospasm (see WARNINGS); headache; tremor; nervousness; and paradoxical bronchospasm (see WARNINGS).

Observed During Clinical Practice: In addition to adverse events reported from clinical trials, the following events have been identified during postapproval use of salmeterol. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, or causal connection to salmeterol or a combination of these factors.

In extensive US and worldwide postmarketing experience with salmeterol, serious exacerbations of asthma, including some that have been fatal, have been reported. In most cases, these have occurred in patients with severe asthma and/or in some patients in whom asthma has been acutely deteriorating (see WARNINGS), but they have also occurred in a few patients with less severe asthma. It was not possible from these reports to determine whether salmeterol contributed to these events.

Respiratory: Reports of upper airway symptoms of laryngeal spasm, irritation, or swelling such as stridor or choking; oropharyngeal irritation.

Cardiovascular: Arrhythmias (including atrial fibrillation, supraventricular tachycardia, extrasystoles), and anaphylaxis.

Non-Site Specific: Very rare anaphylactic reaction in patients with severe milk protein allergy.

OVERDOSAGE

The expected signs and symptoms with overdosage of SEREVENT DISKUS are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and symptoms listed under ADVERSE REACTIONS, e.g., seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, and insomnia. Overdosage with SEREVENT DISKUS may be expected to result in exaggeration of the pharmacologic adverse effects associated with beta-adrenoceptor agonists, including tachycardia

and/or arrhythmia, tremor, headache, and muscle cramps. Overdosage with SEREVENT DISKUS can lead to clinically significant prolongation of the QTc interval, which can produce ventricular arrhythmias. Other signs of overdosage may include hypokalemia and hyperglycemia.

As with all sympathomimetic medications, cardiac arrest and even death may be associated with abuse of SEREVENT DISKUS.

Treatment consists of discontinuation of SEREVENT DISKUS together with appropriate symptomatic 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 SEREVENT DISKUS. Cardiac monitoring is recommended in cases of overdosage.

No deaths were seen in rats at an inhalation dose of 2.9 mg/kg (approximately 240 times the maximum recommended daily inhalation dose in adults and approximately 110 times the maximum recommended daily inhalation dose in children on a mg/m² basis) and in dogs at an inhalation dose of 0.7 mg/kg (approximately 190 times the maximum recommended daily inhalation dose in adults and approximately 90 times the maximum recommended daily inhalation dose in children on a mg/m² basis). By the oral route, no deaths occurred in mice at 150 mg/kg (approximately 6,100 times the maximum recommended daily inhalation dose in adults and approximately 2,900 times the maximum recommended daily inhalation dose in children on a mg/m² basis) and in rats at 1,000 mg/kg (approximately 81,000 times the maximum recommended daily inhalation dose in adults and approximately 38,000 times the maximum recommended daily inhalation dose in children on a mg/m² basis).

DOSAGE AND ADMINISTRATION

SEREVENT DISKUS should be administered by the orally inhaled route only (see Instructions for Using SEREVENT DISKUS in the Medication Guide accompanying the product). The patient must not exhale into the DISKUS and the DISKUS should only be activated and used in a level, horizontal position.

Asthma: Long-acting beta₂-adrenergic agonists, such as salmeterol, the active ingredient in SEREVENT DISKUS, may increase the risk of asthma-related death (see WARNINGS). Therefore, when treating patients with asthma, SEREVENT DISKUS should only be used as additional therapy 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 2 maintenance therapies, including SEREVENT DISKUS. It is not indicated for patients whose asthma can be managed by occasional use of inhaled, short-acting beta₂-agonists or 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.

For maintenance of bronchodilatation and prevention of symptoms of asthma, including the symptoms of nocturnal asthma, the usual dosage for adults and children 4 years of age and older

is 1 inhalation (50 mcg) twice daily (morning and evening, approximately 12 hours apart). If a previously effective dosage regimen fails to provide the usual response, medical advice should be sought immediately as this is often a sign of destabilization of asthma. Under these circumstances, the therapeutic regimen should be reevaluated. If symptoms arise in the period between doses, an inhaled, short-acting beta₂-agonist should be taken for immediate relief.

Chronic Obstructive Pulmonary Disease: For maintenance treatment of bronchospasm associated with COPD (including chronic bronchitis and emphysema), the usual dosage for adults is 1 inhalation (50 mcg) twice daily (morning and evening, approximately 12 hours apart).

For both asthma and COPD, adverse effects are more likely to occur with higher doses of salmeterol, and more frequent administration or administration of a larger number of inhalations is not recommended.

To gain full therapeutic benefit, SEREVENT DISKUS should be administered twice daily (morning and evening) in the treatment of reversible airway obstruction.

Geriatric Use: Based on available data for SEREVENT DISKUS, no dosage adjustment is recommended.

Prevention of Exercise-Induced Bronchospasm: One inhalation of SEREVENT DISKUS at least 30 minutes before exercise has been shown to protect patients against EIB. When used intermittently as needed for prevention of EIB, this protection may last up to 9 hours in adolescents and adults and up to 12 hours in patients 4 to 11 years of age. Additional doses of SEREVENT should not be used for 12 hours after the administration of this drug. Patients who are receiving SEREVENT DISKUS twice daily should not use additional SEREVENT for prevention of EIB. If regular, twice-daily dosing is not effective in preventing EIB, other appropriate therapy for EIB should be considered.

HOW SUPPLIED

SEREVENT DISKUS is supplied as a disposable teal green unit containing 60 blisters. The drug product is packaged within a teal green, plastic-coated, moisture-protective foil pouch (NDC 0173-0521-00).

SEREVENT DISKUS is also supplied in an institutional pack of 1 disposable teal green unit containing 28 blisters. The drug product is packaged within a teal green, plastic-coated, moisture-protective foil pouch (NDC 0173-0520-00).

Store at controlled room temperature (see USP), 20° to 25°C (68° to 77°F) in a dry place away from direct heat or sunlight. Keep out of reach of children. SEREVENT DISKUS should be discarded 6 weeks after removal from the moisture-protective foil pouch or after all blisters have been used (when the dose indicator reads “0”), whichever comes first. The DISKUS is not reusable. Do not attempt to take the DISKUS apart.



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MEDICATION GUIDE

SEREVENT[®] [*ser' uh-vent*] DISKUS[®] (salmeterol xinafoate inhalation powder)

Read the Medication Guide that comes with SEREVENT DISKUS 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 SEREVENT DISKUS?

SEREVENT DISKUS is a medicine called a long-acting beta₂-agonist or LABA. LABA medicines are used in patients with asthma, exercise-induced bronchospasm (EIB), and chronic obstructive pulmonary disease (COPD). LABA medicines help the muscles around the airways in your lungs stay relaxed to prevent 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 cause death if not treated right away.

- **In patients with asthma, LABA medicines, such as SEREVENT DISKUS, may increase the chance of death from asthma problems.** In a large asthma study, more patients who used salmeterol (SEREVENT) died from asthma problems compared with patients who did not use salmeterol (SEREVENT). Talk with your healthcare provider about this risk and the benefits of treating your asthma with SEREVENT DISKUS.
- **SEREVENT DISKUS does not relieve sudden symptoms. Always have a short-acting beta₂-agonist medicine with you to treat sudden symptoms. If you do not have an inhaled, short-acting bronchodilator, contact your healthcare provider to have one prescribed for you.**
- **Do not stop using SEREVENT DISKUS unless told to do so by your healthcare provider because your symptoms might get worse.**

- **SEREVENT DISKUS:**
 - should not be the only medicine prescribed for your asthma
 - 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 SEREVENT DISKUS. 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 SEREVENT DISKUS?

SEREVENT DISKUS is a long-acting beta₂-agonist medicine (LABA). SEREVENT DISKUS is used for asthma, exercise-induced bronchospasm (EIB), and chronic obstructive pulmonary disease (COPD) as follows:

Asthma

SEREVENT DISKUS is used long term, twice a day, to control symptoms of asthma, and prevent symptoms such as wheezing in adults and children ages 4 and older.

Because LABA medicines, such as SEREVENT DISKUS, may increase the chance of death from asthma problems, SEREVENT DISKUS is not for adults and children 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

Exercise-Induced Bronchospasm (EIB)

SEREVENT DISKUS is used for the prevention of wheezing caused by exercise in adults and children 4 years of age and older.

Chronic Obstructive Pulmonary Disease (COPD)

SEREVENT DISKUS is used long term, twice a day in controlling symptoms of COPD and preventing wheezing in adults with COPD.

What should I tell my healthcare provider before using SEREVENT DISKUS?

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**
- **are pregnant or planning to become pregnant.** It is not known if SEREVENT DISKUS may harm your unborn baby.
- **are breastfeeding.** It is not known if SEREVENT DISKUS passes into your milk and if it can harm your baby.
- **are allergic to SEREVENT DISKUS, any other medicines, or food products**

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

Know 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 SEREVENT DISKUS?

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

- Children should use SEREVENT DISKUS with an adult's help, as instructed by the child's healthcare provider.
- Use SEREVENT DISKUS exactly as prescribed. **Do not use SEREVENT DISKUS more often than prescribed.**
- For asthma and COPD, the usual dose is 1 inhalation twice a day (morning and evening). The 2 doses should be about 12 hours apart.
- For preventing exercise-induced bronchospasm, take 1 inhalation at least 30 minutes before exercise. Do not use SEREVENT DISKUS more often than every 12 hours. Do not use extra SEREVENT DISKUS before exercise if you already use it twice a day.
- If you miss a dose of SEREVENT DISKUS, just skip that dose. Take your next dose at your

usual time. Do not take 2 doses at one time.

- Do not use a spacer device with SEREVENT DISKUS.
- Do not breathe into SEREVENT DISKUS.
- **While you are using SEREVENT DISKUS twice a day, do not use other medicines that contain a long-acting beta₂-agonist or LABA for any reason. Other LABA medicines include ADVAIR DISKUS[®] (fluticasone propionate and salmeterol inhalation powder), ADVAIR[®] HFA (fluticasone propionate and salmeterol) Inhalation Aerosol, FORADIL[®] AEROLIZER[®] (formoterol fumarate inhalation powder), SYMBICORT[®] (budesonide and formoterol fumarate dihydrate) Inhalation Aerosol, PERFOROMIST[™] (formoterol fumarate) Inhalation Solution, and BROVANA[™] (arformoterol tartrate) Inhalation Solution.**
- 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 SEREVENT DISKUS.
- **Call your healthcare provider or get medical care right away if:**
 - your breathing problems worsen with SEREVENT DISKUS
 - you need to use your short-acting beta₂-agonist medicine more often than usual
 - your short-acting beta₂-agonist medicine does not work as well for you at relieving symptoms
 - you need to use 4 or more inhalations of your short-acting beta₂-agonist medicine for 2 or more days in a row
 - you use 1 whole canister of your short-acting beta₂-agonist medicine in 8 weeks' time
 - your peak flow meter results decrease. Your healthcare provider will tell you the numbers that are right for you.
 - you have asthma and your symptoms do not improve after using SEREVENT DISKUS regularly for 1 week.

What are the possible side effects with SEREVENT DISKUS?

- **In patients with asthma, LABA medicines, such as SEREVENT, may increase the chance of death from asthma problems.** See “What is the most important information I should know about SEREVENT DISKUS?”

Other possible side effects with SEREVENT DISKUS 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.
- **increased blood pressure**
- **a fast and irregular heartbeat**
- **chest pain**
- **headache**
- **tremor**
- **nervousness**
- **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 SEREVENT DISKUS. Ask your healthcare provider or pharmacist for more information.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How do I store SEREVENT DISKUS?

- Store SEREVENT DISKUS at room temperature between 68° to 77° F (20° to 25° C). Keep in a dry place away from heat and sunlight.
- Safely discard SEREVENT DISKUS 6 weeks after you remove it from the foil pouch, or after the dose indicator reads “0”, whichever comes first.
- **Keep SEREVENT DISKUS and all medicines out of the reach of children.**

General Information about SEREVENT DISKUS

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

This Medication Guide summarizes the most important information about SEREVENT DISKUS. If you would like more information, talk with your healthcare provider or pharmacist. You can ask your healthcare provider or pharmacist for information about SEREVENT DISKUS that was written for healthcare professionals. You can also contact the company that makes SEREVENT DISKUS (toll free) at 1-888-825-5249 or at www.serevent.com.

Instructions for Using SEREVENT DISKUS

Follow the instructions below for using your SEREVENT DISKUS. **You will breathe in**

(inhale) the medicine from the **DISKUS**. If you have any questions, ask your healthcare provider or pharmacist.



Take the SEREVENT DISKUS out of the box and foil pouch. Write the **“Pouch opened”** and **“Use by”** dates on the label on top of the DISKUS. The **“Use by”** date is 6 weeks from date of opening the pouch.

- The DISKUS will be in the closed position when the pouch is opened.
- The **dose indicator** on the top of the DISKUS tells you how many doses are left. The dose indicator number will decrease each time you use the DISKUS. After you have used 55 doses from the DISKUS, the numbers 5 to 0 will appear in **red** to warn you that there are only a few doses left (*see Figure 1*).



Figure 1

Taking a dose from the DISKUS requires the following 3 simple steps: Open, Click, Inhale.

1. OPEN

Hold the DISKUS in one hand and put the thumb of your other hand on the **thumbgrip**. Push your thumb away from you as far as it will go until the mouthpiece appears and snaps into position (*see Figure 2*).



Figure 2

2. CLICK

Hold the DISKUS in a level, flat position with the mouthpiece towards you. Slide the **lever** away from you as far as it will go until it **clicks** (*see Figure 3*). The DISKUS is now ready to use.



Figure 3

Every time the **lever** is pushed back, a dose is ready to be inhaled. This is shown by a decrease in numbers on the dose counter. **To avoid releasing or wasting doses once the DISKUS is ready:**

- Do not close the DISKUS.
- Do not tilt the DISKUS.
- Do not play with the lever.
- Do not move the lever more than once.

3. INHALE

Before inhaling your dose from the DISKUS, breathe out (exhale) fully while holding the DISKUS level and away from your mouth (*see Figure 4*). **Remember, never breathe out into the DISKUS mouthpiece.**



Figure 4

Put the mouthpiece to your lips (*see Figure 5*). Breathe in quickly and deeply through the DISKUS. Do not breathe in through your nose.



Figure 5

Remove the DISKUS from your mouth. Hold your breath for about 10 seconds, or for as

long as is comfortable. Breathe out slowly.

The DISKUS delivers your dose of medicine as a very fine powder. Most patients can taste or feel the powder. Do not use another dose from the DISKUS if you do not feel or taste the medicine.

4. **Close the DISKUS when you are finished taking a dose so that the DISKUS will be ready for you to take your next dose.** Put your thumb on the thumbgrip and slide the thumbgrip back towards you as far as it will go (*see Figure 6*). The DISKUS will click shut. The lever will automatically return to its original position. The DISKUS is now ready for you to take your next scheduled dose, due in about 12 hours. (Repeat steps 1 to 4.)



Figure 6

Remember:

- Never breathe into the DISKUS.
- Never take the DISKUS apart.
- Always ready and use the DISKUS in a level, flat position.
- Do not use the DISKUS with a spacer device.
- Never wash the mouthpiece or any part of the DISKUS. **Keep it dry.**
- Always keep the DISKUS in a dry place.
- Never take an extra dose, even if you did not taste or feel the medicine.

Rx only



GlaxoSmithKline

Research Triangle Park, NC 27709

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SRD:2MG

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

FORADIL[®] AEROLIZER[®]

(formoterol fumarate inhalation powder)

For Oral Inhalation Only

Rx only

Prescribing Information

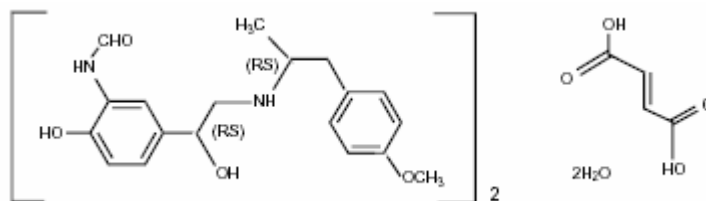
WARNING: Long-acting beta₂-adrenergic agonists may increase the risk of asthma-related death. Therefore, when treating patients with asthma, FORADIL AEROLIZER should only be used as additional therapy for patients not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with two maintenance therapies, including FORADIL AEROLIZER. 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), the active ingredient in FORADIL AEROLIZER (see WARNINGS).

DESCRIPTION

FORADIL[®] AEROLIZER[®] consists of a capsule dosage form containing a dry powder formulation of FORADIL (formoterol fumarate) intended for oral inhalation only with the AEROLIZER Inhaler.

Each clear, hard gelatin capsule contains a dry powder blend of 12 mcg of formoterol fumarate and 25 mg of lactose (which contains trace levels of milk proteins) as a carrier.

The active component of FORADIL is formoterol fumarate, a racemate. Formoterol fumarate is a selective β_2 -adrenergic bronchodilator. Its chemical name is (±)-2-hydroxy-5-[(1RS)-1-hydroxy-2-[(1RS)-2-(4-methoxyphenyl)-1-methylethyl]-amino]ethyl]formanilide fumarate dihydrate; its structural formula is



Formoterol fumarate has a molecular weight of 840.9, and its empirical formula is $(C_{19}H_{24}N_2O_4)_2 \cdot C_4H_4O_4 \cdot 2H_2O$. Formoterol fumarate is a white to yellowish crystalline powder, which is freely soluble in glacial acetic acid, soluble in methanol, sparingly soluble in ethanol and isopropanol, slightly soluble in water, and practically insoluble in acetone, ethyl acetate, and diethyl ether.

The AEROLIZER Inhaler is a plastic device used for inhaling FORADIL. The amount of drug delivered to the lung will depend on patient factors, such as inspiratory flow rate and inspiratory time. Under standardized in vitro testing at a fixed flow rate of 60 L/min for 2 seconds, the AEROLIZER Inhaler delivered 10 mcg of formoterol fumarate from the mouthpiece. Peak inspiratory flow rates (PIFR) achievable through the AEROLIZER Inhaler were evaluated in 33 adult and adolescent patients and 32 pediatric patients with mild-to-moderate asthma. Mean PIFR was 117.82 L/min (range 34-188 L/min) for adult and adolescent patients, and

99.66 L/min (range 43-187 L/min) for pediatric patients. Approximately ninety percent of each population studied generated a PIFR through the device exceeding 60 L/min.

To use the delivery system, a FORADIL capsule is placed in the well of the AEROLIZER Inhaler, and the capsule is pierced by pressing and releasing the buttons on the side of the device. The formoterol fumarate formulation is dispersed into the air stream when the patient inhales rapidly and deeply through the mouthpiece.

CLINICAL PHARMACOLOGY

Mechanism of Action

Formoterol fumarate is a long-acting selective β_2 -adrenergic receptor agonist (β_2 -agonist). 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 β_2 -receptors than at β_1 -receptors. Although β_2 -receptors are the predominant adrenergic receptors in bronchial smooth muscle and β_1 -receptors are the predominant receptors in the heart, there are also β_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 β_2 -agonists may have cardiac effects.

The pharmacologic effects of β_2 -adrenoceptor agonist drugs, including formoterol, are at least in part attributable to stimulation of intracellular adenylyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3', 5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

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

responsiveness. The relevance of these in vitro and animal findings to humans is unknown.

Animal Pharmacology

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

Pharmacokinetics

Information on the pharmacokinetics of formoterol in plasma has been obtained in healthy subjects by oral inhalation of doses higher than the recommended range and in Chronic Obstructive Pulmonary Disease (COPD) patients after oral inhalation of doses at and above the therapeutic dose. Urinary excretion of unchanged formoterol was used as an indirect measure of systemic exposure. Plasma drug disposition data parallel urinary excretion, and the elimination half-lives calculated for urine and plasma are similar.

Absorption

Following inhalation of a single 120 mcg dose of formoterol fumarate by 12 healthy subjects, formoterol was rapidly absorbed into plasma, reaching a maximum drug concentration of 92 pg/mL within 5 minutes of dosing. In COPD patients treated for 12 weeks with formoterol fumarate 12 or 24 mcg b.i.d., the mean plasma concentrations of formoterol ranged between 4.0 and 8.8 pg/mL and 8.0 and 17.3 pg/mL, respectively, at 10 min, 2 h and 6 h post inhalation.

Following inhalation of 12 to 96 mcg of formoterol fumarate by 10 healthy males, urinary excretion of both (R,R)- and (S,S)-enantiomers of formoterol increased proportionally to the dose. Thus, absorption of formoterol following inhalation appeared linear over the dose range studied.

In a study in patients with asthma, when formoterol 12 or 24 mcg twice daily was given by oral inhalation for 4 weeks or 12 weeks, the accumulation index, based

on the urinary excretion of unchanged formoterol ranged from 1.63 to 2.08 in comparison with the first dose. For COPD patients, when formoterol 12 or 24 mcg twice daily was given by oral inhalation for 12 weeks, the accumulation index, based on the urinary excretion of unchanged formoterol was 1.19 - 1.38. This suggests some accumulation of formoterol in plasma with multiple dosing. The excreted amounts of formoterol at steady-state were close to those predicted based on single-dose kinetics. As with many drug products for oral inhalation, it is likely that the majority of the inhaled formoterol fumarate delivered is swallowed and then absorbed from the gastrointestinal tract.

Distribution

The binding of formoterol to human plasma proteins in vitro was 61%-64% at concentrations from 0.1 to 100 ng/mL. Binding to human serum albumin in vitro was 31%-38% over a range of 5 to 500 ng/mL. The concentrations of formoterol used to assess the plasma protein binding were higher than those achieved in plasma following inhalation of a single 120 mcg dose.

Metabolism

Formoterol is metabolized primarily by direct glucuronidation at either the phenolic or aliphatic hydroxyl group and O-demethylation followed by glucuronide conjugation at either phenolic hydroxyl groups. Minor pathways involve sulfate conjugation of formoterol and deformylation followed by sulfate conjugation. The most prominent pathway involves direct conjugation at the phenolic hydroxyl group. The second major pathway involves O-demethylation followed by conjugation at the phenolic 2'-hydroxyl group. Four cytochrome P450 isozymes (CYP2D6, CYP2C19, CYP2C9 and CYP2A6) are involved in the O-demethylation of formoterol. Formoterol did not inhibit CYP450 enzymes at therapeutically relevant concentrations. Some patients may be deficient in CYP2D6 or 2C19 or both. Whether a deficiency in one or both of these isozymes results in elevated systemic exposure to formoterol or systemic adverse effects has not been adequately explored.

Excretion

Following oral administration of 80 mcg of radiolabeled formoterol fumarate to 2 healthy subjects, 59%-62% of the radioactivity was eliminated in the urine and 32%-34% in the feces over a period of 104 hours. Renal clearance of formoterol from blood in these subjects was about 150 mL/min. Following inhalation of a 12 mcg or 24 mcg dose by 16 patients with asthma, about 10% and 15%-18% of the total dose was excreted in the urine as unchanged formoterol and direct conjugates of formoterol, respectively. Following inhalation of 12 mcg or 24 mcg dose by 18 patients with COPD the corresponding values were 7% and 6-9% of the dose, respectively.

Based on plasma concentrations measured following inhalation of a single 120 mcg dose by 12 healthy subjects, the mean terminal elimination half-life was determined to be 10 hours. From urinary excretion rates measured in these subjects, the mean terminal elimination half-lives for the (R,R)- and (S,S)-enantiomers were determined to be 13.9 and 12.3 hours, respectively. The (R,R)- and (S,S)-enantiomers represented about 40% and 60% of unchanged drug excreted in the urine, respectively, following single inhaled doses between 12 and 120 mcg in healthy volunteers and single and repeated doses of 12 and 24 mcg in patients with asthma. Thus, the relative proportion of the two enantiomers remained constant over the dose range studied and there was no evidence of relative accumulation of one enantiomer over the other after repeated dosing.

Special Populations

Gender: After correction for body weight, formoterol pharmacokinetics did not differ significantly between males and females.

Geriatric and Pediatric: The pharmacokinetics of formoterol have not been studied in the elderly population, and limited data are available in pediatric patients.

In a study of children with asthma who were 5 to 12 years of age, when formoterol fumarate 12 or 24 mcg was given twice daily by oral inhalation for 12 weeks, the accumulation index ranged from 1.18 to 1.84 based on urinary excretion

of unchanged formoterol. Hence, the accumulation in children did not exceed that in adults, where the accumulation index ranged from 1.63 to 2.08 (see above). Approximately 6% and 6.5% to 9% of the dose was recovered in the urine of the children as unchanged and conjugated formoterol, respectively.

Hepatic/Renal Impairment: The pharmacokinetics of formoterol have not been studied in subjects with hepatic or renal impairment.

Pharmacodynamics

Systemic Safety and Pharmacokinetic/Pharmacodynamic Relationships

The major adverse effects of inhaled beta₂-agonists occur as a result of excessive activation of the systemic beta-adrenergic receptors. The most common adverse effects in adults and adolescents include skeletal muscle tremor and cramps, insomnia, tachycardia, decreases in plasma potassium, and increases in plasma glucose.

Pharmacokinetic/pharmacodynamic (PK/PD) relationships between heart rate, ECG parameters, and serum potassium levels and the urinary excretion of formoterol were evaluated in 10 healthy male volunteers (25 to 45 years of age) following inhalation of single doses containing 12, 24, 48, or 96 mcg of formoterol fumarate. There was a linear relationship between urinary formoterol excretion and decreases in serum potassium, increases in plasma glucose, and increases in heart rate.

In a second study, PK/PD relationships between plasma formoterol levels and pulse rate, ECG parameters, and plasma potassium levels were evaluated in 12 healthy volunteers following inhalation of a single 120 mcg dose of formoterol fumarate (10 times the recommended clinical dose). Reductions of plasma potassium concentration were observed in all subjects. Maximum reductions from baseline ranged from 0.55 to 1.52 mmol/L with a median maximum reduction of 1.01 mmol/L. The formoterol plasma concentration was highly correlated with the reduction in plasma potassium concentration. Generally, the maximum effect on plasma potassium was noted 1 to 3 hours after peak formoterol plasma concentrations were achieved. A mean maximum increase of pulse rate of 26 bpm

was observed 6 hours post dose. The maximum increase of mean corrected QT interval (QTc) was 25 msec when calculated using Bazett's correction and was 8 msec when calculated using Fridericia's correction. The QTc returned to baseline within 12-24 hours post-dose. Formoterol plasma concentrations were weakly correlated with pulse rate and increase of QTc duration. The effects on plasma potassium, pulse rate, and QTc interval are known pharmacological effects of this class of study drug and were not unexpected at the very high formoterol dose (120 mcg single dose, 10 times the recommended single dose) tested in this study. These effects were well-tolerated by the healthy volunteers.

The electrocardiographic and cardiovascular effects of FORADIL AEROLIZER were compared with those of albuterol and placebo in two pivotal 12-week double-blind studies of patients with asthma. A subset of patients underwent continuous electrocardiographic monitoring during three 24-hour periods. No important differences in ventricular or supraventricular ectopy between treatment groups were observed. In these two studies, the total number of patients with asthma exposed to any dose of FORADIL AEROLIZER who had continuous electrocardiographic monitoring was about 200.

Continuous electrocardiographic monitoring was not included in the clinical studies of FORADIL AEROLIZER that were performed in COPD patients. The electrocardiographic effects of FORADIL AEROLIZER were evaluated versus placebo in a 12-month pivotal double-blind study of patients with COPD. An analysis of ECG intervals was performed for patients who participated at study sites in the United States, including 46 patients treated with FORADIL AEROLIZER 12 mcg twice daily, and 50 patients treated with FORADIL AEROLIZER 24 mcg twice daily. ECGs were performed predose, and at 5-15 minutes and 2 hours post-dose at study baseline and after 3, 6 and 12 months of treatment. The results showed that there was no clinically meaningful acute or chronic effect on ECG intervals, including QTc, resulting from treatment with FORADIL AEROLIZER.

Tachyphylaxis/Tolerance

In a clinical study in 19 adult patients with mild asthma, the bronchoprotective effect of formoterol, as assessed by methacholine challenge, was studied following an initial dose of 24 mcg (twice the recommended dose) and after 2 weeks of 24 mcg twice daily. Tolerance to the bronchoprotective effects of formoterol was observed as evidenced by a diminished bronchoprotective effect on FEV₁ after 2 weeks of dosing, with loss of protection at the end of the 12 hour dosing period.

Rebound bronchial hyper-responsiveness after cessation of chronic formoterol therapy has not been observed.

In three large clinical trials in patients with asthma, while efficacy of formoterol versus placebo was maintained, a slightly reduced bronchodilatory response (as measured by 12-hour FEV₁ AUC) was observed within the formoterol arms over time, particularly with the 24 mcg twice daily dose (twice the daily recommended dose). A similarly reduced FEV₁ AUC over time was also noted in the albuterol treatment arms (180 mcg four times daily by metered-dose inhaler).

CLINICAL TRIALS

Adolescent and Adult Asthma Trials

In a placebo-controlled, single-dose clinical trial, the onset of bronchodilation (defined as a 15% or greater increase from baseline in FEV₁) was similar for FORADIL AEROLIZER and albuterol 180 mcg by metered-dose inhaler.

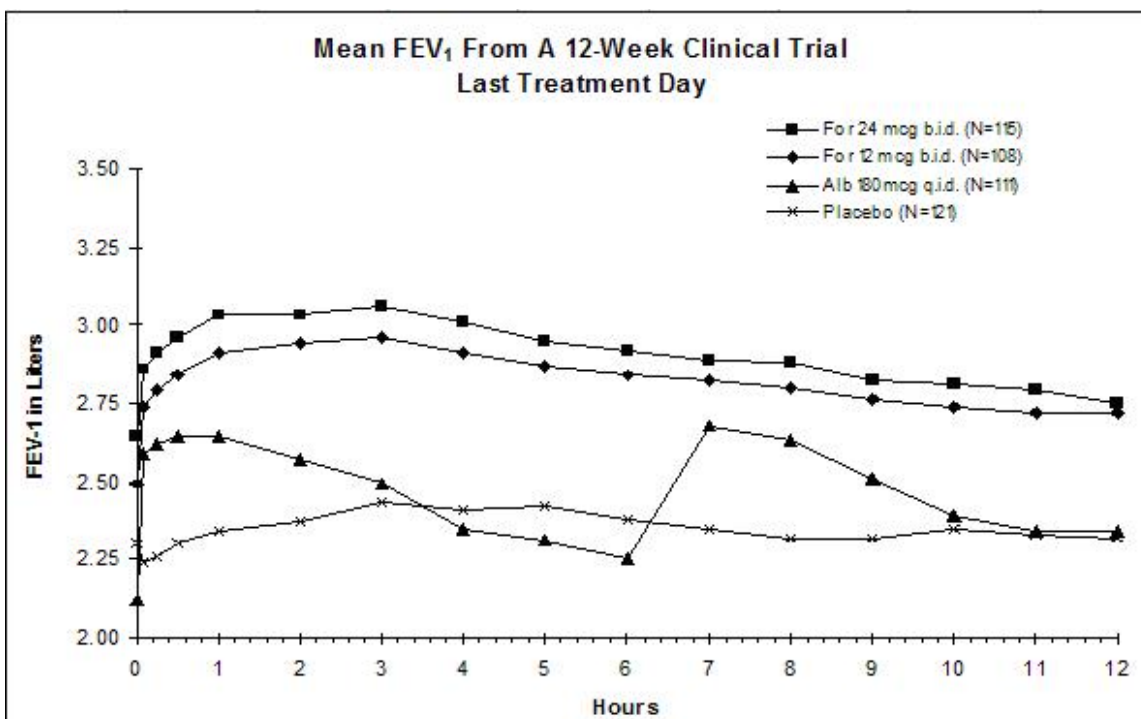
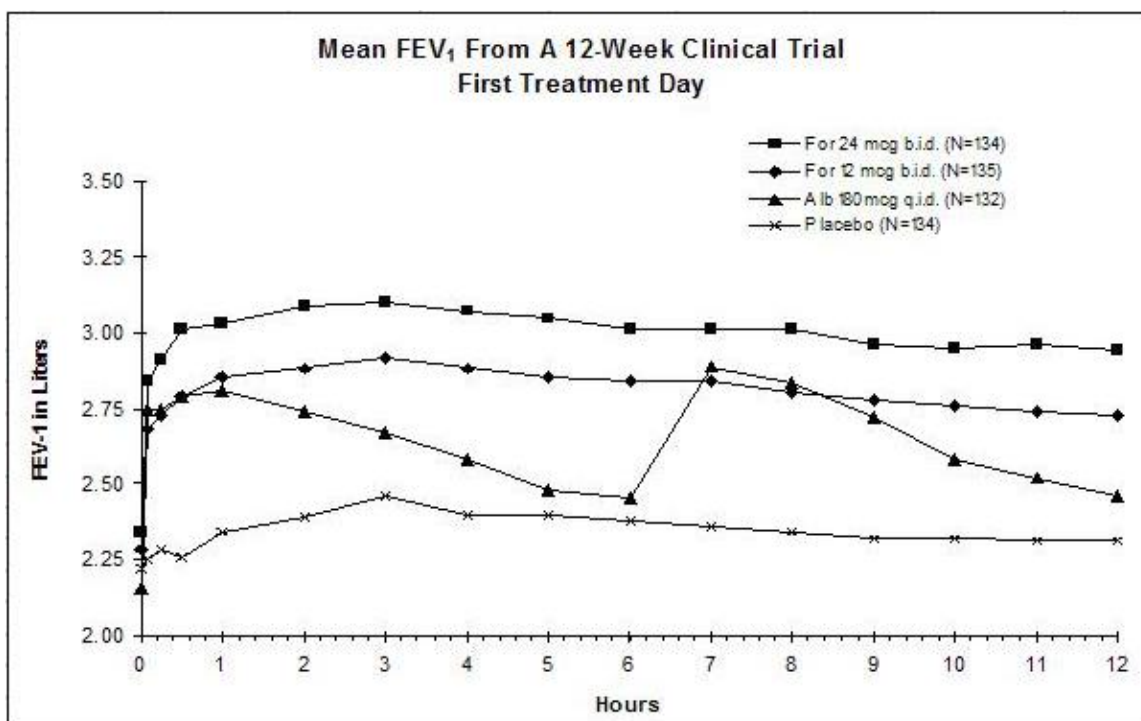
In single-dose and multiple-dose clinical trials, the maximum improvement in FEV₁ for FORADIL AEROLIZER 12 mcg generally occurred within 1 to 3 hours, and an increase in FEV₁ above baseline was observed for 12 hours in most patients.

FORADIL AEROLIZER 12 mcg twice daily was compared to FORADIL AEROLIZER 24 mcg twice daily, albuterol 180 mcg four times daily by metered-dose inhaler, and placebo in a total of 1095 adult and adolescent patients 12 years of age and above with mild-to-moderate asthma (defined as FEV₁ 40%-80% of the patient's

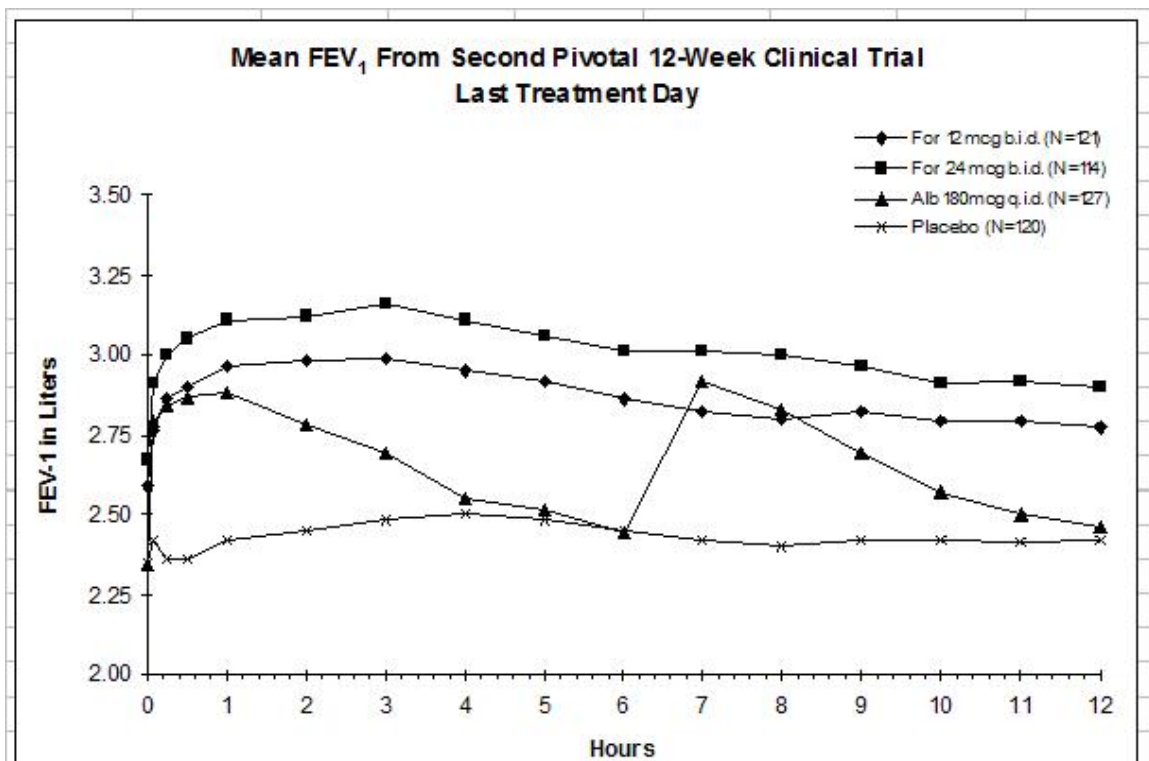
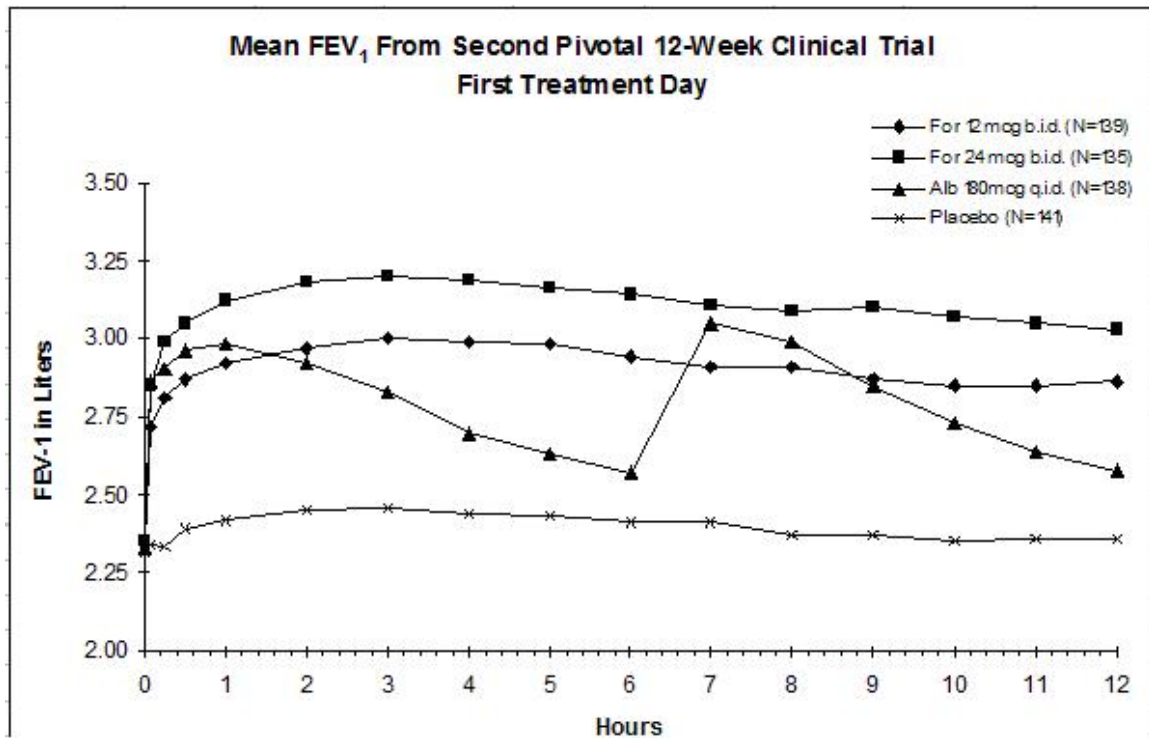
predicted normal value) who participated in two pivotal, 12-week, multi-center, randomized, double-blind, parallel group studies.

The results of both studies showed that FORADIL AEROLIZER 12 mcg twice daily resulted in significantly greater post-dose bronchodilation (as measured by serial FEV₁ for 12 hours post-dose) throughout the 12-week treatment period. There was no significant difference in post-dose bronchodilation between FORADIL AEROLIZER 12 mcg twice daily and FORADIL AEROLIZER 24 mcg twice daily, but serious asthma exacerbations occurred more commonly in the higher dose group (see WARNINGS and ADVERSE REACTIONS). Mean FEV₁ measurements from both studies are shown below for the first and last treatment days (see Figures 1 and 2).

Figures 1a and 1b: Mean FEV₁ from Clinical Trial A



Figures 2a and 2b: Mean FEV₁ from Clinical Trial B



Compared with placebo and albuterol, patients treated with FORADIL AEROLIZER 12 mcg demonstrated improvement in many secondary efficacy endpoints, including improved combined and nocturnal asthma symptom scores, fewer nighttime awakenings, fewer nights in which patients used rescue medication, and higher morning and evening peak flow rates. FORADIL AEROLIZER 24 mcg twice daily did not provide any additional improvements in these secondary endpoints compared to FORADIL AEROLIZER 12 mcg twice daily.

A 16-week, randomized, multi-center, double-blind, parallel-group study enrolled 1568 patients 12 years of age and older with mild-to-moderate asthma (defined as FEV₁ ≥40% of the patient's predicted normal value) in three treatment groups: FORADIL AEROLIZER 12 mcg twice daily, FORADIL AEROLIZER 24 mcg twice daily, and placebo. The study's primary endpoint was the incidence of serious asthma-related adverse events. Serious asthma exacerbations occurred in 3 (0.6%) patients who received FORADIL AEROLIZER 12 mcg twice daily, 2 (0.4%) patients who received FORADIL AEROLIZER 24 mcg twice daily, and 1 (0.2%) patient who received placebo. The size of this study was not adequate to precisely quantify the differences in serious asthma exacerbation rates between treatment groups. All serious asthma exacerbations resulted in hospitalizations. While there were no deaths in the study, the duration and size of this study were not adequate to quantify the rate of asthma-related death. See WARNINGS for information about a study which compared another long-acting beta₂-adrenergic agonist to placebo.

Pediatric Asthma Trial

A 12-month, multi-center, randomized, double-blind, parallel-group, study compared FORADIL AEROLIZER 12 mcg twice daily and FORADIL AEROLIZER 24 mcg twice daily to placebo in a total of 518 children with asthma (ages 5-12 years) who required daily bronchodilators and anti-inflammatory treatment. Efficacy was evaluated on the first day of treatment, at Week 12, and at the end of treatment.

FORADIL AEROLIZER 12 mcg twice daily demonstrated a greater 12-hour FEV₁ AUC compared to placebo on the first day of treatment, after twelve weeks of treatment, and after one year of treatment. FORADIL AEROLIZER 24 mcg twice

daily did not result in any additional improvement in 12-hour FEV₁ AUC compared to FORADIL AEROLIZER 12 mcg twice daily.

Exercise-Induced Bronchospasm Trials

The effect of FORADIL AEROLIZER on exercise-induced bronchospasm (defined as >20% fall in FEV₁) was examined in four randomized, single-dose, double-blind, crossover studies in a total of 77 patients 4 to 41 years of age with exercise-induced bronchospasm. Exercise challenge testing was conducted 15 minutes, and 4, 8, and 12 hours following administration of a single dose of study drug (FORADIL AEROLIZER 12 mcg, albuterol 180 mcg by metered-dose inhaler, or placebo) on separate test days. FORADIL AEROLIZER 12 mcg and albuterol 180 mcg were each superior to placebo for FEV₁ measurements obtained 15 minutes after study drug administration. FORADIL AEROLIZER 12 mcg maintained superiority over placebo at 4, 8, and 12 hours after administration. Most subjects were protected from exercise-induced bronchospasm for up to 12 hours following administration of FORADIL AEROLIZER; however, some were not. The efficacy of FORADIL AEROLIZER in the prevention of exercise-induced bronchospasm when dosed on a regular twice daily regimen has not been studied.

Adult COPD Trials

In multiple-dose clinical trials in patients with COPD, FORADIL AEROLIZER 12 mcg was shown to provide onset of significant bronchodilation (defined as 15% or greater increase from baseline in FEV₁) within 5 minutes of oral inhalation after the first dose. Bronchodilation was maintained for at least 12 hours.

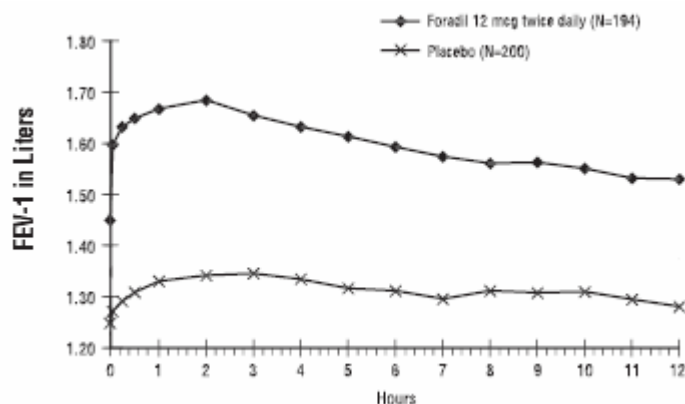
FORADIL AEROLIZER was studied in two pivotal, double-blind, placebo-controlled, randomized, multi-center, parallel-group trials in a total of 1634 adult patients (age range: 34-88 years; mean age: 63 years) with COPD who had a mean FEV₁ that was 46% of predicted. The diagnosis of COPD was based upon a prior clinical diagnosis of COPD, a smoking history (greater than 10 pack-years), age (at least 40 years), spirometry results (prebronchodilator baseline FEV₁ less than 70% of the predicted value, and at least 0.75 liters, with the FEV₁/VC being less than 88% for men and less than 89% for women), and symptom score (greater than zero on at

least four of the seven days prior to randomization). These studies included approximately equal numbers of patients with and without baseline bronchodilator reversibility, defined as a 15% or greater increase FEV₁ after inhalation of 200 mcg of albuterol sulfate. A total of 405 patients received FORADIL AEROLIZER 12 mcg, administered twice daily. Each trial compared FORADIL AEROLIZER 12 mcg twice daily and FORADIL AEROLIZER 24 mcg twice daily with placebo and an active control drug. The active control drug was ipratropium bromide in COPD Trial A, and slow-release theophylline in COPD Trial B (the theophylline arm in this study was open-label). The treatment period was 12 weeks in COPD Trial A, and 12 months in COPD Trial B.

The results showed that FORADIL AEROLIZER 12 mcg twice daily resulted in significantly greater post-dose bronchodilation (as measured by serial FEV₁ for 12 hours post-dose; the primary efficacy analysis) compared to placebo when evaluated after 12 weeks of treatment in both trials, and after 12 months of treatment in the 12-month trial (COPD Trial B). Compared to FORADIL AEROLIZER 12 mcg twice daily, FORADIL AEROLIZER 24 mcg twice daily did not provide any additional benefit on a variety of endpoints including FEV₁.

Mean FEV₁ measurements after 12 weeks of treatment for one of the two major efficacy studies are shown in the figure below.

Figure 3
Mean FEV₁ after 12 Weeks of treatment from COPD Trial A



FORADIL AEROLIZER 12 mcg twice daily was statistically superior to placebo at all post-dose timepoints tested (from 5 minutes to 12 hours post-dose) throughout the 12-week (COPD Trial A) and 12-month (COPD Trial B) treatment periods.

In both pivotal trials compared with placebo, patients treated with FORADIL AEROLIZER 12 mcg demonstrated improved morning pre-medication peak expiratory flow rates and took fewer puffs of rescue albuterol.

INDICATIONS AND USAGE

Asthma

FORADIL AEROLIZER is indicated for long-term, twice-daily (morning and evening) administration in the maintenance treatment of asthma and in the prevention of bronchospasm in adults and children 5 years of age and older with reversible obstructive airways disease, including patients with symptoms of nocturnal asthma.

Long-acting beta₂-adrenergic agonists may increase the risk of asthma-related death (see WARNINGS). Therefore, when treating patients with asthma, FORADIL AEROLIZER should only be used as additional therapy 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, including FORADIL AEROLIZER. It is not indicated for

patients whose asthma can be managed by occasional use of inhaled, short-acting, beta₂-agonists or 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.

Chronic Obstructive Pulmonary Disease

FORADIL AEROLIZER is also indicated for the acute prevention of exercise-induced bronchospasm (EIB) in adults and children 5 years of age and older, when administered on an occasional, as-needed basis.

Chronic Obstructive Pulmonary Disease

FORADIL AEROLIZER is indicated for the long-term, twice daily (morning and evening) administration in the maintenance treatment of bronchoconstriction in patients with Chronic Obstructive Pulmonary Disease including chronic bronchitis and emphysema.

CONTRAINDICATIONS

FORADIL (formoterol fumarate) is contraindicated in patients with a history of hypersensitivity to formoterol fumarate or to any components of this product.

WARNINGS

- **Long-acting beta₂-adrenergic agonists may increase the risk of asthma-related death. Therefore, when treating patients with asthma, FORADIL AEROLIZER should only be used as additional therapy 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, including FORADIL AEROLIZER.**
 - 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 beta₂-adrenergic agonists, including formoterol. No study adequate to determine whether the rate of asthma-related death is increased with FORADIL AEROLIZER has been conducted.

- Clinical studies with FORADIL AEROLIZER suggested a higher incidence of serious asthma exacerbations in patients who received FORADIL AEROLIZER than in those who received placebo (See ADVERSE REACTIONS). The sizes of these studies were not adequate to precisely quantify the differences in serious asthma exacerbation rates between treatment groups.
- **The studies described above enrolled patients with asthma. No studies have been conducted that were adequate to determine whether the rate of death in patients with COPD is increased by long-acting beta₂-adrenergic agonists.**
- **FORADIL AEROLIZER should not be initiated in patients with significantly worsening or acutely deteriorating asthma, which may be a life-threatening condition. The use of FORADIL AEROLIZER in this setting is inappropriate.**
- **FORADIL AEROLIZER should not be used in conjunction with an inhaled, long-acting beta₂-agonist. FORADIL AEROLIZER should not be used with other medications containing long-acting beta₂-agonists.**
- **FORADIL AEROLIZER is not a substitute for inhaled or oral corticosteroids. Corticosteroids should not be stopped or reduced at the time FORADIL AEROLIZER is initiated.**
- **When beginning treatment with FORADIL AEROLIZER, patients who have been taking inhaled, short-acting beta₂-agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular use of**

these drugs and use them only for symptomatic relief of acute asthma symptoms.

- **See PRECAUTIONS, Information for Patients and the accompanying Medication Guide.**

Paradoxical Bronchospasm

As with other inhaled beta₂-agonists, formoterol can produce paradoxical bronchospasm, that may be life-threatening. If paradoxical bronchospasm occurs, FORADIL AEROLIZER should be discontinued immediately and alternative therapy instituted.

Deterioration of Asthma

Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. It is important to watch for signs of worsening asthma, such as increasing use of inhaled, short-acting beta₂-adrenergic agonists or a significant decrease in peak expiratory flow (PEF) or lung function. Such findings require immediate evaluation. Patients should be advised to seek immediate attention should their condition deteriorate. Increasing the daily dosage of FORADIL AEROLIZER beyond the recommended dose in this situation is not appropriate. FORADIL AEROLIZER should not be used more frequently than twice daily (morning and evening) at the recommended dose.

Use of Anti-inflammatory Agents

For the treatment of asthma, FORADIL AEROLIZER should only be used as additional therapy 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, including FORADIL AEROLIZER. There are no data demonstrating that FORADIL has any clinical anti-inflammatory effect and therefore it cannot be expected to take the place of corticosteroids. Patients who already require oral or inhaled corticosteroids for treatment of asthma should be continued on this type of treatment even if they feel better as a result of initiating FORADIL AEROLIZER. Any change in

corticosteroid dosage, in particular a reduction, should be made ONLY after clinical evaluation (see PRECAUTIONS, Information for Patients).

Cardiovascular Effects

Formoterol fumarate, like other beta₂-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of FORADIL AEROLIZER at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce 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. Therefore, formoterol fumarate, like other sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension (see PRECAUTIONS, General).

Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions may occur after administration of FORADIL AEROLIZER, as demonstrated by cases of anaphylactic reactions, urticaria, angioedema, rash, and bronchospasm.

Do Not Exceed Recommended Dose

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 trials with FORADIL AEROLIZER suggest that the use of doses higher than recommended is associated with an increased risk of serious asthma exacerbations (see ADVERSE REACTIONS).

PRECAUTIONS

General

FORADIL AEROLIZER should not be used to treat acute symptoms of asthma. FORADIL AEROLIZER has not been studied in the relief of acute asthma symptoms and extra doses should not be used for that purpose. When prescribing FORADIL AEROLIZER, the physician should 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 FORADIL AEROLIZER. Patients should also be cautioned that increasing inhaled beta₂-agonist use is a signal of deteriorating asthma. (See Information for Patients and the accompanying Medication Guide.)

Formoterol fumarate, like other sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive disorders or thyrotoxicosis; and in patients who are unusually responsive to sympathomimetic amines. Clinically significant changes in systolic and/or diastolic blood pressure, pulse rate and electrocardiograms have been seen infrequently in individual patients in controlled clinical studies with formoterol. Doses of the related beta₂-agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

Beta-agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation.

Clinically significant changes in blood glucose and/or serum potassium were infrequent during clinical studies with long-term administration of FORADIL AEROLIZER at the recommended dose.

FORADIL AEROLIZER contains lactose, which contains trace levels of milk proteins. Allergic reactions to products containing milk proteins may occur in patients with severe milk protein allergy.

FORADIL capsules should ONLY be used with the AEROLIZER Inhaler and SHOULD NOT be taken orally.

FORADIL capsules should always be stored in the blister, and only removed IMMEDIATELY before use.

Information for Patients

Patients should be instructed to read the accompanying Medication Guide with each new prescription and refill. The complete text of the Medication Guide is reprinted at the end of this document. Patients should be given the following information:

1. Patients should be informed that long-acting beta₂-adrenergic agonists may increase the risk of asthma-related death.
2. FORADIL AEROLIZER is not indicated 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, beta₂-agonist (the health-care provider should prescribe the patient with such medication and instruct the patient in how it should be used). Patients should be instructed to seek medical attention if their symptoms worsen, if FORADIL AEROLIZER treatment becomes less effective, or if they need more inhalations of a short-acting beta₂-agonist than usual. Patients should not inhale more than the contents of one capsule at any one time. The daily dosage of FORADIL AEROLIZER should not exceed one capsule twice daily (24 mcg total daily dose).
3. FORADIL AEROLIZER should not be used as a substitute for oral or inhaled corticosteroids. The dosage of these medications should not be changed and they should not be stopped without consulting the physician, even if the patient feels better after initiating treatment with FORADIL AEROLIZER.
4. The active ingredient of FORADIL (formoterol fumarate) is a long-acting, bronchodilator used for the treatment of asthma, including nocturnal asthma, and for the prevention of exercise-induced bronchospasm. FORADIL AEROLIZER

provides bronchodilation for up to 12 hours. Patients should be advised not to increase the dose or frequency of FORADIL AEROLIZER without consulting the prescribing physician. Patients should be warned not to stop or reduce concomitant asthma therapy without medical advice.

5. When FORADIL AEROLIZER is used for the prevention of EIB, the contents of one capsule should be taken at least 15 minutes prior to exercise. Additional doses of FORADIL AEROLIZER should not be used for 12 hours. Prevention of EIB has not been studied in patients who are receiving chronic FORADIL AEROLIZER administration twice daily and these patients should not use additional FORADIL AEROLIZER for prevention of EIB.
6. Patients should be informed that treatment with beta₂-agonists may lead to adverse events which include palpitations, chest pain, rapid heart rate, tremor or nervousness.
7. Patients should be informed never to use FORADIL AEROLIZER with a spacer and never to exhale into the device.
8. Patients should avoid exposing the FORADIL capsules to moisture and should handle the capsules with dry hands. The AEROLIZER Inhaler should never be washed and should be kept dry. The patient should always use the new AEROLIZER Inhaler that comes with each refill.
9. Women should be advised to contact their physician if they become pregnant or if they are nursing.
10. Patients should be told that in rare cases, the gelatin capsule might break into small pieces. These pieces should be retained by the screen built into the AEROLIZER Inhaler. However, it remains possible that rarely, tiny pieces of gelatin might reach the mouth or throat after inhalation. The capsule is less likely to shatter when pierced if: storage conditions are strictly followed, capsules are removed from the blister immediately before use, and the capsules are only pierced once.

11. It is important that patients understand how to use the AEROLIZER Inhaler appropriately and how it should be used in relation to other asthma medications they are taking (see the accompanying Medication Guide).

Drug Interactions

If additional adrenergic drugs are to be administered by any route, they should be used with caution because the pharmacologically predictable sympathetic effects of formoterol may be potentiated.

Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate any hypokalemic effect of adrenergic agonists.

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

Formoterol, as with other beta₂-agonists, should be administered with extreme caution to patients being treated with monamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval because the action of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval have an increased risk of ventricular arrhythmias.

Beta-adrenergic receptor antagonists (beta-blockers) and formoterol may inhibit the effect of each other when administered concurrently. Beta-blockers not only block the therapeutic effects of beta₂-agonists, such as formoterol, but may produce severe bronchospasm in asthmatic patients. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-blockers in patients with asthma. In this

setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of formoterol fumarate has been evaluated in 2-year drinking water and dietary studies in both rats and mice. In rats, the incidence of ovarian leiomyomas was increased at doses of 15 mg/kg and above in the drinking water study and at 20 mg/kg in the dietary study, but not at dietary doses up to 5 mg/kg (AUC exposure approximately 450 times human exposure at the maximum recommended daily inhalation dose). In the dietary study, the incidence of benign ovarian theca-cell tumors was increased at doses of 0.5 mg/kg and above (AUC exposure at the low dose of 0.5 mg/kg was approximately 45 times human exposure at the maximum recommended daily inhalation dose). This finding was not observed in the drinking water study, nor was it seen in mice (see below).

In mice, the incidence of adrenal subcapsular adenomas and carcinomas was increased in males at doses of 69 mg/kg and above in the drinking water study, but not at doses up to 50 mg/kg (AUC exposure approximately 590 times human exposure at the maximum recommended daily inhalation dose) in the dietary study. The incidence of hepatocarcinomas was increased in the dietary study at doses of 20 and 50 mg/kg in females and 50 mg/kg in males, but not at doses up to 5 mg/kg in either males or females (AUC exposure approximately 60 times human exposure at the maximum recommended daily inhalation dose). Also in the dietary study, the incidence of uterine leiomyomas and leiomyosarcomas was increased at doses of 2 mg/kg and above (AUC exposure at the low dose of 2 mg/kg was approximately 25 times human exposure at the maximum recommended daily inhalation dose). Increases in leiomyomas of the rodent female genital tract have been similarly demonstrated with other beta-agonist drugs.

Formoterol fumarate was not mutagenic or clastogenic in the following tests: mutagenicity tests in bacterial and mammalian cells, chromosomal analyses in mammalian cells, unscheduled DNA synthesis repair tests in rat hepatocytes and

human fibroblasts, transformation assay in mammalian fibroblasts and micronucleus tests in mice and rats.

Reproduction studies in rats revealed no impairment of fertility at oral doses up to 3 mg/kg (approximately 1000 times the maximum recommended daily inhalation dose in humans on a mg/m² basis).

Pregnancy, Teratogenic Effects, Pregnancy Category C

Formoterol fumarate has been shown to cause stillbirth and neonatal mortality at oral doses of 6 mg/kg (approximately 2000 times the maximum recommended daily inhalation dose in humans on a mg/m² basis) and above in rats receiving the drug during the late stage of pregnancy. These effects, however, were not produced at a dose of 0.2 mg/kg (approximately 70 times the maximum recommended daily inhalation dose in humans on a mg/m² basis). When given to rats throughout organogenesis, oral doses of 0.2 mg/kg and above delayed ossification of the fetus, and doses of 6 mg/kg and above decreased fetal weight. Formoterol fumarate did not cause malformations in rats or rabbits following oral administration. Because there are no adequate and well-controlled studies in pregnant women, FORADIL AEROLIZER should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in Labor and Delivery

Formoterol fumarate has been shown to cause stillbirth and neonatal mortality at oral doses of 6 mg/kg (approximately 2000 times the maximum recommended daily inhalation dose in humans on a mg/m² basis) and above in rats receiving the drug for several days at the end of pregnancy. These effects were not produced at a dose of 0.2 mg/kg (approximately 70 times the maximum recommended daily inhalation dose in humans on a mg/m² basis). There are no adequate and well-controlled human studies that have investigated the effects of FORADIL AEROLIZER during labor and delivery.

Because beta-agonists may potentially interfere with uterine contractility, FORADIL AEROLIZER should be used during labor only if the potential benefit justifies the potential risk.

Nursing Mothers

In reproductive studies in rats, formoterol was excreted in the milk. It is not known whether formoterol is excreted in human milk, but because many drugs are excreted in human milk, caution should be exercised if FORADIL AEROLIZER is administered to nursing women. There are no well-controlled human studies of the use of FORADIL AEROLIZER in nursing mothers.

Pediatric Use

Asthma

A total of 776 children 5 years of age and older with asthma were studied in three multiple-dose controlled clinical trials. Of the 512 children who received formoterol, 508 were 5-12 years of age, and approximately one third were 5-8 years of age.

Exercise-Induced Bronchospasm

A total of 25 pediatric patients, 4-11 years of age, were studied in two well-controlled single-dose clinical trials.

The safety and effectiveness of FORADIL AEROLIZER in pediatric patients below 5 years of age has not been established. (See CLINICAL TRIALS, Pediatric Asthma Trial, and ADVERSE REACTIONS, Experience in Pediatric, Adolescent and Adult Patients.)

Geriatric Use

Of the total number of patients who received FORADIL AEROLIZER in adolescent and adult chronic dosing asthma clinical trials, 318 were 65 years of age or older and 39 were 75 years of age and older. Of the 811 patients who received FORADIL AEROLIZER in two pivotal multiple-dose controlled clinical studies in patients with COPD, 395 (48.7%) were 65 years of age or older while 62 (7.6%) were 75 years of age or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. A slightly higher frequency of chest infection

was reported in the 39 asthma patients 75 years of age and older, although a causal relationship with FORADIL has not been established. Other reported clinical experience has not identified differences in responses between the elderly and younger adult patients, but greater sensitivity of some older individuals cannot be ruled out. (See PRECAUTIONS, Drug Interactions.)

ADVERSE REACTIONS

Clinical trials with FORADIL AEROLIZER suggested a higher incidence of serious asthma exacerbations in patients who received FORADIL AEROLIZER than in those who received placebo.

Experience in Pediatric, Adolescent and Adult Patients with Asthma

Of the 5,824 patients in multiple-dose controlled clinical trials, 1,985 were treated with FORADIL AEROLIZER at the recommended dose of 12 mcg twice daily. The following table shows adverse events where the frequency was greater than or equal to 1% in the FORADIL twice daily group and where the rates in the FORADIL group exceeded placebo. Three adverse events showed dose ordering among tested doses of 6, 12 and 24 mcg administered twice daily; tremor, dizziness and dysphonia.

NUMBER AND FREQUENCY OF ADVERSE EXPERIENCES IN PATIENTS 5 YEARS OF AGE AND OLDER FROM MULTIPLE-DOSE CONTROLLED CLINICAL TRIALS

Adverse Event	FORADIL AEROLIZER 12 mcg twice daily		Placebo	
	n	(%)	n	(%)
Total Patients	1985	(100)	969	(100)
Infection viral	341	(17.2)	166	(17.1)
Bronchitis	92	(4.6)	42	(4.3)
Chest infection	54	(2.7)	4	(0.4)
Dyspnea	42	(2.1)	16	(1.7)
Chest pain	37	(1.9)	13	(1.3)
Tremor	37	(1.9)	4	(0.4)
Dizziness	31	(1.6)	15	(1.5)
Insomnia	29	(1.5)	8	(0.8)
Tonsillitis	23	(1.2)	7	(0.7)

Rash	22	(1.1)	7	(0.7)
Dysphonia	19	(1.0)	9	(0.9)

In two 12-week controlled trials with combined enrollment of 1095 patients 12 years of age and older, FORADIL AEROLIZER 12 mcg twice daily was compared to FORADIL AEROLIZER 24 mcg twice daily, albuterol 180 mcg four times daily, and placebo. Serious asthma exacerbations (acute worsening of asthma resulting in hospitalization) occurred more commonly with FORADIL AEROLIZER 24 mcg twice daily than with the recommended dose of FORADIL AEROLIZER 12 mcg twice daily, albuterol, or placebo. The results are shown in the following table.

**NUMBER AND FREQUENCY OF SERIOUS ASTHMA EXACERBATIONS IN
PATIENTS 12 YEARS OF AGE AND OLDER FROM TWO 12-WEEK
CONTROLLED CLINICAL TRIALS**

	Foradil 12 mcg twice daily	Foradil 24 mcg twice daily	Albuterol 180 mcg four times daily	Placebo
	Trial #1			
Serious asthma exacerbations	0/136 (0)	4/135 (3.0%) ¹	2/134 (1.5%)	0/136 (0)
	Trial #2			
Serious asthma exacerbations	1/139 (0.7%)	5/136 (3.7%) ²	0/138 (0)	2/141 (1.4%)

¹ 1 patient required intubation

² 2 patients had respiratory arrest; 1 of the patients died

In a 16-week, randomized, multi-center, double-blind, parallel-group trial, patients who received either 24 mcg twice daily or 12 mcg twice daily doses of FORADIL AEROLIZER experienced more serious asthma exacerbations than patients who received placebo (see CLINICAL TRIALS). The results are shown in the following table.

**NUMBER AND FREQUENCY OF SERIOUS ASTHMA EXACERBATIONS IN
PATIENTS 12 YEARS OF AGE AND OLDER FROM A 16-WEEK
TRIAL**

	Foradil 12 mcg twice daily	Foradil 24 mcg twice daily	Placebo
Serious asthma exacerbations	3/527 (0.6%)	2/527 (0.4%)	1/514 (0.2%)

Experience in Children with Asthma

The safety of FORADIL AEROLIZER 12 mcg twice daily compared to FORADIL AEROLIZER 24 mcg twice daily and placebo was investigated in one large, multicenter, randomized, double-blind, 52-week clinical trial in 518 children with asthma (ages 5-12 years) in need of daily bronchodilators and anti-inflammatory treatment. More children who received FORADIL AEROLIZER 24 mcg twice daily than children who received FORADIL AEROLIZER 12 mcg twice daily or placebo experienced serious asthma exacerbations, as shown in the next table.

NUMBER AND FREQUENCY OF SERIOUS ASTHMA EXACERBATIONS IN PATIENTS 5-12 YEARS OF AGE FROM A 52-WEEK TRIAL

	Foradil 12 mcg twice daily	Foradil 24 mcg twice daily	Placebo
Serious asthma exacerbations	8/171 (4.7%)	11/171 (6.4%)	0/176 (0)

The numbers and percent of patients who reported adverse events were comparable in the 12 mcg twice daily and placebo groups. In general, the pattern of the adverse events observed in children differed from the usual pattern seen in adults. The adverse events that were more frequent in the formoterol group than in the placebo group reflected infection/inflammation (viral infection, rhinitis, tonsillitis, gastroenteritis) or abdominal complaints (abdominal pain, nausea, dyspepsia).

Experience in Adult Patients with COPD

Of the 1634 patients in two pivotal multiple-dose Chronic Obstructive Pulmonary Disease (COPD) controlled trials, 405 were treated with FORADIL AEROLIZER 12 mcg twice daily. The numbers and percent of patients who reported adverse events were comparable in the 12 mcg twice daily and placebo groups. Adverse events (AE's) experienced were similar to those seen in asthmatic patients, but with a higher incidence of COPD-related AE's in both placebo and formoterol treated patients.

The following table shows adverse events where the frequency was greater than or equal to 1% in the FORADIL AEROLIZER group and where the rates in the FORADIL AEROLIZER group exceeded placebo. The two clinical trials included

doses of 12 mcg and 24 mcg, administered twice daily. Seven adverse events showed dose ordering among tested doses of 12 and 24 mcg administered twice daily; pharyngitis, fever, muscle cramps, increased sputum, dysphonia, myalgia, and tremor.

**NUMBER AND FREQUENCY OF ADVERSE EXPERIENCES IN
ADULT COPD PATIENTS TREATED IN MULTIPLE-DOSE
CONTROLLED CLINICAL TRIALS**

Adverse Event	FORADIL AEROLIZER 12 mcg twice daily		Placebo	
	n	(%)	n	(%)
Total patients	405	(100)	420	(100)
Upper respiratory tract infection	30	(7.4)	24	(5.7)
Pain back	17	(4.2)	17	(4.0)
Pharyngitis	14	(3.5)	10	(2.4)
Pain chest	13	(3.2)	9	(2.1)
Sinusitis	11	(2.7)	7	(1.7)
Fever	9	(2.2)	6	(1.4)
Cramps leg	7	(1.7)	2	(0.5)
Cramps muscle	7	(1.7)	0	
Anxiety	6	(1.5)	5	(1.2)
Pruritis	6	(1.5)	4	(1.0)
Sputum increased	6	(1.5)	5	(1.2)
Mouth dry	5	(1.2)	4	(1.0)

Overall, the frequency of all cardiovascular adverse events in the two pivotal studies was low and comparable to placebo (6.4% for FORADIL AEROLIZER 12 mcg twice daily, and 6.0% for placebo). There were no frequently-occurring specific cardiovascular adverse events for FORADIL AEROLIZER (frequency greater than or equal to 1% and greater than placebo).

Other adverse reactions to FORADIL AEROLIZER are similar in nature to other selective beta₂-adrenoceptor agonists; e.g., angina, hypertension or hypotension, tachycardia, arrhythmias, nervousness, headache, tremor, dry mouth,

palpitation, muscle cramps, nausea, dizziness, fatigue, malaise, hypokalemia, hyperglycemia, metabolic acidosis and insomnia.

Post Marketing Experience

In extensive worldwide marketing experience with FORADIL, serious exacerbations of asthma, including some that have been fatal, have been reported. While most of these cases have been in patients with severe or acutely deteriorating asthma (see WARNINGS), a few have occurred in patients with less severe asthma. It is not possible to determine from these individual case reports whether FORADIL AEROLIZER contributed to the events.

Rare reports of anaphylactic reactions, including severe hypotension and angioedema, have also been received in association with the use of formoterol fumarate inhalation powder.

DRUG ABUSE AND DEPENDENCE

There was no evidence in clinical trials of drug dependence with the use of FORADIL.

OVERDOSAGE

The expected signs and symptoms with overdosage of FORADIL AEROLIZER are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and symptoms listed under ADVERSE REACTIONS, e.g., angina, hypertension or hypotension, tachycardia, with rates up to 200 beats/min., arrhythmias, nervousness, headache, tremor, seizures, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, hypokalemia, hyperglycemia, and insomnia. Metabolic acidosis may also occur. As with all inhaled sympathomimetic medications, cardiac arrest and even death may be associated with an overdose of FORADIL AEROLIZER.

Treatment of overdosage consists of discontinuation of FORADIL AEROLIZER 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 overdose of FORADIL AEROLIZER. Cardiac monitoring is recommended in cases of overdose.

The minimum acute lethal inhalation dose of formoterol fumarate in rats is 156 mg/kg (approximately 53,000 and 25,000 times the maximum recommended daily inhalation dose in adults and children, respectively, on a mg/m² basis). The median lethal oral doses in Chinese hamsters, rats, and mice provide even higher multiples of the maximum recommended daily inhalation dose in humans.

DOSAGE AND ADMINISTRATION

FORADIL capsules should be administered only by the oral inhalation route and only using the AEROLIZER Inhaler (see the accompanying Medication Guide). **FORADIL capsules should not be ingested (i.e., swallowed) orally.** FORADIL capsules should always be stored in the blister, and only removed IMMEDIATELY BEFORE USE.

For Maintenance Treatment of Asthma

Long-acting beta₂-adrenergic agonists may increase the risk of asthma-related death ([see warnings](#)**WARNINGS**). Therefore, when treating patients with asthma, FORADIL AEROLIZER should only be used as additional therapy 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, including FORADIL AEROLIZER. It is not indicated for patients whose asthma can be managed by occasional use of inhaled, short-acting, beta₂-agonists or 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.

For adults and children 5 years of age and older, the usual dosage is the inhalation of the contents of one 12-mcg FORADIL capsule every 12 hours using the AEROLIZER Inhaler. The patient must not exhale into the device. The total daily dose of FORADIL should not exceed one capsule twice daily (24 mcg total daily

dose). More frequent administration or administration of a larger number of inhalations is not recommended. If symptoms arise between doses, an inhaled short-acting beta₂-agonist should be taken for immediate relief.

If a previously effective dosage regimen fails to provide the usual response, medical advice should be sought immediately as this is often a sign of destabilization of asthma. Under these circumstances, the therapeutic regimen should be re-evaluated.

For Prevention of Exercise-Induced Bronchospasm (EIB)

For adults and children 5 years of age or older, the usual dosage is the inhalation of the contents of one 12-mcg FORADIL capsule at least 15 minutes before exercise administered on an occasional as needed basis. When used intermittently as needed for prevention, protection may last up to 12 hours.

Additional doses of FORADIL AEROLIZER should not be used for 12 hours after the administration of this drug. Regular, twice-daily dosing has not been studied in preventing EIB. Patients who are receiving FORADIL AEROLIZER twice daily for maintenance treatment of their asthma should not use additional doses for prevention of EIB and may require a short-acting bronchodilator.

For Maintenance Treatment of Chronic Obstructive Pulmonary Disease (COPD)

The usual dosage is the inhalation of the contents of one 12 mcg FORADIL capsule every 12 hours using the AEROLIZER inhaler.

A total daily dose of greater than 24 mcg is not recommended.

If a previously effective dosage regimen fails to provide the usual response, medical advice should be sought immediately as this is often a sign of destabilization of COPD. Under these circumstances, the therapeutic regimen should be re-evaluated and additional therapeutic options should be considered.

HOW SUPPLIED

FORADIL AEROLIZER contains: aluminum blister-packaged 12-mcg FORADIL (formoterol fumarate) clear gelatin capsules with "CG" printed on one end and "FXF" printed on the opposite end; one AEROLIZER Inhaler; and [Patient Instructions for Use Medication Guide](#).

Unit Dose (blister pack)

Box of 12 (strips of 6). NDC 0085-1402-01

Unit Dose (blister pack)

Box of 60 (strips of 6). NDC 0085-1401-01

FORADIL capsules should be used with the AEROLIZER Inhaler only. The AEROLIZER Inhaler should not be used with any other capsules.

Prior to dispensing: Store in a refrigerator, 2°C-8°C (36°F-46°F)

After dispensing to patient: Store at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature]. Protect from heat and moisture. CAPSULES SHOULD ALWAYS BE STORED IN THE BLISTER AND ONLY REMOVED FROM THE BLISTER IMMEDIATELY BEFORE USE.

Always discard the FORADIL capsules and AEROLIZER Inhaler by the "Use by" date and always use the new AEROLIZER Inhaler provided with each new prescription.

Keep out of the reach of children.

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SCHERING CORPORATION

Manufactured by:

Novartis Pharma AG, Basle, Switzerland

for

Schering Corporation, Kenilworth, NJ 07033

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Medication Guide

Foradil[®] [FOR-a-dil] Aerolizer[®] (formoterol fumarate inhalation powder)

Important: Do not swallow FORADIL capsules. FORADIL capsules are used only with the Aerolizer inhaler that comes with FORADIL AEROLIZER. Never place a capsule in the mouthpiece of the AEROLIZER Inhaler.

Read the Medication Guide that comes with FORADIL AEROLIZER 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 health care provider about your medical condition or treatment.

What is the most important information I should know about FORADIL AEROLIZER?

FORADIL AEROLIZER is a medicine called a long-acting beta₂-agonist or LABA. LABA medicines are used in patients with asthma, exercise-induced bronchospasm (EIB), and chronic obstructive pulmonary disease (COPD). LABA medicines help the muscles around the airways in your lungs stay relaxed to prevent 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 cause death if not treated right away.

- **In patients with asthma, LABA medicines such as FORADIL AEROLIZER, 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 to

your healthcare provider about this risk and the benefits of treating your asthma with FORADIL AEROLIZER.

- **FORADIL AEROLIZER does not relieve sudden symptoms. Always have a short-acting beta₂-agonist medicine with you to treat sudden symptoms. If you do not have an inhaled, short-acting bronchodilator, contact your healthcare provider to have one prescribed for you.**
- **Do not stop using FORADIL AEROLIZER unless told to do so by your healthcare provider because your symptoms might get worse.**
- **FORADIL AEROLIZER**
 - **should not be the only medicine prescribed for your asthma**
 - **should only be used 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 FORADIL AEROLIZER. 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 FORADIL AEROLIZER?

FORADIL AEROLIZER is a long-acting beta₂-agonist (LABA). FORADIL AEROLIZER is used for asthma, exercise-induced bronchospasm (EIB) and chronic obstructive pulmonary disease (COPD) as follows:

Asthma

FORADIL AEROLIZER is used long-term, twice-a-day, to control symptoms of asthma, and prevent symptoms such as wheezing in adults and children ages 5 and older.

Because LABA medicines such as FORADIL AEROLIZER may increase the chance of death from asthma problems, FORADIL AEROLIZER is not for adults and children with asthma who:

- are well controlled with another asthma-controller medicine, such as a low to medium dose of an inhaled corticosteroid
- only need short-acting beta₂-agonist medicines once in awhile

Exercise-Induced Bronchospasm (EIB)

FORADIL AEROLIZER is used for the prevention of wheezing caused by exercise in adults and children 5 years of age and older.

Chronic Obstructive Pulmonary Disease (COPD)

FORADIL AEROLIZER is used long-term, twice-a-day, in controlling symptoms of COPD and preventing wheezing in adults with COPD.

What should I tell my healthcare provider before using FORADIL AEROLIZER?

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**
- **are pregnant or planning to become pregnant.** It is not known if FORADIL AEROLIZER may harm your unborn baby.
- **are breastfeeding.** It is not known if FORADIL AEROLIZER passes into your milk and if it can harm your baby.
- **are allergic to FORADIL AEROLIZER, any other medicines, or food products.**

FORADIL AEROLIZER contains lactose (milk sugar) and a small amount of milk proteins. It is possible that allergic reactions may happen in patients who have a severe milk protein allergy.

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

Know 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 FORADIL capsules with the Aerolizer inhaler?

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

- Children should use FORADIL AEROLIZER with an adult's help, as instructed by the child's healthcare provider.
- Use FORADIL AEROLIZER exactly as prescribed. **Do not use FORADIL AEROLIZER more often than prescribed.**
- For asthma and COPD, the usual dose is 1 FORADIL capsule inhaled through the AEROLIZER inhaler twice a day (morning and evening). The 2 doses should be about 12 hours apart.
- For preventing exercise-induced bronchospasm, the usual dose is 1 FORADIL capsule inhaled through the AEROLIZER inhaler at least 15 minutes before exercise, as needed. Do not use FORADIL AEROLIZER more often than every 12 hours. Do not use extra FORADIL AEROLIZER before exercise if you already use it twice-a-day.

- If you miss a dose of FORADIL AEROLIZER, just skip that dose. Take your next dose at your usual time. Never take 2 doses at one time.
- Do not use a spacer device with FORADIL AEROLIZER.
- Do not breathe into FORADIL AEROLIZER.
- While you are using FORADIL AEROLIZER twice a day, do not use other medicines that contain a long-acting beta₂-agonist (LABA) for any reason. Other LABA medicines include SEREVENT[®] DISKUS[®] (salmeterol xinafoate inhalation powder) and ADVAIR DISKUS[®] (fluticasone propionate and salmeterol inhalation powder).
- Do not change or stop any of your medicines 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 FORADIL AEROLIZER.
- **Call your healthcare provider or get medical care right away if:**
 - your breathing problems worsen with FORADIL AEROLIZER
 - you need to use your short-acting beta₂-agonist medicine more often than usual
 - your short-acting beta₂-agonist medicine does not work as well for you at relieving symptoms
 - you need to use 4 or more inhalations of your short-acting beta₂-agonist medicine for 2 or more days in a row
 - you use 1 whole canister of your short-acting beta₂-agonist medicine in 8 weeks time

- your peak flow meter results decrease. Your healthcare provider will tell you the numbers that are right for you.
- ~~Y~~y you have asthma and your symptoms do not improve after using FORADIL AEROLIZER regularly for 1 week.

What are the possible side effects with FORADIL AEROLIZER?

- **In patients with asthma, LABA medicines such as FORADIL AEROLIZER may increase the chance of death from asthma problems.** See “What is the most important information I should know about FORADIL AEROLIZER?”

Other possible side effects with FORADIL AEROLIZER 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
- dry mouth
- muscle cramps
- nausea
- dizziness
- tiredness
- low blood potassium
- high blood sugar
- high blood acid
- trouble sleeping

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 FORADIL AEROLIZER. Ask your healthcare provider or pharmacist for more information.

How do I store FORADIL AEROLIZER?

- Store FORADIL AEROLIZER at room temperature between 68 and 77° F (20 to 25° C). Protect FORADIL AEROLIZER from heat and moisture. Do not remove FORADIL capsules from their foil package until just before use.

- Always discard the old AEROLIZER inhaler by the “Use by” date and use the new one provided with each new prescription.
- Safely discard FORADIL capsules and the Aerolizer inhaler if no longer needed or is out-of-date.
- **Keep FORADIL AEROLIZER and all medicines out of the reach of children.**

General Information about FORADIL AEROLIZER

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

This Medication Guide summarizes the most important information about FORADIL AEROLIZER. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about FORADIL AEROLIZER that was written for healthcare professionals. If you have any questions about the use of FORADIL AEROLIZER, go to www.foradil.us.

Instructions for Using FORADIL AEROLIZER

Do not swallow FORADIL capsules.

Follow the instructions below for using your FORADIL AEROLIZER. **You will breathe-in (inhale) the medicine in the FORADIL capsules from the FORADIL AEROLIZER.** If you have any questions, ask your healthcare provider or pharmacist.

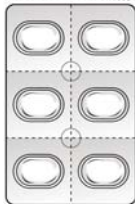
FORADIL AEROLIZER

- **FORADIL AEROLIZER consists of FORADIL capsules and a AEROLIZER Inhaler.**
- **FORADIL capsules come on blister cards and are wrapped in foil pouches. Do not open a foil pouch until you are ready to use FORADIL AEROLIZER.**

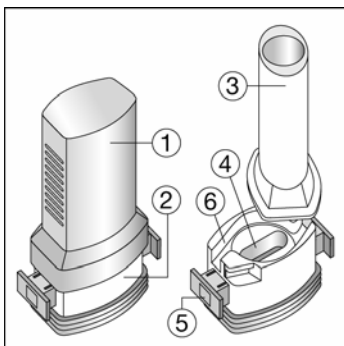
- **Keep your FORADIL and AEROLIZER Inhaler dry. Handle with DRY hands.**



Aluminum pouch covering the foil blister cards



Foil blister card



The Aerolizer consists of the following parts:

1. A cap to protect the mouthpiece of the base
2. A base that allows the proper release of medicine from the capsule

The base consists of:

3. A mouth piece
4. A capsule chamber
5. A button with “winglets” (projecting side pieces) and pins on each side
6. An air inlet channel.

With each new prescription of FORADIL AEROLIZER or refill, your pharmacist should have written the “Use by” date on the sticker on the outside of the FORADIL AEROLIZER box. Remove the “Use by” sticker on the box and place it on the AEROLIZER Inhaler cover that comes with FORADIL. If the sticker is blank, count 4 months from the date you got your FORADIL AEROLIZER from the pharmacy and write this date on the sticker. Also, check the expiration date stamped on the box. If this date is less than 4 months from your purchase date, write this date on the sticker.

Do not use FORADIL capsules with any other capsule inhaler, and do not use the AEROLIZER inhaler to take any other capsule medicine.

Taking a dose of FORADIL AEROLIZER requires the following steps:

1. Open the foil pouch containing a blister card of FORADIL capsules. Do not remove a FORADIL capsule until you are ready for a dose.
2. Pull off the AEROLIZER Inhaler cover. (Figure 1)

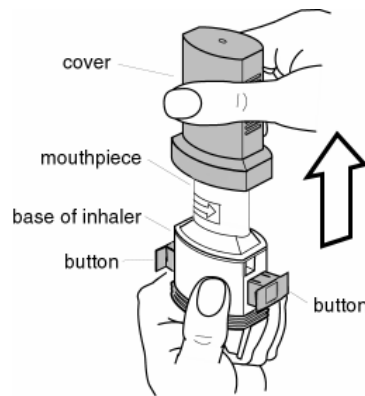


Figure 1

3. Hold the base of the AEROLIZER Inhaler firmly and twist the mouthpiece in the direction of the arrow to open. (Figure 2) Push the buttons in on each side to make sure that you can see 4 pins in the capsule well of the AEROLIZER Inhaler.



Figure 2

4. Separate one FORADIL capsule blister by tearing at the pre-cut lines. (Figure 3)

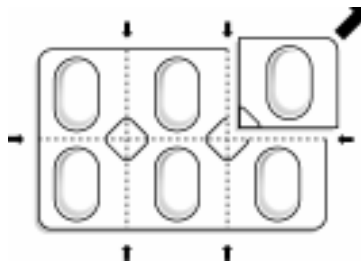


Figure 3

5. Peel the paper backing that covers one FORADIL capsule on the blister card. Push the FORADIL capsule through the foil. (Figure 4)



Figure 4

6. Place the FORADIL capsule in the capsule-chamber in the base of the AEROLIZER Inhaler. **Never place a capsule directly into the mouthpiece.** (Figure 5)

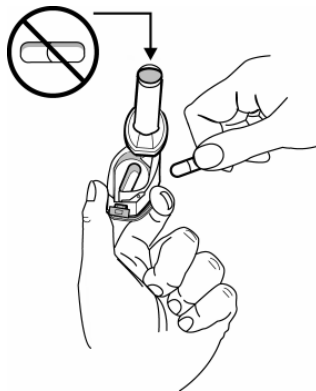


Figure 5

7. Twist the mouthpiece back to the closed position. (Figure 6)



Figure 6

8. Hold the mouthpiece of the AEROLIZER Inhaler upright and press both buttons at the same time. Only press the buttons **ONCE**. You should hear a click as the FORADIL capsule is being pierced. (Figure 7)

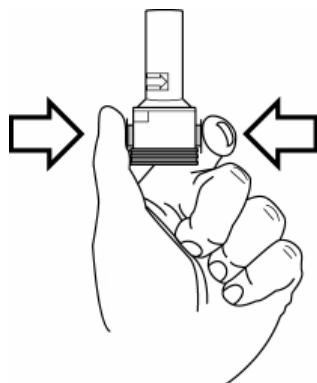


Figure 7

9. Release the buttons. If the buttons stay stuck, grasp the wings on the buttons and pull them out of the stuck position before the next step. Do not push the buttons a second time. This may cause the FORADIL capsule to break into small pieces. There is a screen built into the AEROLIZER Inhaler to hold these small pieces. It is possible that tiny pieces of a FORADIL capsule might reach your mouth or throat when you inhale the medicine. This will not harm you, but to avoid this, only pierce the capsule once. The FORADIL capsules are also less likely to break into small pieces if you store them the right way (See “How do I store FORADIL AEROLIZER?”).

10. Breathe out (exhale) fully. **Do not exhale into the AEROLIZER mouthpiece.**
(Figure 8)



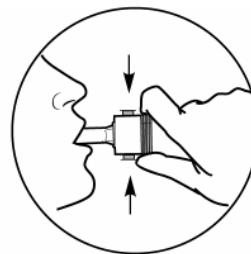
Figure 8

11. Tilt your head back slightly. Keep the AEROLIZER Inhaler level, with the blue buttons to the left and right (**not up and down**). Place the mouthpiece in your mouth and close your lips around the mouthpiece. (Figures 9 and 10)



CORRECT

Figure 9



INCORRECT

Figure 10

12. Breathe in quickly and deeply (Figure 11). This will cause the FORADIL capsule to spin around in the chamber and deliver your dose of medicine. You should hear a whirring noise and experience a sweet taste in your mouth. If you do not hear the whirring noise, the capsule may be stuck. If this occurs, open the AEROLIZER Inhaler and loosen the capsule allowing it to spin freely. **Do not try to loosen the capsule by pressing the buttons again.** (You will have to repeat steps 10 to 12 again to get your dose.)



Figure 11

13. Remove the AEROLIZER Inhaler from your mouth. Continue to hold your breath as long as you can and then exhale.
14. Open the AEROLIZER Inhaler to see if any powder is still in the capsule. If any powder remains in the capsule repeat steps 10 to 13. Most people are able to empty the capsule in one or two inhalations.
15. After use, open the AEROLIZER Inhaler, remove and discard the empty capsule. Do not leave a used capsule in the chamber.
16. Close the mouthpiece and replace the cover.

Remember:

- Never breathe into the AEROLIZER Inhaler.
- Never take the AEROLIZER Inhaler apart.
- Never place a FORADIL capsule directly into the mouthpiece of the AEROLIZER Inhaler.
- Never leave a used FORADIL capsule in the AEROLIZER Inhaler chamber.
- Always use the AEROLIZER Inhaler in a level position.
- Never wash the AEROLIZER Inhaler. **Keep it dry.**
- Always keep the AEROLIZER Inhaler and FORADIL capsules in a dry place.
- Always use the new AEROLIZER Inhaler that comes with your refill.

Rx only



SCHERING CORPORATION

Manufactured by:

Novartis Pharma AG, Basle, Switzerland

for

Schering Corporation, Kenilworth, NJ 07033

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June 2006

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

Effective Date: 04/30/2007

WARNING: INCREASED RISK OF ASTHMA-RELATED DEATH

Long-acting beta2-adrenergic agonists may increase the risk of asthma-related death. 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), the active ingredient in PERFOROMIST Inhalation Solution. [see [WARNINGS AND PRECAUTIONS \(5.1\)](#)]

1 INDICATIONS AND USAGE

1.1 Maintenance Treatment of COPD

PERFOROMIST (formoterol fumarate) Inhalation Solution is indicated for the long-term, twice daily (morning and evening) administration in the maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.

1.2 Important Limitations of Use

PERFOROMIST Inhalation Solution is not indicated to treat acute deteriorations of chronic obstructive pulmonary disease [see [WARNINGS AND PRECAUTIONS \(5.2\)](#)].

PERFOROMIST Inhalation Solution is not indicated to treat asthma. The safety and effectiveness of PERFOROMIST Inhalation Solution in asthma have not been established.

2 DOSAGE AND ADMINISTRATION

The recommended dose of PERFOROMIST (formoterol fumarate) Inhalation Solution is one 20 mcg unit-dose vial administered twice daily (morning and evening) by nebulization. A total daily dose greater than 40 mcg is not recommended.

PERFOROMIST Inhalation Solution should be administered by the orally inhaled route via a standard jet nebulizer connected to an air compressor. The safety and efficacy of PERFOROMIST Inhalation Solution have been established in clinical trials when administered using the PARI-LC Plus® nebulizer (with a facemask or mouthpiece) and the PRONEB® Ultra compressor. The safety and efficacy of PERFOROMIST Inhalation Solution delivered from non-compressor based nebulizer systems have not been established.

PERFOROMIST Inhalation Solution should always be stored in the foil pouch, and only removed IMMEDIATELY BEFORE USE. Contents of any partially used container should be discarded.

If the recommended maintenance treatment regimen fails to provide the usual response, medical advice should be sought immediately, as this is often a sign of destabilization of COPD. Under these circumstances, the therapeutic regimen should be re-evaluated and additional therapeutic options should be considered.

The drug compatibility (physical and chemical), efficacy, and safety of PERFOROMIST Inhalation Solution when mixed with other drugs in a nebulizer have not been established.

3 DOSAGE FORMS AND STRENGTHS

PERFOROMIST (formoterol fumarate) Inhalation Solution is supplied as a sterile solution for nebulization in low-density polyethylene unit-dose vials. Each vial contains formoterol fumarate dihydrate equivalent to 20 mcg/2 mL of formoterol fumarate.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Asthma-Related Deaths and Exacerbations

[See [*BOXED WARNING*](#)]

Data from a large placebo-controlled study in asthma patients showed that long-acting beta₂-adrenergic agonists may increase the risk of asthma-related death. Data are not available to determine whether the rate of death in patients

with COPD is increased by long-acting beta2-adrenergic agonists.

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 beta2-adrenergic agonists, including PERFOROMIST Inhalation Solution. No study adequate to determine whether the rate of asthma related death is increased in patients treated with PERFOROMIST Inhalation Solution has been conducted.

Clinical studies with formoterol fumarate administered as a dry powder inhaler 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.

5.2 Deterioration of Disease and Acute Episodes

PERFOROMIST Inhalation Solution should not be initiated in patients with acutely deteriorating COPD, which may be a life-threatening condition. PERFOROMIST Inhalation Solution has not been studied in patients with acutely deteriorating COPD. The use of PERFOROMIST Inhalation Solution in this setting is inappropriate.

PERFOROMIST Inhalation Solution should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm.

PERFOROMIST Inhalation Solution has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled short-acting beta2-agonist.

When beginning PERFOROMIST Inhalation Solution, patients who have been taking inhaled, short-acting beta2-agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief of acute respiratory symptoms. When prescribing PERFOROMIST Inhalation Solution, the healthcare provider should also prescribe an inhaled, short-acting beta2-agonist and instruct the patient how it should be used.

Increasing inhaled beta2-agonist use is a signal of deteriorating

disease for which prompt medical attention is indicated. COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If PERFOROMIST Inhalation Solution no longer controls the symptoms of bronchoconstriction, or the patient's inhaled, short-acting beta₂-agonist becomes less effective or the patient needs more inhalation of short-acting beta₂-agonist than usual, these may be markers of deterioration of disease. In this setting, a re-evaluation of the patient and the COPD treatment regimen should be undertaken at once. Increasing the daily dosage of PERFOROMIST Inhalation Solution beyond the recommended 20 mcg twice daily dose is not appropriate in this situation.

5.3 Excessive Use of PERFOROMIST Inhalation Solution and Use with Other Long-Acting Beta₂-Agonists

As with other inhaled beta₂-adrenergic drugs, PERFOROMIST Inhalation Solution should not be used more often, at higher doses than recommended, or in conjunction with other medications containing long-acting beta₂-agonists, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

5.4 Paradoxical Bronchospasm

As with other inhaled beta₂-agonists, PERFOROMIST Inhalation Solution can produce paradoxical bronchospasm that may be life-threatening. If paradoxical bronchospasm occurs, PERFOROMIST Inhalation Solution should be discontinued immediately and alternative therapy instituted.

5.5 Cardiovascular Effects

PERFOROMIST Inhalation Solution, like other beta₂-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic and/or diastolic blood pressure, and/or symptoms. If such effects occur, PERFOROMIST Inhalation Solution may need to be discontinued. In addition, beta-agonists have been reported to produce 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. Therefore, PERFOROMIST Inhalation Solution, like other sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

5.6 Coexisting Conditions

PERFOROMIST Inhalation Solution, like other sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis, and in patients who are unusually responsive to sympathomimetic amines. Doses of the related beta2-agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

5.7 Hypokalemia and Hyperglycemia

Beta-agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects [see [CLINICAL PHARMACOLOGY \(12.2\)](#)]. The decrease in serum potassium is usually transient, not requiring supplementation. Beta-agonist medications may produce transient hyperglycemia in some patients.

Clinically significant changes in serum potassium and blood glucose were infrequent during clinical studies with long-term administration of PERFOROMIST Inhalation Solution at the recommended dose.

6 ADVERSE REACTIONS

Long acting beta2-adrenergic agonists such as formoterol may increase the risk of asthma-related death [See [BOXED WARNING](#) and [WARNINGS AND PRECAUTIONS \(5.1\)](#)].

6.1 Beta2-Agonist Adverse Reaction Profile

Adverse reactions to PERFOROMIST Inhalation Solution are expected to be similar in nature to other beta2-adrenergic receptor agonists including: angina, hypertension or hypotension, tachycardia, arrhythmias, nervousness, headache, tremor, dry mouth, muscle cramps, palpitations, nausea, dizziness, fatigue, malaise, insomnia, hypokalemia, hyperglycemia, and metabolic acidosis.

6.2 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adults with COPD

The data described below reflect exposure to PERFOROMIST Inhalation Solution 20 mcg twice daily by oral inhalation in 586 patients, including 232 exposed for 6 months and 155 exposed for at least 1 year. PERFOROMIST Inhalation Solution was studied in a 12-week, placebo- and active-controlled trial (123 subjects treated with PERFOROMIST Inhalation Solution) and a 52-week, active-controlled trial (463 subjects treated with PERFOROMIST Inhalation Solution). Patients were mostly Caucasians (88%) between 40-90 years old (mean, 64 years old) and had COPD, with a mean FEV₁ of 1.33 L. Patients with significant concurrent cardiac and other medical diseases were excluded from the trials.

Table 1 shows adverse reactions from the 12-week, double-blind, placebo-controlled trial where the frequency was greater than or equal to 2% in the PERFOROMIST Inhalation Solution group and where the rate in the PERFOROMIST Inhalation Solution group exceeded the rate in the placebo group. In this trial, the frequency of patients experiencing cardiovascular adverse events was 4.1% for PERFOROMIST Inhalation Solution and 4.4% for placebo. There were no frequently occurring specific cardiovascular adverse events for PERFOROMIST Inhalation Solution (frequency greater than or equal to 1% and greater than placebo). The rate of COPD exacerbations was 4.1% for PERFOROMIST Inhalation Solution and 7.9% for placebo.

TABLE 1

Number of patients with adverse reactions in the 12-week multiple-dose controlled clinical trial				
Adverse Reaction	PERFOROMIST Inhalation Solution 20 mcg		Placebo	
	n	(%)	n	(%)
Total Patients	123	(100)	114	(100)
Diarrhea	6	(4.9)	4	(3.5)

TABLE 1

Number of patients with adverse reactions in the 12-week multiple-dose controlled clinical trial				
Adverse Reaction	PERFOROMIST Inhalation Solution 20 mcg		Placebo	
	n	(%)	n	(%)
Nausea	6	(4.9)	3	(2.6)
Nasopharyngitis	4	(3.3)	2	(1.8)
Dry Mouth	4	(3.3)	2	(1.8)
Vomiting	3	(2.4)	2	(1.8)
Dizziness	3	(2.4)	1	(0.9)
Insomnia	3	(2.4)	0	0

Patients treated with PERFOROMIST Inhalation Solution 20 mcg twice daily in the 52-week open-label trial did not experience an increase in specific clinically significant adverse events above the number expected based on the medical condition and age of the patients.

7 DRUG INTERACTIONS

7.1 Adrenergic Drugs

If additional adrenergic drugs are to be administered by any route, they should be used with caution because the

sympathetic effects of formoterol may be potentiated [see [WARNINGS AND PRECAUTIONS \(5.3, 5.5, 5.6, 5.7\)](#)].

7.2 Xanthine Derivatives, Steroids, or Diuretics

Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate any hypokalemic effect of adrenergic agonists [see [WARNINGS AND PRECAUTIONS \(5.7\)](#)].

7.3 Non-potassium Sparing Diuretics

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

7.4 MAO Inhibitors, Tricyclic Antidepressants, QTc Prolonging Drugs

Formoterol, as with other beta₂-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval because the effect of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval have an increased risk of ventricular arrhythmias.

7.5 Beta-blockers

Beta-adrenergic receptor antagonists (beta-blockers) and formoterol may inhibit the effect of each other when administered concurrently. Beta-blockers not only block the therapeutic effects of beta-agonists, but may produce severe bronchospasm in COPD patients. Therefore, patients with COPD should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-blockers in patients with COPD. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C

Formoterol fumarate administered throughout organogenesis did not cause malformations in rats or rabbits following oral administration. However, formoterol fumarate was found to be teratogenic in rats and rabbits in other testing laboratories. When given to rats throughout organogenesis, oral doses of 0.2 mg/kg (approximately 40 times the maximum recommended daily inhalation dose in humans on a mg/m² basis) and above delayed ossification of the fetus, and doses of 6 mg/kg (approximately 1200 times the maximum recommended daily inhalation dose in humans on a mg/m² basis) and above decreased fetal weight. Formoterol fumarate has been shown to cause stillbirth and neonatal mortality at oral doses of 6 mg/kg and above in rats receiving the drug during the late stage of pregnancy. These effects, however, were not produced at a dose of 0.2 mg/kg. Because there are no adequate and well-controlled studies in pregnant women, PERFOROMIST Inhalation Solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Women should be advised to contact their physician if they become pregnant while taking PERFOROMIST Inhalation Solution.

8.2 Labor and Delivery

There are no adequate and well-controlled human studies that have investigated the effects of PERFOROMIST Inhalation Solution during labor and delivery.

Because beta-agonists may potentially interfere with uterine contractility, PERFOROMIST Inhalation Solution should be used during labor only if the potential benefit justifies the potential risk.

8.3 Nursing Mothers

In reproductive studies in rats, formoterol was excreted in the milk. It is not known whether formoterol is excreted in human milk, but because many drugs are excreted in human milk, caution should be exercised if PERFOROMIST Inhalation Solution is administered to nursing women. There are no well-controlled human studies of the use of PERFOROMIST Inhalation Solution in nursing mothers.

Women should be advised to contact their physician if they are nursing while taking PERFOROMIST Inhalation Solution.

8.4 Pediatric Use

PERFOROMIST Inhalation Solution is not indicated for use in children. The safety and effectiveness of PERFOROMIST Inhalation Solution in pediatric patients have not been established. The pharmacokinetics of formoterol fumarate has not been studied in pediatric patients.

8.5 Geriatric Use

Of the 586 subjects who received PERFOROMIST Inhalation Solution in clinical studies, 284 were 65 years and over, while 89 were 75 years and over. Of the 123 subjects who received PERFOROMIST Inhalation Solution in the 12-week safety and efficacy trial, 48 (39%) were 65 years of age or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger adult patients, but greater sensitivity of some older individuals cannot be ruled out.

The pharmacokinetics of PERFOROMIST Inhalation Solution has not been studied in elderly subjects.

10 OVERDOSAGE

The expected signs and symptoms with overdosage of PERFOROMIST Inhalation Solution are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and symptoms listed under ADVERSE REACTIONS. Signs and symptoms may include angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, seizures, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, insomnia, hyperglycemia, hypokalemia, and metabolic acidosis. As with all inhaled sympathomimetic medications, cardiac arrest and even death may be associated with an overdose of PERFOROMIST Inhalation Solution.

Treatment of overdosage consists of discontinuation of PERFOROMIST Inhalation Solution 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 PERFOROMIST

Inhalation Solution. Cardiac monitoring is recommended in cases of overdose.

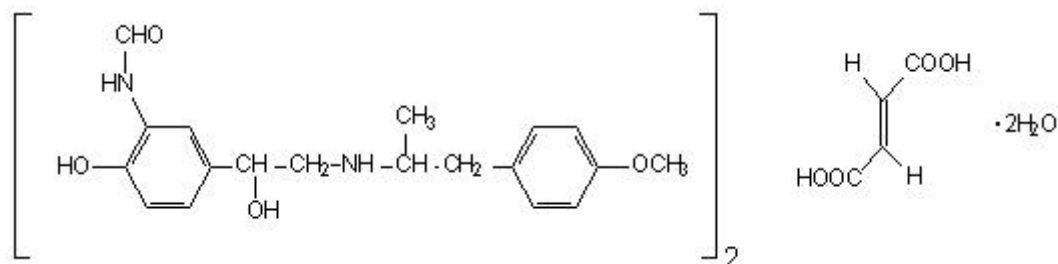
The minimum lethal inhalation dose of formoterol fumarate in rats is 156 mg/kg (approximately 32,000 times the maximum recommended daily inhalation dose in humans on a mg/m² basis). The median lethal oral doses in Chinese hamsters, rats, and mice provide even higher multiples of the maximum recommended daily inhalation dose in humans.

For additional information about overdose treatment, call a poison control center (1-800-222-1222).

11 DESCRIPTION

PERFOROMIST (formoterol fumarate) Inhalation Solution is supplied as 2 mL of formoterol fumarate inhalation solution packaged in a 2.5 mL single-use low-density polyethylene vial and overwrapped in a foil pouch. Each vial contains 2 mL of a clear, colorless solution composed of formoterol fumarate dihydrate equivalent to 20 mcg of formoterol fumarate in an isotonic, sterile aqueous solution containing sodium chloride, pH adjusted to 5.0 with citric acid and sodium citrate.

The active component of PERFOROMIST Inhalation Solution is formoterol fumarate dihydrate, a racemate. Formoterol fumarate dihydrate is a beta₂-adrenergic bronchodilator. Its chemical name is (±)-2-hydroxy-5-[(1RS)-1-hydroxy-2-[(1RS)-2-(4-methoxyphenyl)-1-methylethyl]-amino]ethyl]formanilide fumarate dihydrate; its structural formula is:



Formoterol fumarate dihydrate has a molecular weight of 840.92 and its empirical formula is (C₁₉H₂₄N₂O₄)₂•C₄H₄O₄•2H₂O. Formoterol fumarate dihydrate is a white to yellowish crystalline powder, which is freely soluble in glacial acetic acid, soluble in methanol, sparingly soluble in ethanol and isopropanol, slightly soluble in water,

and practically insoluble in acetone, ethyl acetate, and diethyl ether.

PERFOROMIST Inhalation Solution does not require dilution prior to administration by nebulization. Like all other nebulized treatments, the amount delivered to the lungs will depend on patient factors and the nebulization system used and its performance.

Using the PARI-LC Plus® nebulizer (with a facemask or mouthpiece) connected to a PRONEB® Ultra compressor under in vitro conditions, the mean delivered dose from the mouthpiece was approximately 7.3 mcg (37% of label claim). The mean nebulizer flow rate was 4 LPM and the nebulization time was 9 minutes. PERFOROMIST Inhalation Solution should be administered from a standard jet nebulizer at adequate flow rates via a facemask or mouthpiece.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Formoterol fumarate is a long-acting, beta2-adrenergic receptor agonist (beta2-agonist). 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 beta2-receptors than at beta1-receptors. Although beta2-receptors are the predominant adrenergic receptors in bronchial smooth muscle and beta1-receptors are the predominant receptors in the heart, there are also beta2-receptors in the human heart comprising 10% to 50% of the total beta-adrenergic receptors. The precise function of these receptors has not been established, but they raise the possibility that even highly selective beta2-agonists may have cardiac effects.

The pharmacologic effects of beta2-adrenoceptor agonist drugs, including formoterol, are at least in part attributable to stimulation of intracellular adenylyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3', 5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

In vitro tests show that formoterol is an inhibitor of the release of mast cell mediators, such as histamine and leukotrienes,

from the human lung. Formoterol also inhibits histamine-induced plasma albumin extravasation in anesthetized guinea pigs and inhibits allergen-induced eosinophil influx in dogs with airway hyper-responsiveness. The relevance of these in vitro and animal findings to humans with COPD is unknown.

12.2 Pharmacodynamics

Systemic Safety and Pharmacokinetic / Pharmacodynamic Relationships

The major adverse effects of inhaled beta₂-agonists occur as a result of excessive activation of the systemic beta-adrenergic receptors. The most common adverse effects in adults include skeletal muscle tremor and cramps, insomnia, tachycardia, decreases in plasma potassium, and increases in plasma glucose.

Changes in serum potassium and serum glucose were evaluated in 12 COPD patients following inhalation of single doses of PERFOROMIST Inhalation Solution containing 10, 20 and 244 mcg of formoterol fumarate (calculated on an anhydrous basis) in a crossover study. At 1 hour after treatment with formoterol fumarate inhalation solution, mean (\pm standard deviation) serum glucose rose 26 ± 30 , 29 ± 28 , and 38 ± 44 mg/dL, respectively, and was not significantly different from baseline or trough level at 24 hours post-dose. At 1 hour after dosing with formoterol fumarate inhalation solution 244 mcg, serum potassium fell by 0.68 ± 0.4 mEq/L, and was not different from baseline or trough level at 24 hours post-dose.

Linear pharmacokinetic/pharmacodynamic (PK/PD) relationships between urinary formoterol excretion and decreases in serum potassium, increases in plasma glucose, and increases in heart rate were generally observed with another inhalation formulation of formoterol fumarate and hence would be expected with PERFOROMIST Inhalation Solution also. Following single dose administration of 10-fold the recommended clinical dose of the other formoterol fumarate inhalation formulation having comparable exposure to single dose of 244 mcg of PERFOROMIST Inhalation Solution (approximately 12-fold the recommended clinical dose) in healthy subjects, the formoterol plasma concentration was found to be highly correlated with the reduction in plasma potassium concentration. Data from this study showed that maximum reductions from baseline in plasma potassium ranged from 0.55 to 1.52 mmol/L with a median maximum reduction of 1.01 mmol/L. Generally, the maximum effect on

plasma potassium was noted 1 to 3 hours after peak formoterol plasma concentrations were achieved.

Electrophysiology

In the dose-ranging study of PERFOROMIST Inhalation Solution, ECG-determined heart rate increased by a mean of 6 ± 3 beats per minute at 6 hours after a single dose of 244 mcg, but was back to predose level at 16-24 hours.

The effect of PERFOROMIST Inhalation Solution on heart rate and cardiac rhythm was studied in a 12-week clinical trial comparing PERFOROMIST Inhalation Solution to placebo and an active control treatment. COPD patients, including 105 patients exposed to PERFOROMIST Inhalation Solution, underwent continuous electrocardiographic (Holter) monitoring during two 24-hour periods (study baseline and after 8-12 weeks of treatment). ECGs were performed pre-dose and at 2 to 3 hours post-dose at study baseline (prior to dosing) and after 4, 8 and 12 weeks of treatment. Bazett's and Fridericia's methods were used to correct the QT interval for heart rate (QTcB and QTcF, respectively). The mean increase from baseline in QTcB interval over the 12-week treatment period was ≤ 4.8 msec for PERFOROMIST Inhalation Solution and ≤ 4.6 msec for placebo. The percent of patients who experienced a maximum change in QTc greater than 60 msec at any time during the 12-week treatment period was 0% and 1.8% for PERFOROMIST Inhalation Solution and placebo, respectively, based on Bazett's correction, and 1.6% and 0.9%, respectively, based on Fridericia's correction. Prolonged QT was reported as an adverse event in 1 (0.8%) patient treated with PERFOROMIST Inhalation Solution and 2 (1.8%) placebo patients. No occurrences of atrial fibrillation or ventricular tachycardia were observed during 24-hour Holter monitoring or reported as adverse events in patients treated with PERFOROMIST Inhalation Solution after the start of dosing. No increase in supraventricular tachycardia over placebo-treated subjects was observed. The mean increase in maximum heart rate from baseline to 8-12 weeks after the start of dosing was 0.6 beats per minute (bpm) for patients treated with PERFOROMIST Inhalation Solution twice daily compared to 1.2 bpm for placebo patients. There were no clinically meaningful differences from placebo in acute or chronic effects on heart rate, including QTcB and QTcF, or cardiac rhythm resulting from treatment with PERFOROMIST Inhalation Solution.

At an exposure from formoterol fumarate dry powder formulation comparable to approximately 12-fold the recommended dose of PERFOROMIST Inhalation Solution, a mean maximum increase of pulse rate of 26 bpm was observed 6 hours post dose in healthy subjects. This study showed that the maximum increase of mean corrected QT interval (QTc) was 25 msec when calculated using Bazett's correction and was 8 msec when calculated using Fridericia's correction. The QTc returned to baseline within 12 to 24 hours post-dose. Formoterol plasma concentrations were weakly correlated with pulse rate and increase of QTc duration. The effects on pulse rate and QTc interval are known pharmacological effects of this class of study drug and were not unexpected at this supratherapeutic formoterol fumarate inhalation dose.

Tachyphylaxis / Tolerance

Tolerance to the effects of inhaled beta-agonists can occur with regularly-scheduled, chronic use. In a placebo-controlled clinical trial in 351 adult patients with COPD, the bronchodilating effect of PERFOROMIST Inhalation Solution was determined by the FEV₁ area under the curve over 12 hours following dosing on Day 1 and after 12 weeks of treatment. The effect of PERFOROMIST Inhalation Solution did not decrease after 12 weeks of twice-daily treatment (Figures 1 and 2).

12.3 Pharmacokinetics

Information on the pharmacokinetics of formoterol (dry powder and/or inhalation solution) in plasma and/or urine is available in healthy subjects as well as patients with chronic obstructive pulmonary disease after oral inhalation of doses at and above the therapeutic dose.

Urinary excretion of unchanged formoterol was used as an indirect measure of systemic exposure. Plasma drug disposition data parallel urinary excretion, and the elimination half-lives calculated for urine and plasma are similar.

Absorption

Pharmacokinetic properties of formoterol fumarate were evaluated in 12 COPD patients following inhalation of single doses of PERFOROMIST Inhalation Solution containing 10, 20 and 244 mcg of formoterol fumarate (calculated on an anhydrous basis) and 12 mcg formoterol fumarate dry powder, through 36 hours after single-dose administration. Formoterol

fumarate concentrations in plasma following the 10 and 20 mcg doses of PERFOROMIST Inhalation Solution and the 12 mcg dose of formoterol fumarate dry powder were undetectable or only detected sporadically at very low concentrations. Following a single 244 mcg dose of PERFOROMIST Inhalation Solution (approximately 12 times the recommended clinical dose), formoterol fumarate concentrations were readily measurable in plasma, exhibiting rapid absorption into plasma, and reaching a maximum drug concentration of 72 pg/mL within approximately 12 minutes of dosing.

The mean amount of formoterol excreted unchanged in 24 hour urine following single oral inhalation doses of 10, 20, and 244 mcg PERFOROMIST Inhalation Solution were found to be 109.7 ng, 349.6 ng, and 3317.5 ng, respectively. These findings indicate a near dose proportional increase in systemic exposure within the dose range tested.

When 12 mcg of a dry powder formulation of formoterol fumarate was given twice daily to COPD patients by oral inhalation for 12 weeks, the accumulation index, based on the urinary excretion of unchanged formoterol was 1.19 to 1.38. This suggests some accumulation of formoterol in plasma with multiple dosing. Although multiple-dose pharmacokinetic data is unavailable from PERFOROMIST Inhalation Solution, assumption of linear pharmacokinetics allows a reasonable prediction of minimal accumulation based on single-dose pharmacokinetics. As with many drug products for oral inhalation, it is likely that the majority of the inhaled formoterol fumarate delivered is swallowed and then absorbed from the gastrointestinal tract.

Distribution

The binding of formoterol to human plasma proteins *in vitro* was 61% to 64% at concentrations from 0.1 to 100 ng/mL. Binding to human serum albumin *in vitro* was 31% to 38% over a range of 5 to 500 ng/mL. The concentrations of formoterol used to assess the plasma protein binding were higher than those achieved in plasma following inhalation of a single 244 mcg dose of PERFOROMIST Inhalation Solution.

Metabolism

Formoterol is metabolized primarily by direct glucuronidation at either the phenolic or aliphatic hydroxyl group and O-demethylation followed by glucuronide conjugation at either phenolic hydroxyl groups. Minor pathways involve sulfate

conjugation of formoterol and deformylation followed by sulfate conjugation. The most prominent pathway involves direct conjugation at the phenolic hydroxyl group. The second major pathway involves O-demethylation followed by conjugation at the phenolic 2'-hydroxyl group. *In vitro* studies showed that multiple drug-metabolizing enzymes catalyze glucuronidation (UGT1A1, 1A8, 1A9, 2B7 and 2B15 were the most predominant enzymes) and O-demethylation (CYP2D6, CYP2C19, CYP2C9 and CYP2A6) of formoterol. Formoterol did not inhibit CYP450 enzymes at therapeutically relevant concentrations. Some patients may be deficient in CYP2D6 or 2C19 or both. Whether a deficiency in one or both of these isozymes results in elevated systemic exposure to formoterol or systemic adverse effects has not been adequately explored.

Excretion

Following administration of single 10, 20, and 244 mcg PERFOROMIST Inhalation Solution doses (calculated on an anhydrous basis) delivered via nebulizer in 12 COPD patients, on average, about 1.1% to 1.7% of the dose was excreted in the urine as unchanged formoterol as compared to about 3.4% excreted unchanged following inhalation administration of 12 mcg of formoterol fumarate dry powder. Renal clearance of formoterol following inhalation administration of PERFOROMIST Inhalation Solution in these subjects was about 157 mL/min. Based on plasma concentrations measured following the 244 mcg dose, the mean terminal elimination half-life was determined to be 7 hours.

Gender

As reported for another formoterol fumarate inhalation formulation, upon correction for body weight, pharmacokinetics of formoterol fumarate did not differ significantly between males and females.

Geriatric, Pediatric, Hepatic/Renal Impairment

The pharmacokinetics of formoterol fumarate has not been studied in elderly and pediatric patient populations. The pharmacokinetics of formoterol fumarate has not been studied in subjects with hepatic or renal impairment.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of formoterol fumarate has been evaluated in 2-year drinking water and dietary studies in both rats and mice. In rats, the incidence of ovarian leiomyomas was increased at doses of 15 mg/kg and above in the drinking water study and at 20 mg/kg in the dietary study (AUC exposure approximately 2300 times human exposure at the maximum recommended daily inhalation dose), but not at dietary doses up to 5 mg/kg (AUC exposure approximately 570 times human exposure at the maximum recommended daily inhalation dose). In the dietary study, the incidence of benign ovarian theca-cell tumors was increased at doses of 0.5 mg/kg (AUC exposure was approximately 57 times human exposure at the maximum recommended daily inhalation dose) and above. This finding was not observed in the drinking water study, nor was it seen in mice (see below).

In mice, the incidence of adrenal subcapsular adenomas and carcinomas was increased in males at doses of 69 mg/kg (AUC exposure approximately 1000 times human exposure at the maximum recommended daily inhalation dose) and above in the drinking water study, but not at doses up to 50 mg/kg (AUC exposure approximately 750 times human exposure at the maximum recommended daily inhalation dose) in the dietary study. The incidence of hepatocarcinomas was increased in the dietary study at doses of 20 and 50 mg/kg in females (AUC exposures approximately 300 and 750 times human exposure at the maximum recommended daily inhalation dose, respectively) and 50 mg/kg in males, but not at doses up to 5 mg/kg (AUC exposure approximately 75 times human exposure at the maximum recommended daily inhalation dose). Also in the dietary study, the incidence of uterine leiomyomas and leiomyosarcomas was increased at doses of 2 mg/kg (AUC exposure was approximately 30 times human exposure at the maximum recommended daily inhalation dose) and above. Increases in leiomyomas of the rodent female genital tract have been similarly demonstrated with other beta-agonist drugs.

Formoterol fumarate was not mutagenic or clastogenic in the following tests: mutagenicity tests in bacterial and mammalian cells, chromosomal analyses in mammalian cells, unscheduled DNA synthesis repair tests in rat hepatocytes and human fibroblasts, transformation assay in mammalian fibroblasts and micronucleus tests in mice and rats.

Reproduction studies in rats revealed no impairment of fertility at oral doses up to 3 mg/kg (approximately 600 times the

maximum recommended daily inhalation powder dose in humans on a mg/m² basis).

13.2 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. [See [DRUG INTERACTIONS, Xanthine Derivatives, Steroids, or Diuretics \(7.2\)](#)]

14 CLINICAL STUDIES

14.1 Adult COPD Trial

PERFOROMIST (formoterol fumarate) Inhalation Solution was evaluated in a 12-week, double-blind, placebo- and active-controlled, randomized, parallel-group, multicenter trial conducted in the United States. Of a total enrollment of 351 adults (age range: 40 to 86 years; mean age: 63 years) with COPD who had a mean pre-bronchodilator FEV₁ of 1.34 liters (44% of predicted), 237 patients were randomized to PERFOROMIST Inhalation Solution 20 mcg or placebo, administered twice daily via a PARI-LC Plus® nebulizer with a PRONEB® Ultra compressor. The diagnosis of COPD was based upon a prior clinical diagnosis of COPD, a smoking history (at least 10 pack-years), age (at least 40 years), and spirometry results (pre-bronchodilator baseline FEV₁ at least 30% and less than 70% of the predicted value, and the FEV₁/FVC less than 70%). About 58% of patients had bronchodilator reversibility, defined as a 10% or greater increase in FEV₁ after inhalation of 2 actuations (180 mcg) of albuterol from a metered dose inhaler. About 86% (106) of patients treated with PERFOROMIST Inhalation Solution and 74% (84) of placebo patients completed the trial.

PERFOROMIST Inhalation Solution 20 mcg twice daily resulted in significantly greater post-dose bronchodilation (as measured by serial FEV₁ for 12 hours post-dose; the primary efficacy analysis) compared to placebo when evaluated at endpoint (week 12 for completers and last observation for dropouts). Similar results were seen on Day 1 and at subsequent timepoints during the trial.

Mean FEV₁ measurements at Day 1 (Figure 1) and at endpoint (Figure 2) are shown below.

Figure 1
Mean¹ FEV₁ at Day 1

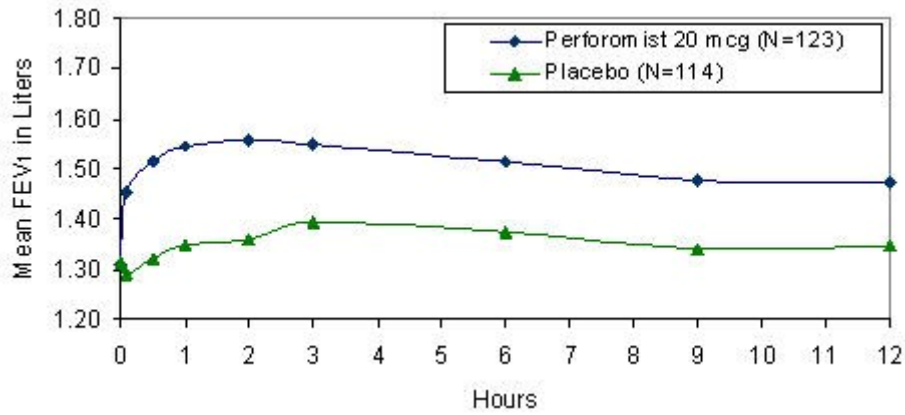
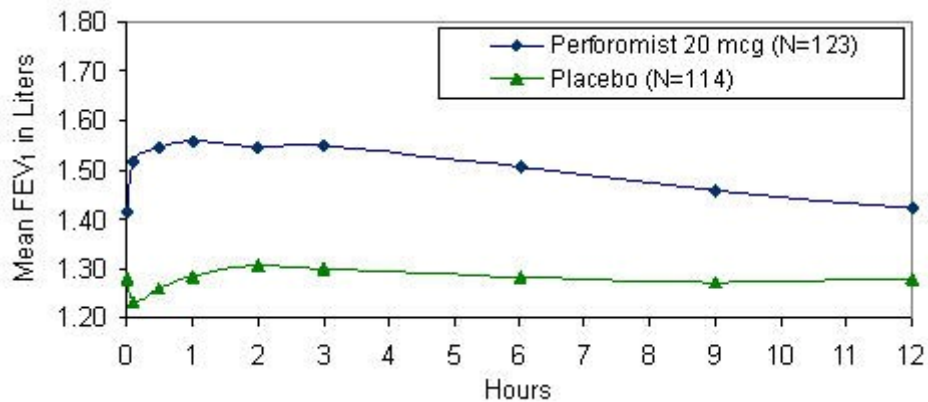


Figure 2
Mean¹ FEV₁ at Endpoint after 12 Weeks of Treatment



¹Figures show least-squares means adjusted for baseline FEV₁

Patients treated with PERFOROMIST Inhalation Solution used less rescue albuterol during the trial compared to patients treated with placebo.

Examination of age (≥ 65 or younger) and gender subgroups did not identify differences in response to PERFOROMIST Inhalation Solution. There were too few non-Caucasian

subjects to assess differences in populations defined by race adequately.

In the 12 week study, 78% of subjects achieved a 15% increase from baseline FEV₁ following the first dose of PERFOROMIST Inhalation Solution 20 mcg. In these subjects, the median time to onset of bronchodilation, defined as 15% increase in FEV₁, was 11.7 minutes. When defined as an increase in FEV₁ of 12% and 200 mL, the time to onset of bronchodilation was 13.1 minutes after dosing. The median time to peak bronchodilator effect was 2 hours after dosing.

16 HOW SUPPLIED/STORAGE AND HANDLING

PERFOROMIST (formoterol fumarate) Inhalation Solution is supplied as a 2 mL sterile solution for nebulization in 2.5 mL low-density polyethylene unit dose vials. Each vial is overwrapped in a foil pouch and supplied in cartons as listed below.

Carton of 60 individually wrapped unit dose vials, **NDC 49502-605-61**

Storage and Handling:

Prior to dispensing to the patient: Store in a refrigerator, 2°C to 8°C (36°F to 46°F)

After dispensing to the patient: Store at 2°C to 25°C (36°F to 77°F) for up to 3 months. Protect pouch from heat.

- PERFOROMIST Inhalation Solution should only be administered via a standard jet nebulizer connected to an air compressor with an adequate airflow and equipped with a facemask or mouthpiece.
- Vial should always be stored in the foil pouch, and only removed IMMEDIATELY before use.
- Do not take by mouth.
- Contents of any partially used container should be discarded.
- Discard the container and top after use.
- Keep out of the reach of children

17 PATIENT COUNSELING INFORMATION

Acute Exacerbations or Deteriorations

PERFOROMIST Inhalation Solution is not indicated for relief of acute symptoms, and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting beta2-agonist (the healthcare provider should provide the patient with such medication and instruct the patient in how it should be used). Patients should be instructed to seek medical attention if their symptoms worsen despite recommended doses of PERFOROMIST Inhalation Solution, if PERFOROMIST Inhalation Solution treatment becomes less effective, or if they need more inhalations of a short-acting beta2-agonist than usual.

Appropriate Dosing

Patients should not stop using PERFOROMIST Inhalation Solution unless told to do so by a healthcare provider because symptoms may get worse. Patients should not inhale more than the prescribed number of vials at any one time. The daily dosage of PERFOROMIST Inhalation Solution should not exceed one vial twice daily (40 mcg total daily dose). Excessive use of sympathomimetics may cause significant cardiovascular effects, and may be fatal.

Concomitant Therapy

Patients who have been taking inhaled, short-acting beta2-agonists (e.g., albuterol) on a regular basis should be instructed to discontinue the regular use of these products and use them only for symptomatic relief of acute symptoms. PERFOROMIST Inhalation Solution should not be used in conjunction with other inhaled medications containing long-acting beta2-agonists. Patients should be warned not to stop or change the dose of other concomitant COPD therapy without medical advice, even if symptoms improve after initiating treatment with PERFOROMIST Inhalation Solution.

Common Adverse Reactions with Beta2-agonists

Patients should be informed that treatment with beta2-agonists may lead to adverse reactions that include palpitations, chest pain, rapid heart rate, increased or decreased blood pressure, headache, tremor, nervousness, dry mouth, muscle cramps, nausea, dizziness, fatigue, malaise, low blood potassium, high blood sugar, high blood acid, or trouble sleeping [see [ADVERSE REACTIONS \(6.1\)](#)].

Instructions for Administration

It is important that patients understand how to use PERFOROMIST Inhalation Solution with a nebulizer

appropriately [see the accompanying [Medication Guide](#)]. Patients should be instructed not to mix other medications with PERFOROMIST Inhalation Solution or ingest PERFOROMIST Inhalation Solution. Patients should throw the plastic dispensing container away immediately after use. Due to their small size, the container and top pose a danger of choking to young children.

FDA-Approved Medication Guide

See the accompanying Medication Guide.

MEDICATION GUIDE

**PERFOROMIST™ (Per-FOR-o-mist)
(formoterol fumarate) Inhalation Solution**

IMPORTANT USE INFORMATION

1. **PERFOROMIST Inhalation Solution is for use with a standard jet nebulizer machine connected to an air compressor. Read the complete instructions for use at the end of this Medication Guide before starting PERFOROMIST Inhalation Solution.**
2. **Do not swallow or inject PERFOROMIST Inhalation Solution. PERFOROMIST Inhalation Solution is for inhalation use only.**

Read the Medication Guide that comes with PERFOROMIST Inhalation Solution 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 PERFOROMIST Inhalation Solution?

PERFOROMIST Inhalation Solution is a medicine called a long-acting beta2-agonist (LABA) or long-acting bronchodilator. PERFOROMIST Inhalation Solution is used to treat chronic obstructive pulmonary disease (COPD).

- **In patients with asthma, LABA medicines such as PERFOROMIST Inhalation Solution may increase the chance of asthma-related death from asthma problems. It is not known if LABA medicines, such as PERFOROMIST Inhalation Solution, increase the**

chance of death in patients with chronic obstructive pulmonary disease (COPD).

- **PERFOROMIST Inhalation Solution does not relieve sudden symptoms of COPD.** Always have a short-acting beta2-agonist bronchodilator medicine with you to treat sudden symptoms. If you do not have an inhaled short-acting bronchodilator, call your healthcare provider to have one prescribed for you.
- **Get emergency medical care if:**
 - **breathing problems worsen quickly**
 - **you use your short-acting beta2-agonist medicine, but it does not relieve your breathing problems**
- **Do not stop using PERFOROMIST Inhalation Solution unless told to do so by your healthcare provider because your symptoms might get worse.**
- **PERFOROMIST Inhalation Solution should not be used in children.** PERFOROMIST Inhalation Solution has not been studied in children.

What is PERFOROMIST Inhalation Solution?

PERFOROMIST Inhalation Solution is used long term, twice a day (morning and evening), in controlling symptoms of chronic obstructive pulmonary disease (COPD) in adults with COPD.

LABA medicines such as PERFOROMIST Inhalation Solution help the muscles around the airways in your lungs stay relaxed to prevent symptoms, such as wheezing, cough, chest tightness, and shortness of breath.

What should I tell my healthcare provider before using PERFOROMIST Inhalation Solution?

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

- **have heart problems**
- **have high blood pressure**
- **have diabetes**
- **have seizures**
- **have thyroid problems**
- **have liver problems**

- **are pregnant or planning to become pregnant.** It is not known if PERFOROMIST Inhalation Solution can harm an unborn baby.
- **are breastfeeding.** It is not known if PERFOROMIST Inhalation Solution passes into breast milk and if it can harm your baby.

Tell your healthcare provider about all the medicines you take including prescription and non-prescription medicines, vitamins and herbal supplements.

PERFOROMIST Inhalation Solution and certain other medicines may interact with each other. This may cause serious side effects.

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

How should I use PERFOROMIST Inhalation Solution?

Read the step-by-step instructions for using PERFOROMIST Inhalation Solution at the end of this Medication Guide.

- Use PERFOROMIST Inhalation Solution exactly as prescribed. One ready-to-use vial of PERFOROMIST Inhalation Solution is one dose. The usual dose of PERFOROMIST Inhalation Solution is 1 ready-to-use vial, twice a day (morning and evening) breathed in through your nebulizer machine. The 2 doses should be about 12 hours apart. **Do not use more than 2 vials of PERFOROMIST Inhalation Solution a day.**
- Do not mix other medicines with PERFOROMIST Inhalation Solution in your nebulizer machine.
- If you miss a dose of PERFOROMIST Inhalation Solution, just skip that dose. Take your next dose at your usual time. Do not take 2 doses at one time.
- While you are using PERFOROMIST Inhalation Solution twice a day:
 - **do not use** other medicines that contain a long-acting beta2-agonist (LABA) for any reason.
 - **do not use** your short-acting beta2-agonist medicine on a regular basis (four times a day).
- 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 PERFOROMIST Inhalation Solution.

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

Call your healthcare provider or get emergency medical care right away if:

- your breathing problems worsen with PERFOROMIST Inhalation Solution
- you need to use your short-acting beta2-agonist medicine more often than usual
- your short-acting beta2-agonist medicine does not work as well for you at relieving symptoms

What are the possible side effects with PERFOROMIST Inhalation Solution?

- **In patients with asthma, LABA medicines such as PERFOROMIST Inhalation Solution may increase the chance of asthma-related death from asthma problems.**
- **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 or decreased blood pressure
- a fast and irregular heartbeat
- headache
- tremor
- nervousness
- dry mouth
- muscle cramps
- nausea, vomiting
- dizziness
- tiredness
- low blood potassium

- **high blood sugar**
- **high blood acid**
- **trouble sleeping**

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

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

How should I store PERFOROMIST Inhalation Solution?

- Store PERFOROMIST Inhalation Solution in a refrigerator between 36° to 46°F (2° to 8°C) in the protective foil pouch. Protect from light and heat. **Do not open a sealed pouch until you are ready to use a dose of PERFOROMIST Inhalation Solution. Once a sealed pouch is opened, PERFOROMIST Inhalation Solution must be used right away.** PERFOROMIST Inhalation Solution may be used directly from the refrigerator.
- PERFOROMIST Inhalation Solution may also be stored at room temperature between 68°F to 77°F (20°C to 25°C) for up to 3 months (90 days). If stored at room temperature, discard PERFOROMIST Inhalation Solution if it is not used after 3 months or if past the expiration date, whichever is sooner. Space is provided on the packaging to record dispense date and use by date.
- Do not use PERFOROMIST Inhalation Solution after the expiration date provided on the foil pouch and vial.
- PERFOROMIST Inhalation Solution should be colorless. Discard PERFOROMIST Inhalation Solution if it is not colorless.
- **Keep PERFOROMIST Inhalation Solution and all medicines out of the reach of children.**

General Information about PERFOROMIST Inhalation Solution

Medicines are sometimes prescribed for purposes that are not mentioned in a Medication Guide. Do not use PERFOROMIST Inhalation Solution for a condition for which it was not prescribed. Do not give PERFOROMIST Inhalation Solution to

other people, even if they have the same condition. It may harm them.

This Medication Guide summarizes the most important information about PERFOROMIST Inhalation Solution. If you would like more information, talk with your health care provider. You can ask your health care provider or pharmacist for information about PERFOROMIST Inhalation Solution that was written for health care professionals.

- For customer service, call 1-800-755-5560
- To report side effects, call 1-800-429-7751
- For medical information, call 1-800-429-7751

Instructions for Using PERFOROMIST (formoterol fumarate) Inhalation Solution

PERFOROMIST Inhalation Solution is used only in a standard jet nebulizer machine connected to an air compressor. Make sure you know how to use your nebulizer machine before you use it to breathe in PERFOROMIST Inhalation Solution or other medicines.

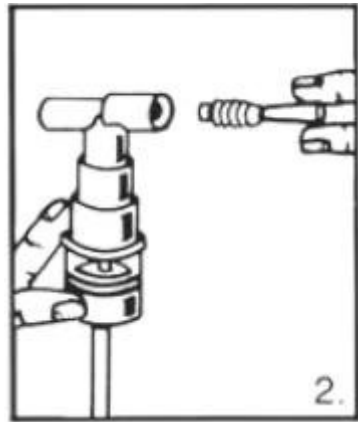
Do not mix PERFOROMIST Inhalation Solution with other medicines in your nebulizer machine.

PERFOROMIST Inhalation Solution comes sealed in a foil pouch. Do not open a sealed pouch until you are ready to use a dose of PERFOROMIST Inhalation Solution.

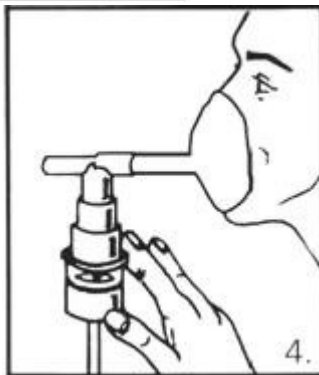
1. Remove vial from the foil pouch.
2. Twist the cap completely off the vial and squeeze all the medicine into the nebulizer medicine cup (reservoir) (Figure 1).



3. Connect the nebulizer reservoir to the mouthpiece or facemask (Figure 2).



4. Connect the nebulizer to the compressor.
5. Sit in a comfortable, upright position. Place the mouthpiece in your mouth (Figure 3) or put on the facemask (Figure 4); and turn on the compressor.



6. Breathe as calmly, deeply and evenly as possible through your mouth until no more mist is formed in the

nebulizer reservoir. The average nebulization time is 9 minutes. At this point, the treatment is finished.

7. Discard the PERFOROMIST Inhalation Solution container and top after use.
8. Clean the nebulizer (see manufacturer's instructions).

Rx Only

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

DEY®, Napa, CA 94558 USA

U.S. Pat. No. 6,667,344

U.S. Pat. No. 6,814,953

April 2007

XX-XXX-XX

Effective Date: 04/30/2007

Brovana (arformoterol tartrate) Solution
[Sepracor Inc.]

*potency expressed as arformoterol

For oral inhalation only

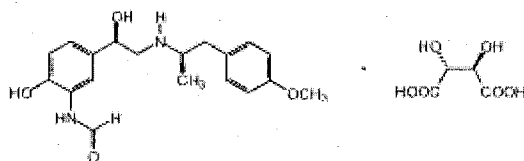
WARNING:

Long-acting beta₂-adrenergic agonists may increase the risk of asthma-related death. 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 arformoterol (a long-acting beta₂-adrenergic agonist), the active ingredient in BROVANA (see WARNINGS).

DESCRIPTION

BROVANA (arformoterol tartrate) Inhalation Solution is a sterile, clear, colorless, aqueous solution of the tartrate salt of arformoterol, the (R,R)-enantiomer of formoterol.

Arformoterol is a selective beta₂-adrenergic bronchodilator. The chemical name for arformoterol tartrate is formamide, N-[2-hydroxy-5-[(1R)-1-hydroxy-2-[[[(1R)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]-, (2R,3R)-2,3-dihydroxybutanedioate (1:1 salt), and its established structural formula is as follows:



The molecular weight of *arformoterol tartrate* is 494.5 g/mol, and its empirical formula is C₁₉H₂₄N₂O₄ · C₄H₆O₆ (1:1 salt). It is a white to off-white solid that is slightly soluble in water.

Arformoterol tartrate is the United States Adopted Name (USAN) for (R,R)-formoterol L-tartrate.

BROVANA is supplied as 2 mL of arformoterol tartrate solution packaged in 2.1 mL unit-dose, low-density polyethylene (LDPE) vials. Each unit-dose vial contains 15 mcg of arformoterol (equivalent to 22 mcg of arformoterol tartrate) in a sterile, isotonic saline solution, pH-adjusted to 5.0 with citric acid and sodium citrate.

BROVANA requires no dilution before administration by nebulization. Like all other nebulized treatments, the amount delivered to the lungs will depend upon patient factors, the nebulizer used, and compressor performance. Using the PARI LC PLUS[®] nebulizer (with mouthpiece) connected to a PARI DURA-NEB[®] 3000 compressor under *in vitro* conditions, the mean delivered dose from the mouthpiece (% nominal) was approximately 4.1 mcg (27.6%) at a mean flow rate of 3.3 L/min. The mean nebulization time was 6 minutes or less. BROVANA should be administered from a standard jet nebulizer at adequate flow rates via face mask or mouthpiece (see **Dosage and Administration**).

Patients should be carefully instructed on the correct use of this drug product (please refer to the

accompanying **Medication Guide**).

CLINICAL PHARMACOLOGY

Mechanism of Action

Arformoterol, the (R,R)-enantiomer of formoterol, is a selective long-acting beta₂-adrenergic receptor agonist (beta₂-agonist) that has two-fold greater potency than racemic formoterol (which contains both the (S,S) and (R,R)-enantiomers). The (S,S)-enantiomer is about 1,000-fold less potent as a beta₂-agonist than the (R,R)-enantiomer. While it is recognized that beta₂-receptors are the predominant adrenergic receptors in bronchial smooth muscle and beta₁-receptors are the predominant receptors in the heart, data indicate that there are also beta₂-receptors in the human heart comprising 10% to 50% of the total beta-adrenergic receptors. The precise function of these receptors has not been established, but they raise the possibility that even highly selective beta₂-agonists may have cardiac effects.

The pharmacologic effects of beta₂-adrenoceptor agonist drugs, including arformoterol, are at least in part attributable to stimulation of intracellular adenylyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cyclic AMP). Increased intracellular 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 arformoterol is an inhibitor of the release of mast cell mediators, such as histamine and leukotrienes, from the human lung. Arformoterol also inhibits histamine-induced plasma albumin extravasation in anesthetized guinea pigs and inhibits allergen-induced eosinophil influx in dogs with airway hyper-responsiveness. The relevance of these *in vitro* and animal findings to humans is unknown.

Animal Pharmacology

In animal studies investigating its cardiovascular effects, arformoterol induced dose-dependent increases in heart rate and decreases in blood pressure consistent with its pharmacology as a beta-adrenergic agonist. In dogs, at systemic exposures higher than anticipated clinically, arformoterol also induced exaggerated pharmacologic effects of a beta-adrenergic agonist on cardiac function as measured by electrocardiogram (sinus tachycardia, atrial premature beats, ventricular escape beats, PVCs).

Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of 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

The pharmacokinetics (PK) of arformoterol have been investigated in healthy subjects, elderly subjects, renally and hepatically impaired subjects, and chronic obstructive pulmonary disease (COPD) patients following the nebulization of the recommended therapeutic dose and doses up to 96 mcg.

Absorption

In COPD patients administered 15 mcg arformoterol every 12 hours for 14 days, the mean steady-state peak (R,R)-formoterol plasma concentration (C_{max}) and systemic exposure (AUC_{0-12h}) were 4.3 pg/mL and 34.5 pg*hr/mL, respectively. The median steady-state peak (R,R)-formoterol plasma concentration time (t_{max}) was observed approximately one half hour after drug administration.

Systemic exposure to (R,R)-formoterol increased linearly with dose in COPD patients following arformoterol doses of 5 mcg, 15 mcg, or 25 mcg twice daily for 2 weeks or 15 mcg, 25 mcg, or 50 mcg

once daily for 2 weeks.

In a crossover study in patients with COPD, when arformoterol 15 mcg inhalation solution and 12 and 24 mcg formoterol fumarate inhalation powder (Foradil® Aerolizer™) was administered twice daily for 2 weeks, the accumulation index was approximately 2.5 based on the plasma (R,R)-formoterol concentrations in all three treatments. At steady state, geometric means of systemic exposure (AUC_{0-12h}) to (R,R)-formoterol following 15 mcg of arformoterol inhalation solution and 12 mcg of formoterol fumarate inhalation powder were 39.33 pg*hr/mL and 33.93 pg*hr/mL, respectively (ratio 1.16; 90% CI 1.00, 1.35), while the geometric means of the C_{max} were 4.30 pg/mL and 4.75 pg/mL, respectively (ratio 0.91; 90% CI 0.76, 1.09).

In a study in patients with asthma, treatment with arformoterol 50 mcg with pre- and post-treatment with activated charcoal resulted in a geometric mean decrease in (R,R)-formoterol AUC_{0-6h} by 27% and C_{max} by 23% as compared to treatment with arformoterol 50 mcg alone. This suggests that a substantial portion of systemic drug exposure is due to pulmonary absorption.

Distribution

The binding of arformoterol to human plasma proteins *in vitro* was 52-65% at concentrations of 0.25, 0.5 and 1.0 ng/mL of radiolabeled arformoterol. The concentrations of arformoterol used to assess the plasma protein binding were higher than those achieved in plasma following inhalation of multiple doses of 50 mcg arformoterol.

Metabolism

In vitro profiling studies in hepatocytes and liver microsomes have shown that arformoterol is primarily metabolized by direct conjugation (glucuronidation) and secondarily by O-demethylation. At least five human uridine diphosphoglucuronosyltransferase (UGT) isozymes catalyze arformoterol glucuronidation *in vitro*. Two cytochrome P450 isozymes (CYP2D6 and secondarily CYP2C19) catalyze the O-demethylation of arformoterol.

Arformoterol did not inhibit CYP1A2, CYP2A6, CYP2C9/10, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, or CYP4A9/11 enzymes at >1,000-fold higher concentrations than the expected peak plasma concentrations following a therapeutic dose.

Arformoterol was almost entirely metabolized following oral administration of 35 mcg of radiolabeled arformoterol in eight healthy subjects. Direct conjugation of arformoterol with glucuronic acid was the major metabolic pathway. Most of the drug-related material in plasma and urine was in the form of glucuronide or sulfate conjugates of arformoterol. O-Desmethylation and conjugates of the O-desmethyl metabolite were relatively minor metabolites accounting for less than 17% of the dose recovered in urine and feces.

Elimination

After administration of a single oral dose of radiolabeled arformoterol to eight healthy male subjects, 63% of the total radioactive dose was recovered in urine and 11% in feces within 48 hours. A total of 89% of the total radioactive dose was recovered within 14 days, with 67% in urine and 22% in feces. Approximately 1% of the dose was recovered as unchanged arformoterol in urine over 14 days. Renal clearance was 8.9 L/hr for unchanged arformoterol in these subjects.

In COPD patients given 15 mcg inhaled arformoterol twice a day for 14 days, the mean terminal half-life of arformoterol was 26 hours.

Special Populations

Gender

A population PK analysis indicated that there was no effect of gender upon the pharmacokinetics of arformoterol.

Race

The influence of race on arformoterol pharmacokinetics was assessed using a population PK analysis and data from healthy subjects. There was no clinically significant impact of race upon the pharmacokinetic profile of arformoterol.

Geriatric

The pharmacokinetic profile of arformoterol in 24 elderly subjects (aged 65 years or older) was compared to a younger cohort of 24 subjects (18-45 years) that were matched for body weight and gender. No significant differences in systemic exposure (AUC and C_{\max}) were observed when the two groups were compared.

Pediatric

The pharmacokinetics of arformoterol have not been studied in pediatric subjects.

Hepatic Impairment

The pharmacokinetic profile of arformoterol was assessed in 24 subjects with mild, moderate, and severe hepatic impairment. The systemic exposure (C_{\max} and AUC) to arformoterol increased 1.3 to 2.4-fold in subjects with hepatic impairment compared to 16 demographically matched healthy control subjects. No clear relationship between drug exposure and the severity of hepatic impairment was observed. BROVANA should be used cautiously in patients with hepatic impairment.

Renal Impairment

The impact of renal disease upon the pharmacokinetics of arformoterol was studied in 24 subjects with mild, moderate, or severe renal impairment. Systemic exposure (AUC and C_{\max}) to arformoterol was similar in renally impaired patients compared with demographically matched healthy control subjects.

Pharmacogenetics

Arformoterol is eliminated through the action of multiple drug metabolizing enzymes. Direct glucuronidation of arformoterol is mediated by several UGT enzymes and is the primary elimination route. O-Desmethylation is a secondary route catalyzed by the CYP enzymes CYP2D6 and CYP2C19. In otherwise healthy subjects with reduced CYP2D6 and/or UGT1A1 enzyme activity, there was no impact on systemic exposure to arformoterol compared to subjects with normal CYP2D6 and/or UGT1A1 enzyme activities.

Pharmacodynamics

Systemic Safety and Pharmacokinetic/ Pharmacodynamic Relationships

The predominant adverse effects of inhaled beta₂-agonists occur as a result of excessive activation of systemic beta-adrenergic receptors. The most common adverse effects may include skeletal muscle tremor and cramps, insomnia, tachycardia, decreases in plasma potassium, and increases in plasma glucose.

Effects on Serum Potassium and Serum Glucose Levels

Changes in serum potassium and serum glucose were evaluated in a dose ranging study of twice daily (5 mcg, 15 mcg, or 25 mcg; 215 patients with COPD) and once daily (15 mcg, 25 mcg, or 50 mcg; 191 patients with COPD) BROVANA in COPD patients. At 2 and 6 hours post dose at week 0 (after the first dose), mean changes in serum potassium ranging from 0 to -0.3 mEq/L were observed in the BROVANA groups with similar changes observed after 2 weeks of treatment. Changes in mean serum glucose levels, ranging from a decrease of 1.2 mg/dL to an increase of 32.8 mg/dL were observed for BROVANA dose groups at both 2 and 6 hours post dose, both after the first dose and 14 days of daily treatment.

Electrophysiology

The effect of BROVANA on QT interval was evaluated in a dose ranging study following multiple doses of BROVANA 5 mcg, 15 mcg, or 25 mcg twice daily or 15 mcg, 25 mcg, or 50 mcg once daily for 2 weeks in patients with COPD. ECG assessments were performed at baseline, time of peak plasma concentration and throughout the dosing interval. Different methods of correcting for heart rate were employed, including a subject-specific method and the Fridericia method.

Relative to placebo, the mean change in subject-specific QT_c averaged over the dosing interval ranged from -1.8 to 2.7 msec, indicating little effect of BROVANA on cardiac repolarization after 2 weeks of treatment. The maximum mean change in subject-specific QT_c for the BROVANA 15 mcg twice daily dose was 17.3 msec, compared with 15.4 msec in the placebo group. No apparent correlation of QT_c with arformoterol plasma concentration was observed.

Electrocardiographic Monitoring in Patients with COPD

The effect of different doses of BROVANA on cardiac rhythm was assessed using 24-hour Holter monitoring in two 12-week double-blind, placebo-controlled studies of 1,456 patients with COPD (873 received BROVANA at 15 or 25 mcg twice daily or 50 mcg once daily doses; 293 received placebo; 290 received salmeterol). The 24-hour Holter monitoring occurred once at baseline, and up to 3 times during the 12-week treatment period. The rates of new-onset cardiac arrhythmias not present at baseline over the double-blind 12-week treatment period were similar (approximately 33-34%) for patients who received BROVANA 15 mcg twice daily to those who received placebo. There was a dose-related increase in new, treatment emergent arrhythmias seen in patients who received BROVANA 25 mcg twice daily and 50 mcg once daily, 37.6% and 40.1 %, respectively. The frequencies of new treatment emergent events of non-sustained (3-10 beat run) and sustained (>10 beat run) ventricular tachycardia were 7.4% and 1.1% in BROVANA 15 mcg twice daily and 6.9% and 1.0% in placebo. In patients who received BROVANA 25 mcg twice daily and 50 mcg once daily the frequencies of non-sustained (6.2% and 8.2%, respectively) and sustained ventricular tachycardia (1.0% and 1.0%, respectively) were similar. Five cases of ventricular tachycardia were reported as adverse events (1 in BROVANA 15 mcg twice daily and 4 in placebo), with two of these events leading to discontinuation of treatment (2 in placebo).

There were no baseline occurrences of atrial fibrillation/ flutter observed on 24-hour Holter monitoring in patients treated with BROVANA 15 mcg twice daily or placebo. New, treatment emergent atrial fibrillation/ flutter occurred in 0.4% of patients who received BROVANA 15 mcg twice daily and 0.3% of patients who received placebo. There was a dose-related increase in the frequency of atrial fibrillation/ flutter reported in the BROVANA 25 mcg twice daily and 50 mcg once daily dose groups of 0.7% and 1.4%, respectively. Two cases of atrial fibrillation/ flutter were reported as adverse events (1 in BROVANA 15 mcg twice daily and 1 in placebo).

Dose-related increases in mean maximum change in heart rate in the 12 hours after dosing were also observed following 12 weeks of dosing with BROVANA 15 mcg twice daily (8.8 bpm), 25 mcg twice daily (9.9 bpm) and 50 mcg once daily (12 bpm) versus placebo (8.5 bpm).

Tachyphylaxis/ Tolerance

In two placebo-controlled clinical trials in patients with COPD involving approximately 725 patients in each, the overall efficacy of BROVANA was maintained throughout the 12-week trial duration. However, tolerance to the bronchodilator effect of BROVANA was observed after 6 weeks of dosing, evidenced by a decrease in bronchodilator effect as measured by FEV₁. FEV₁ improvement at the end of the 12-hour dosing interval decreased by approximately one third (22.1% mean improvement after the first dose compared to 14.6% at week 12). Tolerance to the FEV₁ bronchodilator effect of BROVANA was not accompanied by other clinical manifestations of tolerance in these trials.

CLINICAL TRIALS

Adult COPD Trials

BROVANA (arformoterol tartrate) Inhalation Solution was studied in two identical, 12-week, double-blind, placebo- and active-controlled, randomized, multi-center, parallel group trials conducted in the United States (Clinical Trial A and Clinical Trial B). A total of 1,456 adult patients (age range: 34 to 89 years; mean age: 63 years) with COPD who had a mean FEV₁ of 1.3 L (42% of predicted) were enrolled in the two clinical trials. The diagnosis of COPD was based on a prior clinical diagnosis of COPD, a smoking history (greater than 15 pack-years), age (at least 35 years), spirometry results (baseline FEV₁ ≤ 65% of-predicted value and >0.70 L, and a FEV₁/ forced vital capacity (FVC) ratio ≤70%). About 80% of patients in these studies had bronchodilator reversibility, defined as a 10% or greater increase FEV₁ after inhalation of 2 actuations (180 mcg racemic albuterol from a metered dose inhaler). Both trials compared BROVANA 15 mcg twice daily (288 patients), 25 mcg twice daily (292 patients), 50 mcg once daily (293 patients) with placebo (293 subjects). Both trials included salmeterol inhalation aerosol, 42 mcg twice daily as an active comparator (290 patients).

In both 12-week trials, BROVANA 15 mcg twice daily resulted in significantly greater post-dose bronchodilation (as measured by percent change from study baseline FEV₁ at the end of the dosing interval over the 12 weeks of treatment, the primary efficacy endpoint) compared to placebo. Compared to BROVANA 15 mcg twice daily, BROVANA 25 mcg twice daily and 50 mcg once daily did not provide sufficient additional benefit on a variety of endpoints, including FEV₁, to support the use of higher doses. Plots of the mean change in FEV₁ values obtained over the 12 hours after dosing for the BROVANA 15 mcg twice daily dose group and for the placebo group are provided in **Figures 1 and 2** for Clinical Trial A, below. The plots include mean FEV₁ change observed after the first dose and after 12 weeks of treatment. The results from Clinical Trial B were similar.

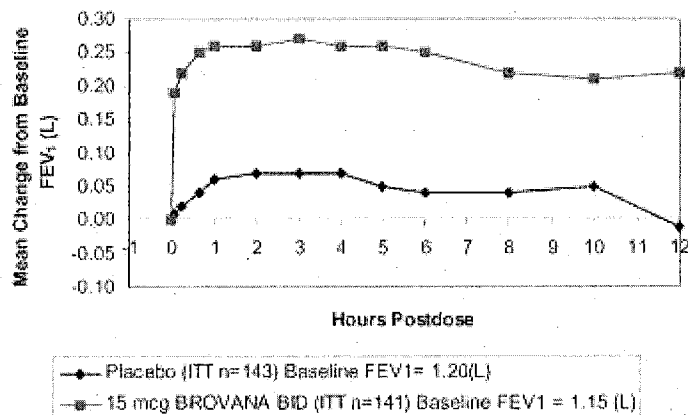


Figure 1 Mean Change in FEV₁ Over Time for Clinical Trial A at Week 0 (Day 1)

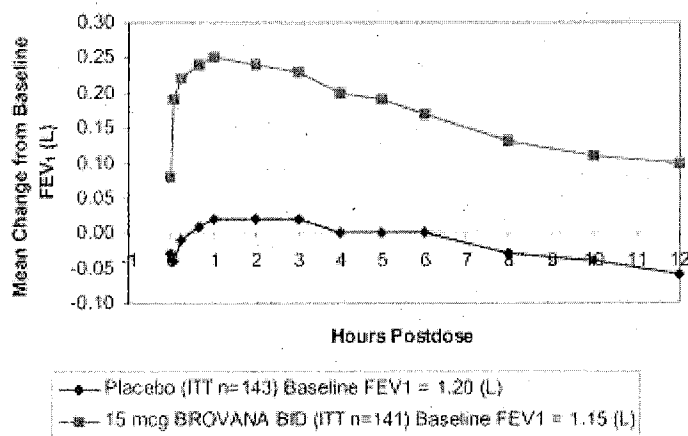


Figure 2 Mean Change in FEV₁ Over Time for Clinical Trial A at Week 12

BROVANA 15 mcg twice daily significantly improved bronchodilation compared to placebo over the 12 hours after dosing (FEV₁ AUC_{0-12h}). This improvement was maintained over the 12 week study period.

Following the first dose of BROVANA 15 mcg, the median time to onset of bronchodilation, defined by an FEV₁ increase of 15%, occurred at 6.7 min. When defined as an increase in FEV₁ of 12% and 200 mL, the time to onset of bronchodilation was 20 min after dosing. Peak bronchodilator effect was generally seen within 1-3 hours of dosing.

In both clinical trials, compared to placebo, patients treated with BROVANA demonstrated improvements in peak expiratory flow rates, supplemental ipratropium and rescue albuterol use.

INDICATIONS AND USAGE

BROVANA (arformoterol tartrate) Inhalation Solution is indicated for the long term, twice daily (morning and evening) maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. BROVANA is for use by nebulization only.

CONTRAINDICATIONS

BROVANA (arformoterol tartrate) Inhalation Solution is contraindicated in patients with a history of hypersensitivity to arformoterol, racemic formoterol or to any other components of this product.

WARNINGS

- **Long-acting beta₂-adrenergic agonists may increase the risk of asthma-related death.**
 - 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 beta₂-adrenergic agonists, including BROVANA. No study adequate to determine whether the rate of asthma related death is increased in patients treated with BROVANA has been conducted.
 - Clinical studies with racemic formoterol (Foradil[®] Aerolizer[™]) suggested a higher incidence of serious asthma exacerbations in patients who received racemic 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.
- **The studies described above enrolled patients with asthma. Data are not available to determine whether the rate of death in patients with COPD is increased by long-acting beta₂-adrenergic agonists.**
- **BROVANA is indicated for the long term, twice daily (morning and evening) maintenance treatment for bronchoconstriction in chronic obstructive pulmonary disease (COPD), and is not indicated for the treatment of acute episodes of bronchospasm, i.e., rescue therapy.**
- **BROVANA should not be initiated in patients with acutely deteriorating COPD, which may be a life-threatening condition. The use of BROVANA in this setting is inappropriate.**
- **BROVANA should not be used in children as the safety and efficacy of BROVANA have not been established in pediatric patients.**
- **BROVANA should not be used in conjunction with other inhaled, long-acting beta₂-agonists. BROVANA should not be used with other medications containing long-acting beta₂-agonists.**
- **When beginning treatment with BROVANA, patients who have been taking inhaled, short-acting beta₂-agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief of acute respiratory symptoms.**
- **See PRECAUTIONS, Information for Patients and the accompanying Medication Guide.**

Paradoxical Bronchospasm

As with other inhaled beta₂-agonists, BROVANA can produce paradoxical bronchospasm that may be life-threatening. If paradoxical bronchospasm occurs, BROVANA should be discontinued immediately and alternative therapy instituted.

Deterioration of Disease

COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If BROVANA no longer controls the symptoms of bronchoconstriction, or the patient's inhaled, short-acting beta₂-agonist becomes less effective or the patient needs more inhalation of short-acting beta₂-agonist than usual, these may be markers of deterioration of disease. In this setting, a re-evaluation of the patient and the COPD treatment regimen should be undertaken at once. Increasing the daily dosage of BROVANA beyond the recommended 15 mcg twice daily dose is not appropriate in this situation.

Cardiovascular Effects

BROVANA, like other beta₂-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of BROVANA at the recommended dose, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QT_c interval, and ST segment depression. The clinical significance of these findings is unknown. BROVANA, as with other sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension (see **PRECAUTIONS, General**).

Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions may occur after administration of BROVANA as demonstrated by cases of anaphylactic reaction, urticaria, angioedema, rash and bronchospasm.

Do Not Exceed Recommended Dose

Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. As with other inhaled beta₂-adrenergic drugs, BROVANA should not be used more often, at higher doses than recommended, or with other long-acting beta-agonists.

PRECAUTIONS

General

BROVANA (arformoterol tartrate) Inhalation Solution should not be used to treat acute symptoms of COPD. BROVANA has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. When prescribing BROVANA, the physician should also provide the patient with an inhaled, short-acting beta₂-agonist for treatment of COPD symptoms that occur acutely, despite regular twice-daily (morning and evening) use of BROVANA. Patients should also be cautioned that increasing inhaled beta₂-agonist use is a signal of deteriorating disease for which prompt medical attention is indicated (see **Information for Patients** and the accompanying **Medication Guide**).

BROVANA, like other sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive disorders or thyrotoxicosis; and in patients who are unusually responsive to sympathomimetic amines. Clinically significant changes in systolic and/or diastolic blood pressure, pulse rate and electrocardiograms have been seen infrequently in individual patients in controlled clinical studies with arformoterol tartrate. Doses of the related beta₂-agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

Beta-agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation.

Clinically significant changes in blood glucose and/or serum potassium were infrequent during clinical studies with long-term administration of BROVANA at the recommended dose.

Information for Patients

Patients should be instructed to read the accompanying Medication Guide with each new

prescription and refill. The complete text of the Medication Guide is reprinted at the end of this document. Patients should be given the following information:

1. Patients should be informed that long-acting beta₂-adrenergic agonists may increase the risk of asthma-related death.
2. BROVANA is not indicated to relieve acute respiratory symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting, beta₂-agonist (the health-care provider should prescribe the patient with such medication and instruct the patient in how it should be used). Patients should be instructed to seek medical attention if their symptoms worsen, if BROVANA treatment becomes less effective, or if they need more inhalations of a short-acting beta₂-agonist than usual. Patients should not inhale more than one dose at any one time. The daily dosage of BROVANA should not exceed one vial (15 mcg) by inhalation twice daily (30 mcg total daily dose).
3. Patients should be informed that treatment with beta₂-agonists may lead to adverse events which include palpitations, chest pain, rapid heart rate, tremor, or nervousness.
4. Patients should be instructed to use BROVANA by nebulizer only and not to inject or swallow this inhalation solution.
5. Patients should protect BROVANA single-use low-density polyethylene (LDPE) vials from light and excessive heat. The protective foil pouches should be stored under refrigeration between 2°C and 8°C (36°–46°F). They should not be used after the expiration date stamped on the container. After opening the pouch, unused vials should be returned to, and stored in, the pouch. An opened vial should be used right away. Discard any vial if the solution is not colorless.
6. The drug compatibility (physical and chemical), efficacy and safety of BROVANA when mixed with other drugs in a nebulizer have not been established.
7. Women should be advised to contact their physician if they become pregnant or if they are nursing.
8. It is important that patients understand how to use BROVANA appropriately and how it should be used in relation to other medications to treat COPD they are taking (see the accompanying **Medication Guide** and the **Instructions for Using BROVANA**).

Drug Interactions

If additional adrenergic drugs are to be administered by any route, they should be used with caution because the pharmacologically predictable sympathetic effects of BROVANA may be potentiated.

When paroxetine, a potent inhibitor of CYP2D6, was co-administered with BROVANA at steady-state, exposure to either drug was not altered. Dosage adjustments of BROVANA are not necessary when the drug is given concomitantly with potent CYP2D6 inhibitors.

Concomitant treatment with methylxanthines (aminophylline, theophylline), steroids, or diuretics may potentiate any hypokalemic effect of adrenergic agonists.

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

BROVANA, as with other beta₂-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QT_c interval because the action of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QT_c interval have an increased risk of ventricular

arrhythmias. The concurrent use of intravenously or orally administered methylxanthines (e.g., aminophylline, theophylline) by patients receiving BROVANA has not been completely evaluated. In two combined 12-week placebo controlled trials that included BROVANA doses of 15 mcg twice daily, 25 mcg twice daily, and 50 mcg once daily, 54 of 873 BROVANA -treated subjects received concomitant theophylline at study entry. In a 12-month controlled trial that included a 50 mcg once daily BROVANA dose, 30 of the 528 BROVANA -treated subjects received concomitant theophylline at study entry. In these trials, heart rate and systolic blood pressure were approximately 2-3 bpm and 6-8 mm Hg higher, respectively, in subjects on concomitant theophylline compared with the overall population.

Beta-adrenergic receptor antagonists (beta-blockers) and BROVANA may interfere with the effect of each other when administered concurrently. Beta-blockers not only block the therapeutic effects of beta-agonists, but may produce severe bronchospasm in COPD patients. Therefore, patients with COPD should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-blockers in patients with COPD. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

In a 24-month carcinogenicity study in CD-1 mice, arformoterol caused a dose-related increase in the incidence of uterine and cervical endometrial stromal polyps and stromal cell sarcoma in female mice at oral doses of 1 mg/kg and above (AUC exposure approximately 70 times adult exposure at the maximum recommended daily inhalation dose).

In a 24-month carcinogenicity study in Sprague-Dawley rats, arformoterol caused a statistically significant increase in the incidence of thyroid gland c-cell adenoma and carcinoma in female rats at an inhalation dose of 200 mcg/kg (AUC exposure approximately 130 times adult exposure at the maximum recommended daily inhalation dose). There were no tumor findings with an inhalation dose of 40 mcg/kg (AUC exposure approximately 55 times adult exposure at the maximum recommended daily inhalation dose).

Arformoterol was not mutagenic or clastogenic in the following tests: mutagenicity tests in bacteria, chromosome aberration analyses in mammalian cells, and micronucleus test in mice.

Arformoterol had no effects on fertility and reproductive performance in rats at oral doses up to 10 mg/kg (approximately 2700 times the maximum recommended daily inhalation dose in adults on a mg/m² basis).

Pregnancy: Teratogenic Effects

Pregnancy Category C

Arformoterol has been shown to be teratogenic in rats based upon findings of omphalocele (umbilical hernia), a malformation, at oral doses of 1 mg/kg and above (AUC exposure approximately 370 times adult exposure at the maximum recommended daily inhalation dose). Increased pup loss at birth and during lactation and decreased pup weights were observed in rats at oral doses of 5 mg/kg and above (AUC exposure approximately 1100 times adult exposure at the maximum recommended daily inhalation dose). Delays in development were evident with an oral dose of 10 mg/kg (AUC exposure approximately 2400 times adult exposure at the maximum recommended daily inhalation dose).

Arformoterol has been shown to be teratogenic in rabbits based upon findings of malpositioned right kidney, a malformation, at oral doses of 20 mg/kg and above (AUC exposure approximately 8400 times adult exposure at the maximum recommended daily inhalation dose). Malformations including brachydactyly, bulbous aorta, and liver cysts were observed at doses of 40 mg/kg and above (approximately 22,000 times the maximum recommended daily inhalation dose in adults on a mg/m² basis). Malformation including adactyly, lobular dysgenesis of the lung, and interventricular septal defect were observed at 80 mg/kg (approximately 43,000 times the maximum recommended daily inhalation dose in adults on a mg/m² basis). Embryo lethality was observed at 80 mg/kg/day (approximately 43,000 times the maximum recommended daily inhalation dose in adults on a mg/m² basis). Decreased pup body weights were observed at doses of 40 mg/kg/day and above (approximately 22,000 times the maximum recommended daily inhalation dose in adults on a mg/m² basis). There were no teratogenic findings in rabbits with oral dose of 10 mg/kg and lower (AUC exposure approximately 4900 times adult exposure at the maximum recommended daily inhalation dose).

There are no adequate and well-controlled studies in pregnant women. BROVANA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in Labor and Delivery

There are no human studies that have investigated the effects of BROVANA on preterm labor or labor at term.

Because beta-agonists may potentially interfere with uterine contractility, BROVANA should be used during labor and delivery only if the potential benefit justifies the potential risk.

Nursing Mothers

In reproductive studies in rats, arformoterol was excreted in the milk. It is not known whether arformoterol is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when BROVANA is administered to a nursing woman.

Pediatric

BROVANA is approved for use in the long term maintenance treatment of bronchoconstriction associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema. This disease does not occur in children. The safety and effectiveness of BROVANA in pediatric patients have not been established.

Geriatric

Of the 873 patients who received BROVANA in two placebo-controlled clinical studies in adults with COPD, 391 (45%) were 65 years of age or older while 96 (11%) were 75 years of age or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Among subjects age 65 years and older, 129 (33%) received BROVANA at the recommended dose of 15 mcg twice daily, while the remainder received higher doses. ECG alerts for ventricular ectopy in patients 65 to ≤ 75 years of age were comparable among patients receiving 15 mcg twice daily, 25 mcg twice daily, and placebo (3.9%, 5.2%, and 7.1%, respectively). A higher frequency (12.4%) was observed when BROVANA was dosed at 50 mcg once daily. The clinical significance of this finding is not known. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Experience in Adult Patients with COPD

Of the 1,456 COPD patients in the two 12-week, placebo-controlled trials, 288 were treated with BROVANA (arformoterol tartrate) Inhalation Solution 15 mcg twice daily and 293 were treated with placebo. Doses of 25 mcg twice daily and 50 mcg once daily were also evaluated. The numbers and percent of patients who reported adverse events were comparable in the 15 mcg twice daily and placebo groups.

The following table shows adverse events where the frequency was greater than or equal to 2% in the BROVANA 15 mcg twice daily group and where the rates of adverse events in the BROVANA 15 mcg twice daily group exceeded placebo. Ten adverse events demonstrated a dose relationship: asthenia, fever, bronchitis, COPD, headache, vomiting, hyperkalemia, leukocytosis, nervousness, and tremor.

Table 1: Number of Patients Experiencing Adverse Events from Two 12-Week, Double-Blind, Placebo Controlled Clinical Trials

	BROVANA 15 mcg twice daily		Placebo	
	n	(%)	n	(%)
Total Patients	288	(100)	293	(100)
Pain	23	(8)	16	(5)
Chest Pain	19	(7)	19	(6)
Back Pain	16	(6)	6	(2)
Diarrhea	16	(6)	13	(4)
Sinusitis	13	(5)	11	(4)
Leg Cramps	12	(4)	6	(2)
Dyspnea	11	(4)	7	(2)
Rash	11	(4)	5	(2)
Flu Syndrome	10	(3)	4	(1)
Peripheral Edema	8	(3)	7	(2)
Lung Disorder*	7	(2)	2	(1)

* Reported terms coded to "Lung Disorder" were predominantly pulmonary or chest congestion.

Adverse events occurring in patients treated with BROVANA 15 mcg twice daily with a frequency of <2%, but greater than placebo were as follows:

Body as a Whole: abscess, allergic reaction, digitalis intoxication, fever, hernia, injection site pain, neck rigidity, neoplasm, pelvic pain, retroperitoneal hemorrhage

Cardiovascular: arteriosclerosis, atrial flutter, AV block, congestive heart failure, heart block, myocardial infarct, QT interval prolonged, supraventricular tachycardia, inverted T-wave

Digestive: constipation, gastritis, melena, oral moniliasis, periodontal abscess, rectal hemorrhage

Metabolic and Nutritional Disorders: dehydration, edema, glucose tolerance decreased, gout, hyperglycemia, hyperlipemia, hypoglycemia, hypokalemia

Musculoskeletal: arthralgia, arthritis, bone disorder, rheumatoid arthritis, tendinous contracture

Nervous: agitation, cerebral infarct, circumoral paresthesia, hypokinesia, paralysis, somnolence, tremor

Respiratory: carcinoma of the lung, respiratory disorder, voice alteration

Skin and Appendages: dry skin, herpes simplex, herpes zoster, skin discoloration, skin hypertrophy

Special Senses: abnormal vision, glaucoma

Urogenital: breast neoplasm, calcium crystalluria, cystitis, glycosuria, hematuria, kidney calculus, nocturia, PSA increase, pyuria, urinary tract disorder, urine abnormality.

Overall, the frequency of all cardiovascular adverse events for BROVANA in the two placebo controlled trials was low and comparable to placebo (6.9% in BROVANA 15 mcg twice daily and 13.3% in the placebo group). There were no frequently occurring specific cardiovascular adverse events for BROVANA (frequency $\geq 1\%$ and greater than placebo). The rate of COPD exacerbations was also comparable between the BROVANA 15 mcg twice daily and placebo groups, 12.2% and 15.1%, respectively.

Other adverse reactions which may occur with selective beta₂-adrenoceptor agonists such as BROVANA include: angina, hypertension or hypotension, tachycardia, arrhythmias, nervousness, headache, tremor, dry mouth, palpitation, muscle cramps, nausea, dizziness, fatigue, malaise, hypokalemia, hyperglycemia, metabolic acidosis and insomnia.

Drug Abuse and Dependence

There were no reported cases of abuse or evidence of drug dependence with the use of BROVANA in the clinical trials.

OVERDOSAGE

The expected signs and symptoms associated with overdosage of BROVANA (arformoterol tartrate) Inhalation Solution are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and symptoms listed under **ADVERSE REACTIONS**, e.g., angina, hypertension or hypotension, tachycardia, with rates up to 200 bpm, arrhythmias, nervousness, headache, tremor, dry mouth, palpitation, muscle cramps, nausea, dizziness, fatigue, malaise, hypokalemia, hyperglycemia, metabolic acidosis and insomnia. As with all inhaled sympathomimetic medications, cardiac arrest and even death may be associated with an overdose of BROVANA.

Treatment of overdosage consists of discontinuation of BROVANA 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 BROVANA. Cardiac monitoring is recommended in cases of overdosage.

Clinical signs in dogs included flushing of the body surface and facial area, reddening of the ears and gums, tremor, and increased heart rate. A death was reported in dogs after a single oral dose of 5 mg/kg (approximately 4500 times the maximum recommended daily inhalation dose in adults on a mg/m² basis). Death occurred for a rat that received arformoterol at a single inhalation dose of 1600 mcg/kg (approximately 430 times the maximum recommended daily inhalation dose in adults on a mg/m² basis).

DOSAGE AND ADMINISTRATION

The recommended dose of BROVANA (arformoterol tartrate) Inhalation Solution for COPD patients is 15 mcg administered twice a day (morning and evening) by nebulization. A total daily dose greater than 30 mcg (15 mcg twice daily) is not recommended. BROVANA should be administered by the inhaled route via a standard jet nebulizer connected to an air compressor (see the accompanying **Medication Guide**). BROVANA should not be swallowed. BROVANA™ should be stored refrigerated in foil pouches. After opening the pouch, unused vials should be returned to, and stored in, the pouch. An

opened vial should be used right away.

If the recommended maintenance treatment regimen fails to provide the usual response, medical advice should be sought immediately, as this is often a sign of destabilization of COPD. Under these circumstances, the therapeutic regimen should be re-evaluated and additional therapeutic options should be considered.

No dose adjustment is required for patients with renal or hepatic impairment. However, since the clearance of BROVANA is prolonged in patients with hepatic impairment, they should be monitored closely.

The drug compatibility (physical and chemical), efficacy, and safety of BROVANA when mixed with other drugs in a nebulizer have not been established.

The safety and efficacy of BROVANA have been established in clinical trials when administered using the PARI LC PLUS[®] nebulizers and PARI DURA-NEB[®] 3000 compressors. The safety and efficacy of BROVANA when administered using other nebulizer systems has not been established.

HOW SUPPLIED

BROVANA (arformoterol tartrate) Inhalation Solution is supplied in a single strength (15 mcg of arformoterol, equivalent to 22 mcg of arformoterol tartrate) as 2 mL of a sterile solution in unit-dose, low-density polyethylene (LDPE) vials overwrapped in foil. BROVANA is available in a shelf-carton containing 30 or 60 vials.

NDC 63402-911-30: carton of 30 unit-dose individually pouched vials.

NDC 63402-911-64: carton of 60 unit-dose vials (15x4 vial pouches).

CAUTION: Federal law (U.S.) prohibits dispensing without prescription.

Storage

Store BROVANA in the protective foil pouch under refrigeration at 36°-46°F (2°-8°C). Protect from light and excessive heat. After opening the pouch, unused vials should be returned to, and stored in, the pouch. An opened vial should be used right away. Discard any vial if the solution is not colorless. Unopened foil pouches of BROVANA can also be stored at room temperature 68°-77°F, (20°-25°C) for up to 6 weeks. If stored at room temperature, discard if not used after 6 weeks or if past the expiration date, whichever is sooner.

Sepracor

Manufactured for:

Sepracor Inc.

Marlborough, MA 01752 USA

For customer service, call 1-888-394-7377.

To report adverse events, call 1-877-737-7226.

For medical information, call 1-800-739-0565.

May 2007

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MEDICATION GUIDE

BROVANA/*Brō vă `-nah*/

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