

Safety of Long-Acting Beta-Agonist Bronchodilators

Pulmonary-Allergy Drugs Advisory Committee Meeting

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GlaxoSmithKline

Briefing Document

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TABLE OF CONTENTS

	PAGE
1. EXECUTIVE SUMMARY	1
1.1. Introduction	1
1.2. Overall Assessment	1
1.3. Development of Salmeterol	1
1.4. Marketing Approvals and Indications	2
1.5. Beta-agonist Debate and the Introduction of Salmeterol.....	2
1.6. Post-marketing Surveillance Studies.....	3
1.7. Additional Safety Analyses of GlaxoSmithKline Clinical Trials.....	3
1.8. Epidemiology Studies.....	4
1.9. Post-marketing Safety Data	4
1.10. Overall Benefit-to-Risk	4
2. SALMETEROL EFFICACY FROM RANDOMIZED CONTROLLED CLINICAL TRIALS IN ASTHMA.....	5
2.1. Lung Function	5
2.2. Effect on Asthma Symptoms, Nighttime Awakenings, Rescue Albuterol Use and Health-related Quality of Life	5
2.3. Salmeterol Administered with Inhaled Corticosteroids	6
2.4. Potential Development of Tolerance with Salmeterol.....	6
2.5. Summary.....	6
3. POST-MARKETING CLINICAL STUDIES.....	7
3.1. Serevent Nationwide Surveillance (SNS) Study.....	7
3.2. Salmeterol Multicenter Asthma Research Trial (SMART)	8
3.2.1. Statistical Considerations.....	9
3.2.2. Study Population Results.....	10
3.2.3. Demographic Characteristics.....	11
3.2.3.1. Baseline Characteristics.....	11
3.2.3.2. Demographic and Baseline Characteristics for Ethnic Subgroups	12
3.2.4. Concurrent Asthma Medications at Baseline	13
3.2.4.1. Concurrent Asthma Medications at Baseline for Ethnic Subgroups	13
3.2.5. Study Results.....	13
3.2.6. Analysis of Population Subgroups	14
3.2.6.1. Ethnic Origin.....	14
3.2.6.2. Inhaled Corticosteroid Use Reported at Baseline.....	16
3.2.7. Summary of SMART	20
4. SALMETEROL SAFETY FROM ASTHMA CLINICAL TRIALS.....	21
4.1. Serious Adverse Events from US Asthma Clinical Trials (excluding SMART)	21
4.2. Analysis of Asthma Exacerbations	22
4.2.1. Results	23
4.2.2. Exacerbations	23
4.2.3. Exacerbations Resulting in Hospitalization	24

4.3.	Summary	25
5.	SALMETEROL PHARMACOEPIDEMIOLOGY STUDIES IN ASTHMA	26
5.1.	Introduction	26
5.2.	Observational Studies in Asthma	27
5.2.1.	Cohort Studies	27
5.2.2.	Case-control Studies.....	27
5.3.	Summary.....	28
6.	SALMETEROL IN COPD	29
6.1.	Summary of Serious Adverse Events from US COPD Clinical Trials.....	29
6.2.	Pooled Analysis of Cardiovascular Safety Data	30
6.3.	Observational Studies in COPD	30
6.4.	Summary.....	30
7.	POST-MARKETING EXPERIENCE FROM WORLDWIDE SPONTANEOUS ADVERSE EVENT REPORTS	31
7.1.	Post-marketing Exposure	31
7.1.1.	Post-marketing Exposure to Salmeterol Alone	31
7.1.2.	Post-marketing Exposure to Salmeterol Administered with FP in a Single Device.....	32
7.1.3.	Summary of Post-marketing Exposure to Salmeterol	33
7.2.	Spontaneous Reports	33
7.2.1.	All Spontaneous Reports for Salmeterol.....	33
7.2.1.1.	Fatal Cases Originating from New Zealand	34
7.2.2.	All Spontaneous Reports for Salmeterol Administered with FP in a Single Device.....	35
7.2.3.	Summary of Spontaneous Reports with Salmeterol- Containing Products.....	35
7.3.	Disproportionality Analyses for Salmeterol and Salmeterol Administered with FP in a Single Device.....	36
7.3.1.	Background and Methods	36
7.3.2.	Results	37
7.3.2.1.	Cumulative Reporting of Life-Threatening Respiratory-Related Events and Fatal Outcomes	38
7.3.2.2.	Reporting Patterns Over Time.....	42
7.3.3.	Summary of Disproportionality Analyses	45
8.	SAFETY INFORMATION FROM CURRENT PRESCRIBING INFORMATION.....	46
8.1.	Warnings Prior to the Results of SMART	46
8.2.	Additional Safety Information Following the Results of SMART.....	48
9.	PHARMACOGENETICS OF BETA ₂ -AGONISTS	50
10.	ONGOING STUDIES	54
10.1.	Randomized Controlled Trials.....	54
10.2.	Observational Studies	54
10.3.	Exploratory Pharmacogenetic Analyses.....	55
11.	BENEFIT-TO-RISK PROFILE.....	56

12. REFERENCES	58
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1. APPENDIX

1.1. Table - US Phase II to IV Multi-dose Studies Evaluating Salmeterol

1.2. SEREVENT® DISKUS® Package Insert

1.3. ADVAIR DISKUS® Package Insert

1. EXECUTIVE SUMMARY

1.1. Introduction

The US Food and Drug Administration (FDA) Division of Pulmonary and Allergy Drug Products has called for an Advisory Committee to meet on July 13, 2005 to discuss data related to the safety of long-acting beta₂-agonist bronchodilators. The purpose of this briefing package is to provide the Pulmonary and Allergy Drugs Advisory Committee members and consultants with information pertinent to the evaluation of the safety and benefits of the long-acting beta₂-agonist, **SEREVENT**[†] (salmeterol xinafoate). This document will review key data from the GlaxoSmithKline post-marketing surveillance studies, a pooled analysis of Phase II through IV clinical trials, relevant epidemiology and genetics research, and worldwide spontaneous adverse event reports. The primary focus of this document will be to review the safety and efficacy data available in asthma and the relevance to COPD will be discussed briefly. Because salmeterol is one of the components of **ADVAIR DISKUS**[†] (fluticasone propionate and salmeterol inhalation powder), data on **ADVAIR**[†] has been included to further assess the safety of salmeterol.

1.2. Overall Assessment

Salmeterol continues to exhibit a favorable benefit-to-risk profile based on a comprehensive review of safety and efficacy data. GlaxoSmithKline remains committed to the ongoing surveillance of the therapeutic use of salmeterol and continues to gather additional valuable information regarding its safety and efficacy.

1.3. Development of Salmeterol

Salmeterol, an inhaled long-acting beta₂-agonist has a 12-hour duration of action, and represents a clinical advance from short-acting beta₂-agonists, such as albuterol, which have a 4- to 6-hour duration of action. Prior to the introduction of salmeterol, short-acting beta₂-agonists were widely used on an as needed basis or on a regular basis, to treat or to prevent airway smooth muscle contraction. Because inhaled short-acting beta₂-agonists are only effective for 4-6 hours, they require frequent daily administration and are often ineffective in preventing common nighttime asthma episodes. In modern treatment guidelines for asthma, regular use of short-acting beta₂-agonists has been replaced with maintenance use of long-acting beta₂-agonists in conjunction with inhaled corticosteroids. Short-acting beta₂-agonists are recommended to be used as rescue therapy to treat breakthrough asthma symptoms associated with bronchoconstriction.

The clinical development program conducted by GlaxoSmithKline has established that salmeterol improves lung function, enhances symptom control, including nocturnal symptoms, with an associated improvement in health-related quality of life and reduction in the use of rescue medication as compared with placebo. Data from these and other

[†] **ADVAIR DISKUS, ADVAIR, DISKUS, and SEREVENT** are registered trademarks of the GlaxoSmithKline group of companies.

studies have demonstrated that salmeterol provides clinically meaningful benefit to patients and has an important role in the management of asthma.

1.4. Marketing Approvals and Indications

Approval has been granted to market salmeterol in over 100 countries. Salmeterol was first approved as a CFC-MDI (chlorofluorocarbon-containing metered dose inhaler) in the United Kingdom (UK) in 1990 and in the United States (US) in 1994. Salmeterol was later developed as **SEREVENT® DISKUS®†** (salmeterol xinafoate inhalation powder). This powder formulation is available worldwide, and was approved in the United States (US) in 1997. Additionally, salmeterol is a component of **ADVAIR**, which was first approved in Sweden in 1998 and the US in 2000. Consistent with the Montreal Protocol and the resulting phase out of CFCs, GlaxoSmithKline elected to discontinue salmeterol CFC-MDI in the US in 2002 as part of the process to remove all CFC-containing products from the marketplace.

As of April 30, 2005 the worldwide exposure to salmeterol alone was estimated to be 24.3 million patient years for treatment of asthma and COPD. Additionally, worldwide exposure to salmeterol administered with fluticasone propionate (FP) in a single device was estimated to be 20.9 million patient years. Therefore, in total there has been an estimated 45 million patient years of exposure to salmeterol-containing products.

In the US, **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, who require regular treatment with inhaled, short-acting beta₂-agonists. It is not indicated for patients whose asthma can be managed by occasional use of inhaled, short-acting beta₂-agonists.”

Salmeterol is also indicated for “prevention of exercise-induced bronchospasm in patients 4 years of age and older.”

Additionally, salmeterol 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).”

1.5. Beta-agonist Debate and the Introduction of Salmeterol

The approval of salmeterol was based upon the demonstration of a positive clinical benefit with an acceptable safety profile. However, there was continued concern that regular use of short-acting beta₂-agonists may lead to worsening of asthma control. This concern was highlighted in a study of fenoterol which showed that four-times daily administration was associated with worse asthma outcomes as compared with as-needed use of fenoterol. Studies with small numbers of subjects also showed that the protection afforded by beta₂-agonists against bronchoconstrictor stimuli was lost during regular use; in fact, some studies showed a rebound increase in bronchial

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hyperresponsiveness following cessation of regular beta₂-agonist treatment. There were also concerns that long-acting bronchodilators without concomitant anti-inflammatory treatment would mask worsening asthma, leading to an increase in exacerbations. Consequently, unlike the previous studies of short-acting beta₂-agonists, long-term clinical trials with salmeterol were specifically designed to more thoroughly assess its safety and effectiveness. The key studies are summarized.

1.6. Post-marketing Surveillance Studies

Shortly after the launch of salmeterol in the UK in 1990, to further characterize the use of salmeterol for the treatment of asthma, GlaxoSmithKline conducted the Serevent Nationwide Surveillance (SNS) study. SNS was a randomized controlled trial that studied over 25,000 subjects treated with salmeterol or albuterol. The SNS study showed that the overall incidence of serious events from all causes was similar between salmeterol and albuterol. The incidence of asthma-related death was numerically, though not statistically, greater in patients taking salmeterol compared with the albuterol group.

Salmeterol was launched in the US in 1994 during the ongoing debate concerning the regular use of beta₂-agonists. Following the launch of **SEREVENT**, there were spontaneous adverse event reports and reports in the lay press of deaths linked to beta₂-agonists. In November 1994, in consultation with the FDA, GlaxoSmithKline agreed to conduct a large, prospective clinical trial to obtain safety surveillance information. The Salmeterol Multicenter Asthma Research Trial (SMART) was initiated in 1996 and terminated in 2003 with data from over 26,000 subjects. Results for the total population showed that there was no statistically significant difference in the primary outcome (combined respiratory-related death or life-threatening experiences) in patients receiving salmeterol versus placebo. However, there were small, but statistically significant increases in the secondary endpoint of combined asthma-related death or life-threatening experiences and in asthma-related death alone in the salmeterol group compared with placebo. In addition, SMART suggested that the risk of asthma-related death or life-threatening experiences may be greater in African Americans.

The results of these trials led to the inclusion of a boxed warning and additional safety information in the prescribing information for products containing salmeterol, summarizing the outcome of the SNS and SMART trials

1.7. Additional Safety Analyses of GlaxoSmithKline Clinical Trials

A retrospective pooled analysis of all US GlaxoSmithKline Phase II to IV asthma clinical trials was conducted to review cardiac and respiratory serious adverse events. The analysis included all studies that contained a salmeterol BID treatment arm (50mcg via **DISKUS**[®] or 42mcg via MDI). The analysis indicated that the incidence of respiratory-related serious adverse events (SAEs) was low across treatment groups; however, a higher incidence was observed in the salmeterol group compared with placebo. The incidence was similar for the salmeterol plus ICS and ICS alone groups. In addition, the incidence of cardiac-related SAEs was similar across groups.

A subset of these studies provided data for review of all available exacerbations and hospitalizations. These data demonstrated that a slightly lower percentage of patients receiving salmeterol reported exacerbations compared with those receiving placebo (prn albuterol). Conversely, patients receiving salmeterol had a slightly higher percentage of asthma hospitalizations compared with placebo. The occurrence of exacerbations and hospitalizations was similar for patients receiving salmeterol plus ICS compared with ICS alone.

1.8. Epidemiology Studies

Epidemiology studies are an important way to characterize rare safety outcomes in large populations. Numerous, large cohort and case-controlled studies designed to explore serious respiratory- and asthma-related outcomes have not shown an association between salmeterol use and serious asthma outcomes, including death.

1.9. Post-marketing Safety Data

The reporting of spontaneous events peaked with approvals of salmeterol in the UK and US and with publicity around SMART. In general, the absolute number of spontaneously reported events (including fatal events) is low and has not increased relative to exposure to salmeterol. Because of the limitations of spontaneously reported data and common confounders (e.g., age, disease severity, co-morbidity), a definitive link between the use of salmeterol and respiratory-related spontaneously reported adverse events cannot be ascertained.

1.10. Overall Benefit-to-Risk

Salmeterol represents an important contribution to the therapeutic armamentarium for the treatment of asthma and COPD. Salmeterol has been shown to improve lung function, enhance symptom control, including nocturnal symptoms, with associated improvement in asthma-related quality of life and reduction in the use of rescue medication as compared with placebo. These substantial therapeutic benefits of salmeterol are firmly established by extensive clinical trial data. Data regarding an association between salmeterol use and serious asthma episodes or asthma-related death have been seen in SNS and SMART, but a cause and effect relationship or other explanation for the observed association cannot be established from these data. Nonetheless, the prescribing information for salmeterol-containing products provides detailed information about the possibility of these rare events. In addition, large population-based studies have not shown an association between salmeterol and rare serious asthma episodes or asthma-related death. Based on a comprehensive review of the safety and efficacy of salmeterol, GlaxoSmithKline firmly believes that salmeterol continues to exhibit a favorable benefit-to-risk profile.

2. SALMETEROL EFFICACY FROM RANDOMIZED CONTROLLED CLINICAL TRIALS IN ASTHMA

A meeting of the Pulmonary and Allergy Drugs Advisory Committee has been called to discuss the safety data available with long-acting beta₂-agonist bronchodilators. However, to put the safety data in context, it is important to note that the efficacy of these products and the benefits to patients are well established.

GlaxoSmithKline has extensively studied the regular use of both the inhalation aerosol and powder formulations of salmeterol for the treatment of asthma. In the US, GlaxoSmithKline has conducted 52 phase II to IV multi-dose studies for salmeterol, involving over 6500 pediatric, adolescent, and adult subjects who were randomized to salmeterol 50mcg BID. The duration of these studies has ranged from one to 52 weeks and efficacy endpoints included measures of lung function (i.e., FEV₁ and PEF), symptoms, nighttime awakenings, rescue albuterol use, and quality of life. Studies with salmeterol evaluated patients who were and were not receiving concurrent inhaled corticosteroid therapy. Efficacy findings for salmeterol are briefly summarized below.

2.1. Lung Function

Treatment with salmeterol results in clinically significant increases in lung function ($\geq 15\%$ increase in FEV₁) within the first hour of treatment with maintenance of bronchodilator effect for up to 12 hours in the majority of patients.^{1,2} In two 12-week studies, the 12-hour serial FEV₁ area under the curve (AUC) value was significantly increased with salmeterol compared with placebo and albuterol administered four times daily (QID).^{1,2} Additionally, the AUC values following the first and last dose of salmeterol were similar, demonstrating maintenance of bronchodilator effect with regular treatment. Similar findings were observed in a 1-year study that compared salmeterol with placebo.³ In this study, the mean 12-hour FEV₁ AUC value was significantly greater for salmeterol compared with placebo at Day 1 and after 48 weeks of treatment. Further, the FEV₁ AUC values for salmeterol at Day 1 and after 48 weeks were similar.

2.2. Effect on Asthma Symptoms, Nighttime Awakenings, Rescue Albuterol Use and Health-related Quality of Life

Numerous studies have shown that salmeterol significantly reduced asthma symptoms, nighttime awakenings, and rescue albuterol use compared with placebo.^{1,2,3,4,5,6} For example, over 12 weeks of treatment, salmeterol significantly reduced a combined asthma symptom score for coughing, wheezing, shortness of breath, and chest tightness and reduced the number of nights with awakenings due to asthma compared with placebo.² In the same study, rescue use of albuterol was significantly reduced with salmeterol compared with placebo.

Regular treatment with salmeterol also improved health-related quality of life. Patients receiving salmeterol showed significant improvement in global and domain scores (activity limitation, symptoms, emotional function, and exposure to environmental stimuli) for the Asthma Quality of Life Questionnaire compared with placebo.^{3,5,7}

2.3. Salmeterol Administered with Inhaled Corticosteroids

In patients symptomatic on inhaled corticosteroids alone, the addition of salmeterol to inhaled corticosteroids results in significantly greater improvement in lung function, symptoms, and rescue albuterol use as compared with increasing the inhaled corticosteroid dose alone.^{8,9,10,11,12}

2.4. Potential Development of Tolerance with Salmeterol

Studies of up to one year in duration have shown that the bronchodilator effect of salmeterol is maintained with regular treatment.^{1,2,4,6} The maintenance of bronchodilator effect has been shown in trough measurements for up to one year and in post-dose measurements for up to 12 weeks.

Additional studies have evaluated tolerance to the bronchodilator effects of short-acting beta₂-agonists in patients using salmeterol. In a 4-week cross-over study of 17 patients, there was no difference in the peak response (maximal FEV₁) to albuterol in patients treated with salmeterol as compared with placebo.¹³ Salmeterol-treated patients had a smaller increase in FEV₁ than placebo-treated patients, but this was associated with a higher baseline FEV₁. In other studies of 1 and 6 months in duration, the bronchodilator response to albuterol was maintained following salmeterol treatment as compared with placebo.^{14,15,16,17}

Other studies have shown a decrease in the maximal bronchoprotective effect or duration of protective effect against methacholine, allergen, and exercise challenge with regular dosing of salmeterol.^{18,19,20,21,22,23,24,25} However, salmeterol continues to provide bronchoprotection with long-term use.^{4,25,26}

2.5. Summary

The efficacy of salmeterol for the treatment of asthma has been demonstrated in a large number of clinical trials (see [Section 1.1 in the Appendix](#)). In the US alone, GlaxoSmithKline has conducted 52 studies, involving over 6500 subjects randomized to salmeterol 50mcg BID, to evaluate the regular use of salmeterol for periods up to 1 year in duration. These studies have established that salmeterol improves lung function, enhances symptom control, including nocturnal symptoms with an associated improvement in health-related quality of life and reduction in the use of rescue medication as compared with placebo. Data from these and other studies have demonstrated that salmeterol provides clinically meaningful benefit to patients and has an important role in the management of asthma. The extensive clinical data on salmeterol is embodied in current evidence based asthma treatment guidelines which supports the use of long-acting beta₂-agonists with inhaled corticosteroids as the preferred treatment option for patients with moderate to severe persistent asthma.²⁷

3. POST-MARKETING CLINICAL STUDIES

GlaxoSmithKline has conducted two large post-marketing studies with salmeterol; one following the launch of the product in the UK and one following the launch of the product in the US. The findings from these studies are summarized below.

3.1. Serevent Nationwide Surveillance (SNS) Study

The Serevent Nationwide Surveillance (SNS) study was performed in the UK between 1990 and 1992, following the launch of salmeterol.²⁸ This 16-week, randomized, double-dummy, parallel study compared salmeterol 50mcg twice daily (42mcg ex-actuator) with regular use of albuterol 200mcg four times daily when added to current therapy. The study utilized a 2:1 randomization (salmeterol:albuterol) in 25,180 patients (>12 years of age) with moderate to severe asthma who required regular bronchodilator treatment. Patients continued all other medications that they were currently taking, throughout the study. Study physicians were asked to prescribe appropriate therapy for symptom relief. At baseline, 69% of patients in both groups were receiving inhaled corticosteroids. Patients returned for clinic visits after 4, 8 and 16 weeks of treatment.

The primary outcome measures in SNS were all-cause serious adverse events and reasons for withdrawal from the study (medical and non-medical), whether or not they were considered to be related to the study medication. The overall incidence of serious events from all causes was similar (4% for salmeterol vs. 4.1% for albuterol). For overall withdrawals, there was no difference between groups; however, there were fewer 'asthma-related withdrawals' in the salmeterol group (2.91%) versus the albuterol group (3.79%; p=0.0002). The table below summarizes the key secondary findings from the SNS study.

Table 3.1 All Serious Events and Withdrawals in Patients with Asthma Receiving Salmeterol or Albuterol

Outcome, n (%)	Salmeterol (n=16,787)	Albuterol (n=8393)	RR (p value)
Asthma-related deaths	0.07% n=12	0.02% n=2	3.00 (0.105)
Asthma-related hospitalizations	1.15% n=193	1.22% n=102	0.95 (0.651)
Non-asthma-related hospitalizations*	0.07% n=12	0.08% n=7	0.86 (0.746)
Asthma-related serious events	1.18% n=198	1.19% n=100	0.99 (0.935)
Non-asthma-related serious events*	0.13% n=22	0.19% n=16	0.69 (0.251)
Asthma-related withdrawals	2.91% n=488	3.79% n=318	0.77 (0.0002)
Non-asthma-related withdrawals*	0.72% n=121	0.60% n=50	1.21 (0.256)
*respiratory, but not related to asthma			

The incidence of asthma-related death was numerically, though not statistically, greater in patients taking salmeterol compared with the albuterol group. All 14 of the patients who died were categorized as having severe asthma. Significantly more patients withdrew from the albuterol group due to worsening asthma than the salmeterol group, thus all asthma-related events in the albuterol group may not have been captured due to the greater number of withdrawals.

3.2. Salmeterol Multicenter Asthma Research Trial (SMART)

As described previously, salmeterol was introduced into the US at a time when the appropriateness of regular use of beta₂-agonists was being questioned. Following the launch of **SEREVENT** there were spontaneous adverse event reports and reports in the lay press of deaths associated with the use of beta₂-agonists. GlaxoSmithKline in consultation with the FDA agreed to conduct a large, prospective clinical trial to obtain safety surveillance information. SMART (Salmeterol Multicenter Asthma Research Trial [Protocol SLGA5011]) was conducted in order to further characterize the safety of salmeterol.

SMART was a multi-center, randomized, double-blind, parallel-group, placebo-controlled study conducted over 28 weeks at 6163 sites in the US. Males and non-pregnant females 12 years of age and older, with a clinical diagnosis of asthma who had no previous use of inhaled long-acting beta₂-agonist bronchodilators were eligible to enroll. Concurrent use of prescription asthma medication(s) other than long-acting beta₂-agonists (salmeterol and formoterol) was permitted. Salmeterol 42mcg twice-daily via MDI added to concurrent pharmacotherapy was compared with placebo twice-daily via MDI added to concurrent therapy.

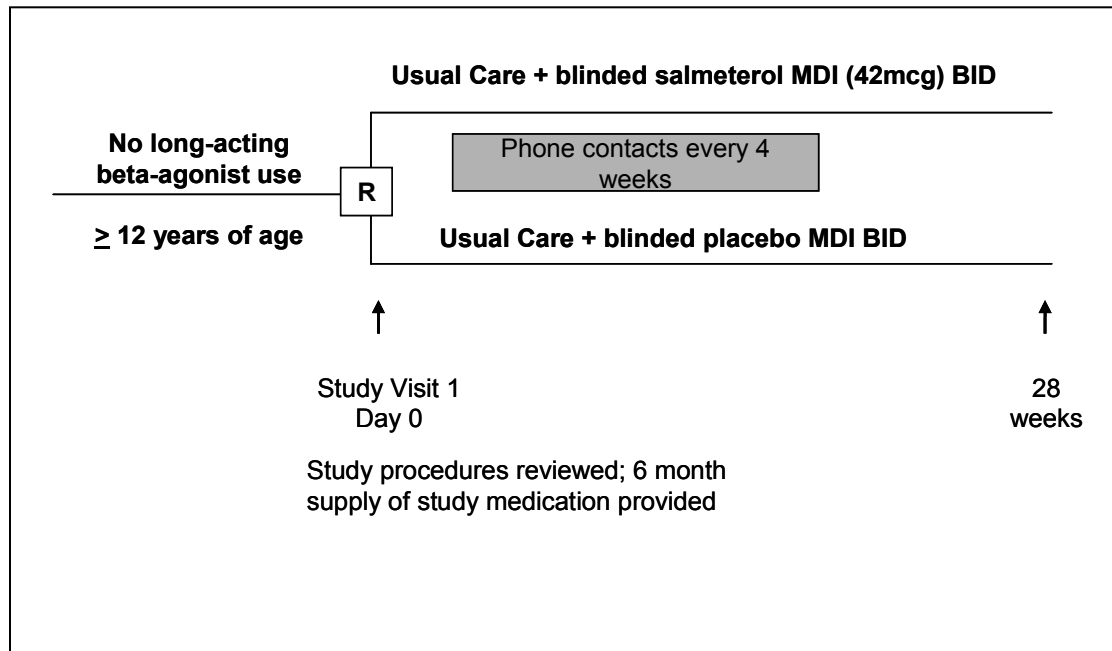
Because asthma-related events are rare (see [Statistical Considerations, Section 3.2.1](#)), the protocol-defined primary endpoint was the combined occurrence of respiratory-related death or life-threatening experiences (intubation and mechanical ventilation). This classification was determined following a review of all of the all-cause deaths by an independent Morbidity and Mortality Review Committee [MMRC]. All deaths were adjudicated initially as respiratory-related (or not) by selecting one of the following categories: 1) unrelated, 2) unlikely related, 3) possibly related, or 4) almost certainly related. If category 3 or 4 was selected, the event was recorded as respiratory-related. Once an event was adjudicated as respiratory-related, the same categories were utilized in determining if it was asthma-related.

Protocol-defined secondary endpoints were 1) respiratory-related death, 2) asthma-related deaths or life-threatening experiences, 3) asthma-related deaths, 4) all cause death, 5) all cause death or life-threatening experiences, 6) all cause hospitalization, 7) the relative frequency of all cause serious adverse events, 8) reason(s) for withdrawal from the study, 9) changes in concurrent medications and the addition of new medications, and 10) subject-reported status (overall quality of life, activity limitations, emotions, and symptoms), as related to their asthma.

For this summary, only information related to the primary endpoint (combined respiratory-related death or life-threatening experiences) and the secondary endpoints of respiratory-related death, combined asthma-related death or life-threatening experiences and asthma-related death will be included.

The study consisted of a single clinic visit (Visit 1) during which eligibility status was determined, written informed consent and baseline information were obtained, eligible subjects were randomized to treatment, and study procedures were reviewed (see Figure 3.2). Following Visit 1, subjects were provided with 28 weeks of blinded study medication (7 canisters) and contacted every four weeks (for 28 weeks) by an independent call center for evaluation and collection of data related to the study endpoints. There were no other protocol-defined office visits. Total duration of study participation was 28 weeks with an additional 6 month post-study period to collect any spontaneously reported serious adverse events.

Figure 3.2 SMART Study Design



3.2.1. Statistical Considerations

Asthma-related death is rare and therefore difficult to study in a randomized controlled clinical trial. As a result, certain practical accommodations had to be made in designing the trial. Because the rate of asthma-related death in the US was estimated to be low, and therefore would require too large of a sample size to be practical, the broader combined endpoint of respiratory-related death or life-threatening experiences was selected as the primary endpoint. Furthermore, in light of sample size considerations, consultations between GlaxoSmithKline and FDA resulted in a study design that provided approximately 80% power to rule out a 40% increase in this primary endpoint for subjects receiving salmeterol or placebo added to concurrent pharmacotherapy for 28 weeks.

The original sample size was determined using the reported prevalence of asthma deaths in the US in 1994 along with the rate of asthma-related intubations and mechanical ventilation.²⁹ The rate of asthma-related intubations and mechanical ventilation was estimated based on hospital surveys conducted by GlaxoSmithKline. At study initiation, the yearly asthma death rate was reported as 5,106 per 12 million asthma sufferers. It was also estimated that for every death due to asthma, there were

five occurrences of intubation and mechanical ventilation for an acute asthma attack. These estimates lead to an original sample size estimate of 30,000. It was estimated that approximately 238 primary outcome events would be required to detect a 40% difference between treatment groups in the primary endpoint. The study also provided approximately 90% power to rule out a tripling of asthma deaths for subjects receiving salmeterol as compared with subjects receiving placebo. However, due to the lower than expected rate of primary outcome events, primarily due to lower than projected intubations and mechanical ventilation, and after discussions with the Drug Safety Monitoring Board (DSMB) and FDA, the sample size was increased to 60,000 subjects in 1999.

Per the protocol, an interim analysis was planned when approximately one-half of the expected number of subjects was enrolled. At the time of the interim analysis, there were 79 primary events reported. Pre-defined criteria for study termination were not met at the interim analysis. However, following review of the interim data, the DSMB made a recommendation that either the study be completed within a timely manner (i.e., two years) or if that was not possible, the study be terminated and the results disseminated. This recommendation was made because of the findings seen in the African American subgroup. After informing the FDA, GlaxoSmithKline elected to terminate the study due to difficulties in enrollment and in light of the findings in African Americans. This allowed for dissemination of the preliminary findings.

The preliminary findings included data from the 28-week treatment period as well as a follow-up period of six months (n=25,858). The final analysis was limited to the 28-week treatment period only, following agreement with FDA, and included 26,355 patients. Data from the final analysis is reported in the current prescribing information for **SEREVENT** and **ADVAIR** and is summarized below.

3.2.2. Study Population Results

Of the 26,355 subjects enrolled in the study, 13,176 and 13,179 subjects were randomized to the salmeterol and placebo groups, respectively. In the total population, 19,128 (73%) subjects completed the study through 28 weeks.

Subject accountability and reasons for discontinuation in the salmeterol and placebo groups are summarized as follows:

Table 3.2.2 Summary of Subject Accountability, n (%)

	Salmeterol	Placebo
Randomized	13,176	13,179
Completed	9654 (73)	9474 (72)
Prematurely Discontinued	2959 (22)	3143 (24)
Reasons: n (%)		
Serious Adverse Event	143 (1)	134 (1)
Consent Withdrawn	1704 (13)	1912 (15)
Lost to Follow-up	826 (6)	827 (6)
Other	62 (<1)	62 (<1)
Sponsor Stopped Study	224 (2)	208 (2)
Unknown and alive*	476 (4)	475 (4)
Unknown†	87 (<1)	87 (<1)

* includes those subjects lost to follow-up, but for whom verification of their status (alive) was subsequently obtained from a relative or investigator

† unknown category who had case report form (CRF) data, but who did not register for follow-up telephone interviews; no additional information is available for these subjects after Visit 1

3.2.3. Demographic Characteristics

Demographic characteristics of subjects (including age, sex, and ethnic origin) are summarized below. Demographic characteristics were similar in the salmeterol and placebo groups.

Table 3.2.3 Summary of Demographic Characteristics

	Salmeterol (n=13,176)	Placebo (n=13,179)
Age, mean	39.2	39.1
Sex, n (%)		
Female	8334 (64)	8337 (64)
Male	4703 (36)	4686 (36)
Ethnic Origin, n (%)		
Caucasian	9281 (71)	9361 (72)
African American	2366 (18)	2319 (18)
Hispanic	996 (8)	999 (8)
Asian	173 (1)	149 (1)
Other	230 (2)	224 (2)

3.2.3.1. Baseline Characteristics

Baseline characteristics (including asthma and smoking history, and peak expiratory flow) are provided below. Baseline characteristics were similar across treatment groups.

Table 3.2.3.1 Summary of Baseline Characteristics

	Salmeterol (n=13,176)	Placebo (n=13,179)
Age at asthma diagnosis, mean	23.1	23.0
Emergency room visit for asthma last 12 months, n (%)		
None	9747 (74)	9710 (74)
≥ 1 visit	3426 (26)	3464 (26)
Hospitalization for asthma last 12 months, n (%)		
None	12,122 (92)	12,086 (92)
≥ 1 hospitalization	1051 (8)	1088 (8)
Frequency of nocturnal symptoms, n (%)		
None	4962 (39)	5080 (40)
1-3 nights per week	5509 (43)	5485 (43)
≥ 4 nights per week	2331 (18)	2248 (18)
Tobacco use, n (%)		
Never smoked	6456 (50)	6440 (50)
Former smoker	4274 (33)	4326 (34)
Current smoker	2106 (16)	2089 (16)
Peak expiratory flow		
L/min, mean	354.9	355.6
% predicted normal, mean	84.0	83.8

3.2.3.2. Demographic and Baseline Characteristics for Ethnic Subgroups

At the time of the interim analysis, the DSMB reviewed data stratified by age, gender, and ethnic origin. Demographic and baseline characteristics were similar when stratified by age and gender, while mean values for demographic and baseline characteristics showed slight differences between the Caucasian and African American subgroups. For example, mean age was slightly higher in the Caucasian subgroup (40.3 years) compared with 36.5 years in African Americans.

Data for asthma history and pulmonary function indicates greater disease severity at baseline in the African American subgroup as compared with the Caucasian subgroup.

Table 3.2.3.2 Summary of Disease Severity Characteristics (% subjects)

	African American (n=4685)	Caucasian (n=18,642)
≥1 ER Visit in last 12 months	41%	22%
≥1 ER Visit Lifetime	72%	59%
≥1 Hospitalization last 12 months	15%	6%
≥1 Hospitalization Lifetime	44%	30%
≥1 Intubations for Asthma Lifetime	8%	4%
Nocturnal Symptoms Present	64%	57%
Mean Percent Predicted PEF	78%	85%

3.2.4. Concurrent Asthma Medications at Baseline

Baseline use of concurrent asthma medications was reported for 97% and 96% of subjects in the salmeterol and placebo groups, respectively. The most commonly reported class of concurrent asthma medication was short-acting beta₂-agonists which were reported for 92% of subjects in the salmeterol group and 91% of subjects in the placebo group. Inhaled corticosteroid use was reported for 47% of subjects in both groups. Use of methylxanthines and leukotriene modifiers was reported by 13% and 11% of subjects in both groups. No other class of asthma medication was reported for greater than 10% of subjects in either treatment group.

In order to simulate a real-world environment as much as possible, compliance with study medication or concurrent asthma medication(s) was not reinforced during the study.

3.2.4.1. Concurrent Asthma Medications at Baseline for Ethnic Subgroups

The percentage of subjects in the Caucasian and African American subgroups who reported the use of asthma medications at baseline was similar (96%). However, a lower percentage of subjects in the African American subgroup reported the use of inhaled corticosteroids (38% vs. 49% in African American and Caucasian subgroups, respectively). The percentage of subjects using other categories of asthma medications was similar.

3.2.5. Study Results

The final results included data for 26,355 subjects and comprised 86 primary events (combined respiratory-related death or life-threatening experiences), 59 combined asthma-related death or life-threatening experiences and 16 asthma-related deaths.

The results for the primary endpoint (combined respiratory-related death or life-threatening experiences) and key secondary outcomes are summarized in [Figure 3.2.6.1](#) below.

The incidence of the primary endpoint (combined respiratory-related death or life-threatening experiences) for the total population was not statistically different

between the salmeterol and placebo groups. Statistically significant differences between the salmeterol and placebo treatment groups were observed for respiratory-related death (24 events versus 11 events, respectively; RR=2.16, 95%CI 1.06, 4.41), combined asthma-related death or life-threatening experiences (37 events versus 22 events, respectively; RR=1.71, 95%CI 1.01, 2.89), and asthma-related death (13 events versus 3 events, respectively; RR=4.37, 95%CI 1.25, 15.34).

There were similar numbers of patients reporting serious adverse events in the cardiovascular system between the salmeterol (n=95) and placebo (n=100) treatment groups.

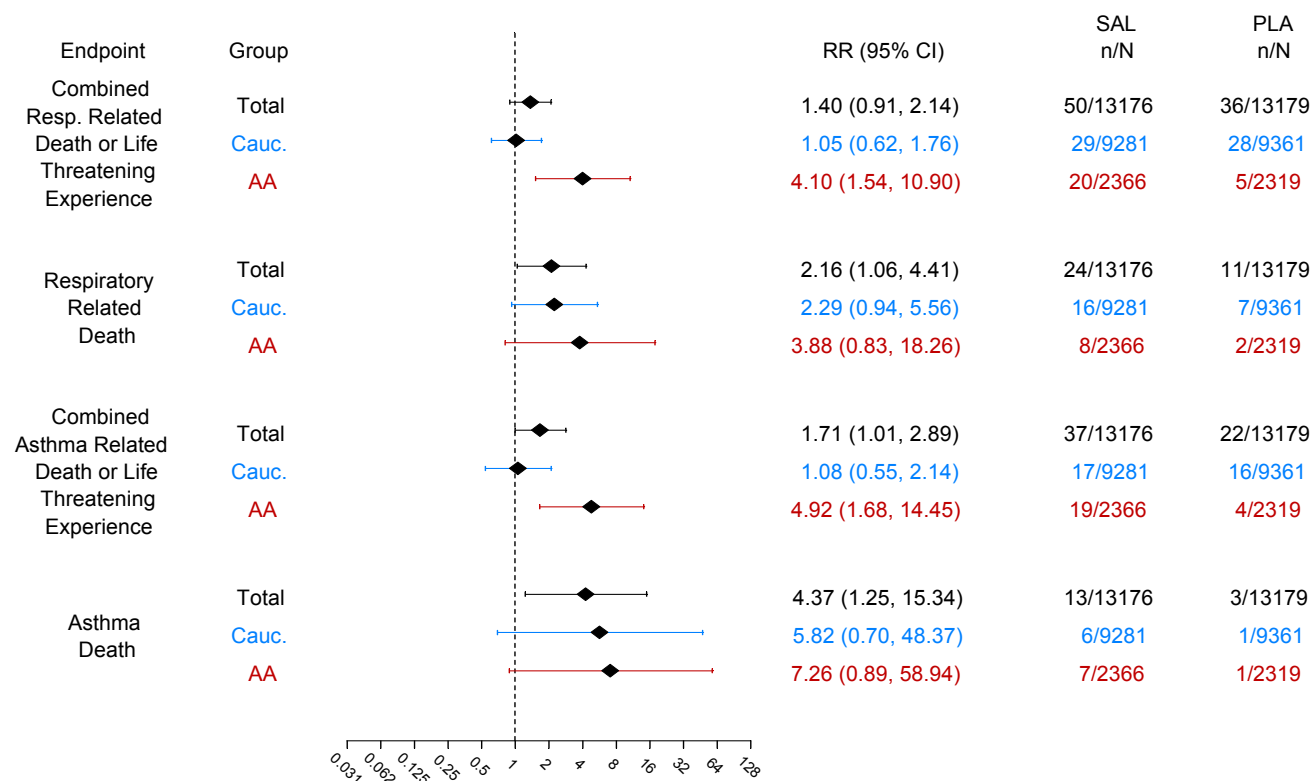
3.2.6. Analysis of Population Subgroups

The incidence of primary (combined respiratory-related death or life-threatening experiences) and secondary events was analyzed by covariates such as ethnic origin and baseline use of inhaled corticosteroids. However, caution should be exercised when interpreting the subgroup analyses given that the total number of primary events in the interim analysis only provided about 1/3 of the events needed to provide 80% power for the primary outcome.

3.2.6.1. Ethnic Origin

In Caucasians (n=18,642), there were no significant differences between groups for the primary outcome (combined respiratory-related death or life-threatening experiences) or asthma-related events. In African Americans (n=4685), a significantly greater number of primary events and secondary events of combined asthma-related death or life-threatening experience occurred in the salmeterol group. The relative risk of primary and secondary outcome events for Caucasians and African Americans are shown in [Figure 3.2.6.1](#) below

Figure 3.2.6.1 Relative Risk and 95% Confidence Interval of Salmeterol to Placebo for Combined Respiratory-Related Death or Life-Threatening Experiences (Primary Endpoint) and Key Secondary Endpoints



SAL=salmeterol; PLA=placebo; n=number of events; N=study population; RR=relative risk; Total=includes all subjects in the ITT population, including all ethnic subgroups; Cauc= Caucasian; AA=African American

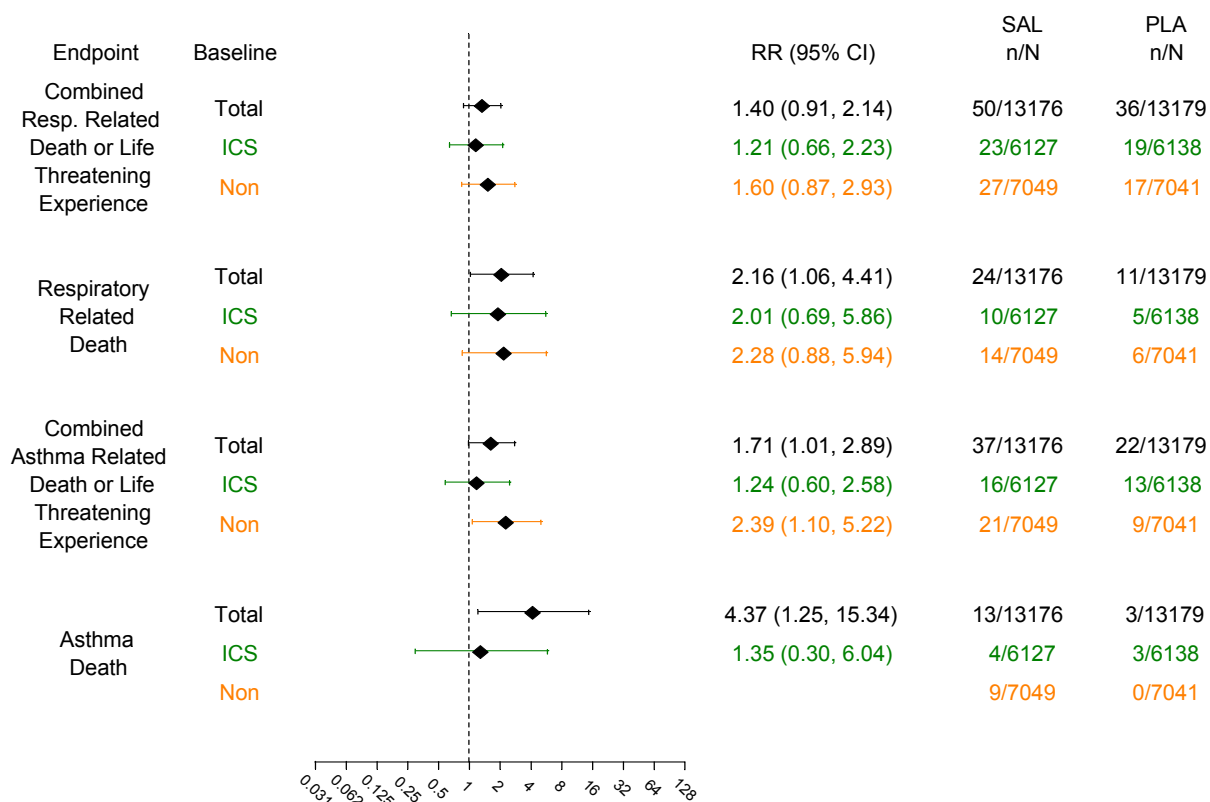
3.2.6.2. Inhaled Corticosteroid Use Reported at Baseline

The subpopulation of patients reporting baseline ICS was of particular interest to the DSMB and GlaxoSmithKline in light of the reported effects of ICS in modulating beta-receptor function and positive effects on asthma morbidity and mortality.^{30,31,32}

In the total population 47% of subjects reported ICS use at baseline. In Caucasians, 49% of subjects (n=9223) reported baseline ICS use compared with 38% in African Americans (n=1781).

In subjects reporting ICS use at baseline, there was no significant difference between groups for the primary outcome (combined respiratory-related death or life-threatening experiences) or secondary endpoints and relative risk (RR) values were lower than those observed in the total population. For subjects not reporting ICS use at baseline, the incidence of asthma-related death and combined asthma-related death or life-threatening experiences was higher in the salmeterol group compared with the placebo group. Comparatively, for subjects reporting ICS use at baseline, the incidence of asthma-related death and combined asthma-related death or life-threatening experiences was similar in the salmeterol group and the placebo group. These results are summarized in [Figure 3.2.6.2a](#) below

Figure 3.2.6.2a Relative Risk and 95% Confidence Interval of Salmeterol to Placebo for Primary Outcome and Key Secondary Outcomes in Subjects Receiving ICS at Baseline



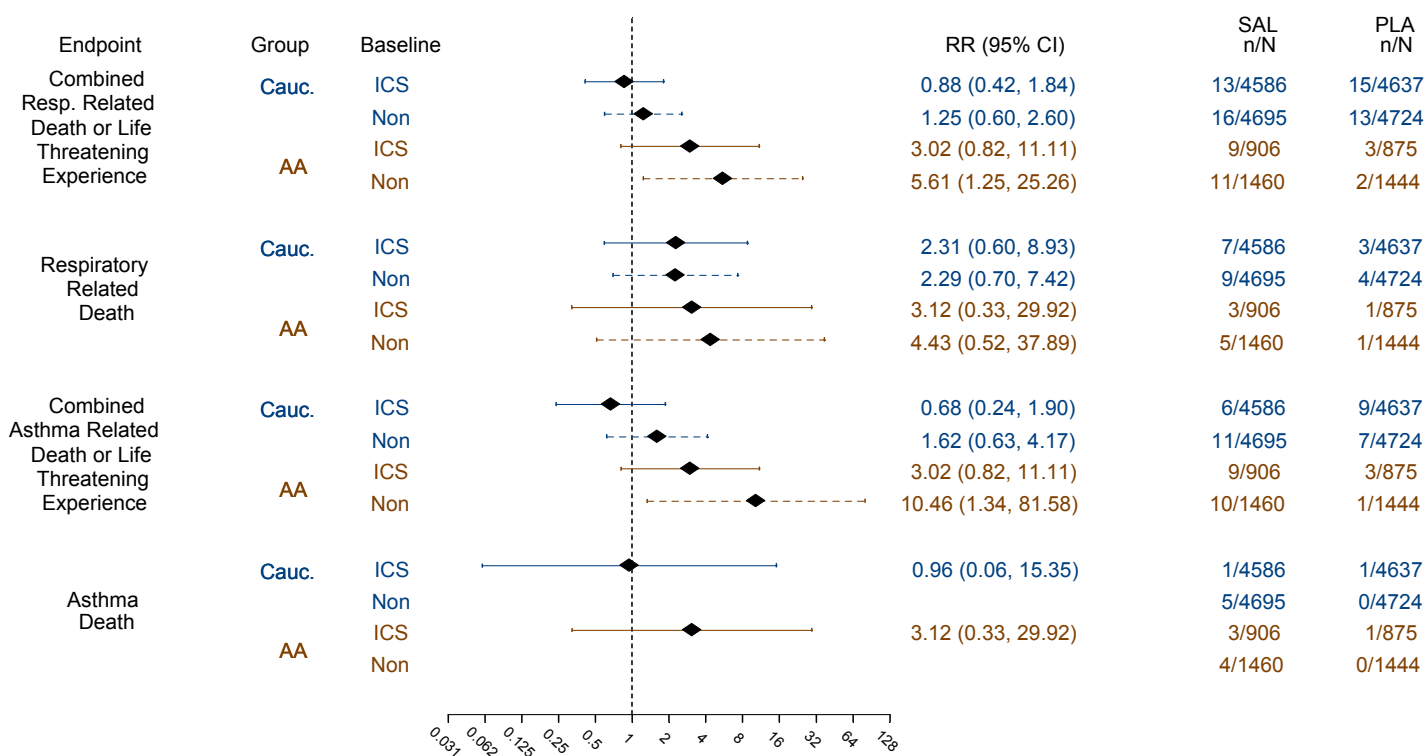
SAL=salmeterol; PLA=placebo; n=number of events; N=study population; RR=relative risk; Total=includes all subjects in the ITT population, including all ethnic subgroups; ICS=subjects reporting baseline ICS use; Non=subjects who did not report baseline ICS use

Note: the RR and associated 95% CI could not be directly computed with zero events occurring in one treatment group

In the Caucasian subgroup, there were no statistically significant differences between treatment groups for primary or secondary events regardless of ICS use at baseline (see [Figure 3.2.6.2b](#) below). In subjects not reporting ICS use at baseline, the RR and associated 95% CI could not be directly computed for asthma-related death since there were zero events occurring in one treatment group.

In African Americans who did not report use of ICS at baseline, a significantly greater number of primary events (combined respiratory-related death or life-threatening experiences), combined asthma-related death and life-threatening experiences, and asthma-related death occurred in the salmeterol group as compared with placebo. There were no significant differences between groups for primary or secondary events for African Americans who reported the use of ICS at baseline (see [Figure 3.2.6.2b](#) below).

Figure 3.2.6.2b Relative Risk and 95% Confidence Interval of Salmeterol to Placebo for Primary Outcome and Key Secondary Outcomes in Subjects by Ethnicity Receiving ICS at Baseline



SAL=salmeterol; PLA=placebo; n=number of events; N=study population; RR=relative risk; Cauc=Caucasian; AA=African American; ICS=subjects reporting baseline ICS use; Non=subjects who did not report baseline ICS use

Note: the RR and associated 95% CI could not be directly computed with zero events occurring in one treatment group

3.2.7. Summary of SMART

For the total population, there was no statistically significant difference in the primary outcome (combined respiratory-related death or life-threatening experiences) between the two treatment groups. However, there were small, but statistically significant increases in respiratory- and asthma-related death as well as combined asthma-related death or life-threatening experiences in the salmeterol group compared with placebo. When examined by ethnic subgroups, there were no statistically significant differences in the primary or secondary outcomes for Caucasians. However, for African Americans, there were statistically significant differences in the primary outcome, and for combined asthma-related death or life-threatening experiences between the two treatment groups. In those subjects not using ICS at entry, the differences between treatment groups were more pronounced in both the total population and the African American sub-population.

A careful analysis of the data has not provided a clear explanation for the observation of an apparent increase in risk with salmeterol. The results in African Americans contributed substantially to the results for the total population. The African American population had more severe asthma than the Caucasian population and the baseline data showed that African Americans were less likely to use ICS than Caucasians. In the total population, the greater number of asthma-related events in salmeterol-treated subjects who were not also taking an inhaled corticosteroid at baseline may be important given the recognized role of ICS in the treatment of asthma.²⁷

4. SALMETEROL SAFETY FROM ASTHMA CLINICAL TRIALS

In isolation, a single well-controlled study with a smaller sample size is unable to adequately detect rare events such as death or life-threatening experiences. Because very few serious adverse events have been reported in clinical trials, data from the GlaxoSmithKline US asthma clinical trials database was pooled and reviewed for these rare events.

4.1. Serious Adverse Events from US Asthma Clinical Trials (excluding SMART)

All US repeat dose studies containing a salmeterol treatment arm have been included in the analysis. This assessment included 63 phase II to IV studies with salmeterol, involving over 17,000 pediatric, adolescent, and adult subjects. The duration of these studies ranged from one to 52 weeks and efficacy endpoints included measures of lung function (i.e., FEV₁ and PEF), symptoms, nighttime awakenings, rescue albuterol use, and health-related quality of life. Safety endpoints included collection of adverse events and exacerbations.

The following treatment groups were evaluated: salmeterol 50mcg BID, placebo, salmeterol 50mcg BID plus ICS, and ICS alone; all groups received as-needed albuterol. The salmeterol group represents patients randomized to salmeterol as monotherapy. In this group, patients may or may not have been using concurrent ICS therapy. The salmeterol plus ICS group represents patients randomized to salmeterol and an inhaled corticosteroid, and includes studies with salmeterol administered with FP in a single device and studies where the ICS was administered from a separate inhaler. The comparisons of interest (salmeterol versus placebo and salmeterol plus ICS versus ICS alone) generally represent similar pre-study populations and randomized treatments within each of the clinical trials.

For this *post hoc* analysis of SAEs, all coding terms that fell within the general categories of respiratory-, cardiovascular-, and metabolic-related were included. SAEs were reported as events that resulted in death, were life-threatening, required hospitalization or prolongation of hospitalization, or resulted in disability or incapacity.

Serious adverse events from the cardiovascular and respiratory systems are presented in [Table 4.1a](#). The incidence of SAEs in the metabolic body system was low relative to events in the respiratory and cardiovascular systems (0 to $\leq 0.02\%$ across groups) and is not reported.

Table 4.1a Number of Subjects Reporting Serious Adverse Events by Cardiovascular and Respiratory Systems

	Salmeterol* (n=5299)	Placebo (n=3976)	Salmeterol plus ICS† (n=4142)	ICS (n=4022)
Cardiovascular, n (%)	6 (0.11%)	5 (0.13%)	7 (0.17%)	9 (0.22%)
Respiratory, n (%)	68 (1.28%)	23 (0.58%)	12 (0.29%)	14 (0.35%)

* salmeterol=all studies where patients were randomized to salmeterol 50mcg BID

† salmeterol plus ICS=all studies where patients were randomized to salmeterol 50mcg BID and an inhaled corticosteroid (ICS)

There were 3 deaths reported in the 17,439 patients enrolled in these trials. One respiratory-related death (respiratory arrest) occurred in a patient receiving salmeterol.

Respiratory-related SAEs that occurred in ≥ 5 patients in any group are reported in Table 4.1b.

Table 4.1b Respiratory Serious Adverse Events Reported by ≥ 5 Subjects

SAE	Salmeterol* (n=5299)	Placebo (n=3976)	Salmeterol plus ICS† (n=4142)	ICS (n=4022)
Asthma, n (%)	16 (0.30%)	6 (0.15%)	0	0
Asthma exacerbation, n (%)	32 (0.60%)	5 (0.13%)	5 (0.12%)	7 (0.17%)
Status asthmaticus, n (%)	11 (0.21%)	7 (0.18%)	0	0

* salmeterol=all studies where patients were randomized to salmeterol 50mcg BID

† salmeterol plus ICS=all studies where patients were randomized to salmeterol 50mcg BID and an inhaled corticosteroid (ICS)

An analysis of all serious adverse events from GlaxoSmithKline's US asthma studies indicated that the incidence of respiratory-related SAEs was low; however, a higher incidence was observed in the salmeterol group compared with placebo. The incidence was similar for the salmeterol plus ICS and ICS alone groups.

4.2. Analysis of Asthma Exacerbations

To further characterize the benefits and risks of salmeterol, GlaxoSmithKline analyzed outcomes from 37 US studies in which exacerbations were protocol-defined and specific details about each exacerbation, including site of treatment (i.e., hospital) were captured. The most common definition of an exacerbation in these studies was an event that required medication beyond study drug or albuterol. Other definitions included a combination of the following: ER visit and/or hospitalization, unscheduled MD visit, treatment with inhaled, oral or parenteral steroids, or >12 puffs albuterol in 24 hours.

Results are compared for the total population as well as for African American and Caucasian subjects and are presented below.

4.2.1. Results

Table 4.2.1a describes the baseline characteristics of all subjects in the trials receiving salmeterol alone or placebo.

Table 4.2.1a Baseline Characteristics of Subjects Randomized to Salmeterol or Placebo

	All Subjects		African American Subjects		Caucasian Subjects	
	Salmeterol n=3333	Placebo n=2710	Salmeterol n=203	Placebo n=169	Salmeterol n=2962	Placebo n=2412
Age, years (mean)	35.3	33.1	31.1	31.0	35.6	33.4
Sex, M/F (%)	49/51	53/47	49/51	54/46	49/51	53/47
% predicted FEV ₁ (mean)	68.0	68.3	65.5	64.5	68.2	68.6
Duration of asthma (%)						
<15 years	56	65	57	56	56	66
≥15 years	44	35	43	44	44	34
# ER visits secondary to asthma, previous year (mean)	0.3	0.4	0.5	0.7	0.3	0.4
# Hospitalizations secondary to asthma, previous year (mean)	0.0	0.0	0.0	0.1	0.0	0.0

Table 4.2.1b describes the baseline characteristics of subjects in the trials receiving salmeterol plus ICS therapy or ICS therapy alone.

Table 4.2.1b Baseline Characteristics of Subjects Randomized to Salmeterol plus ICS or ICS Alone

	All Subjects		African American Subjects		Caucasian Subjects	
	Salmeterol plus ICS n=2005	ICS n=2015	Salmeterol plus ICS n=141	ICS n=169	Salmeterol plus ICS n=1771	ICS n=1760
Age, years (mean)	38.0	37.7	34.3	35.9	38.5	38.1
Sex, M/F (%)	43/57	41/59	35/65	44/56	43/57	40/60
% predicted FEV ₁ (mean)	66.0	66.7	68.0	67.8	65.8	66.6
Duration of asthma (%)						
<15 years	42	46	34	35	42	48
≥ 15 years	58	54	66	65	58	52
# ER visits secondary to asthma, previous year (mean)	0.2	0.1	0.3	0.2	0.1	0.1
# Hospitalizations secondary to asthma, previous year (mean)	0.0	0.0	0.0	0.0	0.0	0.0

4.2.2. Exacerbations

A summary of all exacerbations in subjects receiving salmeterol or placebo is presented in [Table 4.2.2a](#).

Table 4.2.2a Exacerbations in Subjects Randomized to Salmeterol or Placebo

	All Subjects		African American Subjects		Caucasian Subjects	
	Salmeterol n=3333	Placebo n=2710	Salmeterol n=203	Placebo n=169	Salmeterol n=2962	Placebo n=2412
Subjects with at least one exacerbation (%)	525 (16)	702 (26)	28 (14)	42 (25)	470 (16)	624 (26)

All Subjects=includes all subjects in the ITT population, including all ethnic subgroups

There was a lower percentage of subjects experiencing exacerbations in all populations receiving salmeterol compared with placebo.

A summary of all exacerbations in subjects receiving salmeterol plus ICS therapy or ICS therapy alone is presented in Table 4.2.2b.

Table 4.2.2b Exacerbations in Subjects Randomized to Salmeterol plus ICS or ICS Alone

	All Subjects		African American Subjects		Caucasian Subjects	
	Salmeterol plus ICS n=2005	ICS n=2015	Salmeterol plus ICS n=141	ICS n=169	Salmeterol plus ICS n=1771	ICS n=1760
Subjects with at least one exacerbation (%)	143 (7)	255 (13)	15 (11)	22 (13)	119 (7)	218 (12)

All Subjects=includes all subjects in the ITT population, including all ethnic subgroups

There was a lower percentage of subjects experiencing exacerbations in all populations receiving salmeterol plus ICS therapy compared with ICS therapy alone.

4.2.3. Exacerbations Resulting in Hospitalization

An analysis of the exacerbation data resulting in hospitalization is shown in Table 4.2.3. An additional subgroup analysis for Caucasians and African Americans is also included in the table.

Table 4.2.3 Subjects Requiring Hospitalization for an Exacerbation

Population		Salmeterol	Placebo	Salmeterol plus ICS	ICS
All Subjects (n=10,063)	# Subjects	3333	2710	2005	2015
	Hospitalizations, n (%)	31 (0.93%)	11 (0.04%)	4 (0.20%)	7 (0.35%)
African Americans (n=682; 7%)	# Subjects	203	169	141	169
	Hospitalizations, n (%)	3 (1.48%)	1 (0.59%)	0	1 (0.59%)
Caucasian (n=8905; 88%)	# Subjects	2962	2412	1771	1760
	Hospitalizations, n (%)	25 (0.84%)	9 (0.37%)	3 (0.17%)	6 (0.34%)

All Subjects=includes all subjects in the ITT population, including all ethnic subgroups

There analysis shows similar results for hospitalizations due to asthma for subjects receiving ICS compared with salmeterol plus ICS. For subjects not receiving concomitant ICS, there were a higher number of events in salmeterol recipients compared with placebo. Due to limited numbers of events and uncontrolled nature of these data, caution should be used in interpreting results.

4.3. Summary

An analysis of all serious adverse events from GlaxoSmithKline's US asthma studies indicated that the incidence of respiratory-related SAEs was low; however, a higher incidence was observed in the salmeterol group compared with placebo. The incidence was similar for the salmeterol plus ICS and ICS alone groups.

A subset of these studies specifically designed to collect exacerbation data showed a lower percentage of exacerbations in subjects receiving salmeterol compared with placebo and in subjects receiving salmeterol plus ICS compared with ICS alone.

There was no difference in hospitalizations due to asthma for subjects receiving an ICS compared with salmeterol administered with an ICS. For subjects not receiving concomitant ICS, there were a higher number of hospitalizations in salmeterol recipients compared with placebo.

5. SALMETEROL PHARMACOEPIDEMIOLOGY STUDIES IN ASTHMA

5.1. Introduction

Observational study methods are well suited to determine whether use of a particular medication is associated with rare events. Case-control or incident drug cohort studies can be conducted efficiently by using historic, automated population-based data sources (e.g. linked vital statistics, hospital discharge data, healthcare claims, and prescriptions/pharmacy dispensings). Advantages to using observational designs in place of or in addition to randomized clinical trials are numerous. First, observational designs usually offer greater statistical power through use of large population-based patient databases and more efficient study conduct. Further, results of observational studies can be generalized to large populations treated in the community with a wider range of comorbid conditions, disease severity, and demographic characteristics than highly selected patients enrolled in clinical trials.

In a cohort study design, patients are enrolled based on exposure status (e.g., drug of interest versus comparator) and followed up for occurrence of safety events. This study design enables the calculation of incidence rates for multiple outcomes and has a lower likelihood of selection bias.³³ Limitations of cohort studies can include difficulties in choosing an appropriate comparison drug exposure group and accounting for changes in exposure over the observation period (e.g., discontinuation, treatment switching).

Case-control studies compare cases (with a defined event of interest) to controls (without the event of interest) with respect to their past exposure to a particular factor (e.g., drug). Case-control methodology has been argued to be the most appropriate method to estimate the association between an exposure and the risk of rare events (e.g., asthma-related death) because of the statistical efficiency gained.³⁴ Another strength of case-control studies is the availability of detailed exposure information on all drugs dispensed to the patients in the time periods prior to the event of interest, enabling analysis of cumulative dose, and concomitant medications. The largest challenge to case-control studies is the selection of appropriate controls from the same population at risk.

Generally, the primary limitations of pharmacoepidemiology studies are related to potential confounding since treatment assignment is not random and any observed effect of a drug or adverse event may be related to imbalances in underlying disease severity or other unmeasured factors by treatment group (e.g., socioeconomic status) and not a direct effect of the treatment studied. To minimize bias in risk estimates, high quality observational studies employ multiple techniques to match the baseline risk of comparison groups, for example restricting the analysis to patients at highest risk for a given outcome or similar utilization history or through adjustment of potential confounding variables (e.g., disease severity).

5.2. Observational Studies in Asthma

5.2.1. Cohort Studies

Mann et al.³⁵ observed a cohort of over 15,000 patients in the UK who had a prescription for salmeterol within the prior year. Of the cases identified as asthma-related death (n=73), patients were mostly elderly and those receiving salmeterol within the last month of life (n=39) also had evidence of severe disease. Based on a review of these cases, the authors concluded that there was no evidence that salmeterol contributed to asthma-related death.

After the launch of salmeterol in the US, Lanes et al.³⁶ reported a population-based healthcare claims study that compared salmeterol and theophylline use from 1993 to 1995 in patients with asthma. This study demonstrated that salmeterol was prescribed preferentially to patients with more severe asthma as shown by higher baseline rates of asthma polypharmacy, emergency department visits, hospitalizations, and ICU stays for asthma in the year prior to receiving salmeterol. After adjusting for increased asthma severity, salmeterol recipients were at no greater risk of asthma-related hospitalizations, ED visits or ICU stays than were theophylline recipients.

In addition, respiratory death associated with salmeterol use relative to use of other asthma medications was assessed in a retrospective cohort study by Meier and Jick.³⁷ In this study, respiratory death rates at 16 weeks were compared among incident cohorts of salmeterol users (n=8386) relative to ipratropium bromide (n=4305) and theophylline users (n=4228). After adjusting for appropriate risk factors, the relative risk of respiratory death was similar for those receiving ipratropium bromide, theophylline, and salmeterol.

5.2.2. Case-control Studies

In addition to retrospective cohort studies, three case-control studies were also conducted to evaluate the association of use of salmeterol and the risk of near-fatal or fatal asthma. Williams, et al compared exposure to salmeterol among 48 cases admitted to the ICU for asthma with 185 controls admitted to the same UK hospital for asthma and found preferential prescribing for salmeterol to patients with more severe asthma.³⁸ After controlling for severity, those given salmeterol were at no greater risk of a near fatal asthma attack than were patients not using salmeterol.

A retrospective UK study of the effect of respiratory medications and the risk of asthma death between 1994 and 1998 examined 43 cases and 860 matched controls from the GPRD (General Practice Research Database).³⁹ After adjusting for confounding variables, there was no significant difference in the risk of asthma death associated with 0, 1 to 6, or ≥ 7 prescriptions for long acting beta₂-agonists in the in the past year. Excessive use of short acting beta₂-agonists was associated with an increased risk of asthma death.

The most comprehensive population-based study evaluating salmeterol use and risk of asthma death was recently published by Anderson, et al.⁴⁰ This UK study evaluated a population sample (532 asthma deaths, <65 years of age) with date, age and geographic area-matched controls with an admission for acute asthma. Blinded data on asthma prescriptions were obtained over the previous five years. Odds ratios for death

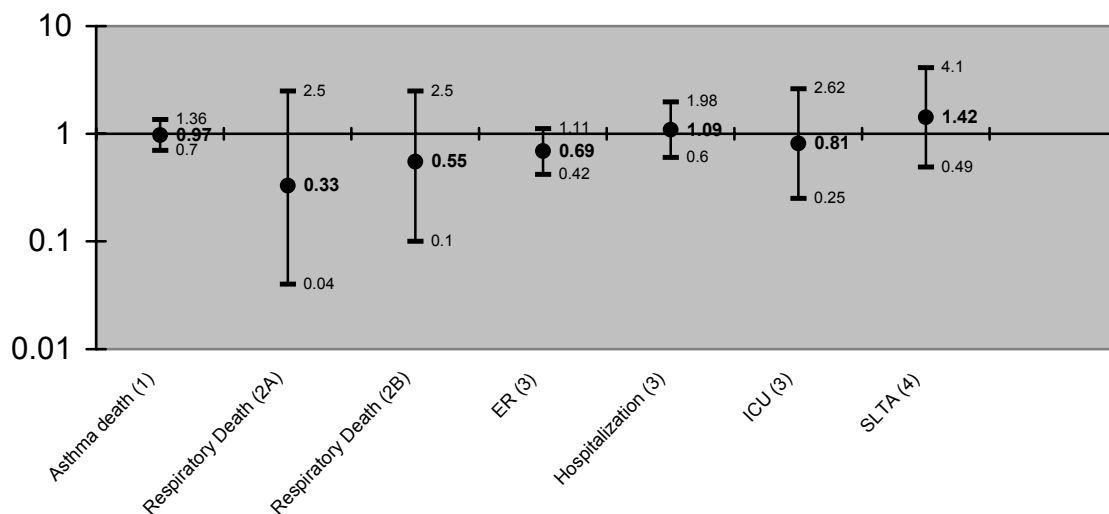
associated with prescription of drugs in the time prior to the index date were estimated using conditional logistic regression. Recent or past use of salmeterol was not associated with an increased risk of asthma mortality. Further, in a sensitivity analysis restricted to more severe patients (n=122 pairs) defined as cases and matched controls with at least one asthma hospital admission in the year prior to index date, salmeterol use was not associated with an increased risk of asthma death.

In addition, observational studies have shown that the use of salmeterol has not been associated with an increased risk of cardiac events. Martin et al⁴¹ found no increased age and sex-adjusted risk of either non-fatal cardiac failure or non-fatal ischemic heart disease among salmeterol users (n=15,407) relative to users of nedocromil (n=12,294).

5.3. Summary

Figure 5.3 summarizes the adjusted relative risk estimates of asthma mortality, severe morbidity and cardiac events published in the four observational studies conducted to date. All the estimates show no increased risk for these adverse outcomes following salmeterol use.

Figure 5.3 Adjusted Relative Risk (95% Confidence Intervals) of Asthma Mortality, Ischemic Events and Severe Asthma Morbidity Associated with Salmeterol Use from Published Observational Studies



1. Anderson, 2005 [salmeterol use in prior 3 months versus none]
2. Meier, 1997 [A: relative to theophylline use (OR=0.33); B: relative to ipratropium bromide (OR=0.55)]
3. Lanes, 1998
4. Williams, 1998 [SLTA=Severe Life Threatening Attack of asthma]

Current evidence from several large, population-based observational studies conducted in the UK and US indicates that use of salmeterol is not associated with a significant increase in the risk of severe asthma morbidity, asthma mortality, ischemic heart disease or cardiac failure after controlling for confounding by severity or preferential prescribing of salmeterol to patients with more severe asthma.

6. SALMETEROL IN COPD

The primary focus of this briefing document is to review the safety and efficacy data for salmeterol available in asthma. However, it is important to review the safety data for salmeterol in patients with COPD

GlaxoSmithKline has evaluated the efficacy and safety of salmeterol in over 4300 patients with COPD in trials of four to 24 weeks in duration.^{42,43,44,45,46,47,48,49,50,51,52} These clinical trials have established that salmeterol is an effective bronchodilator in the management of COPD. In addition, these trials have contributed to a large and growing body of evidence supporting the favorable safety profile of salmeterol in patients with COPD.

6.1. Summary of Serious Adverse Events from US COPD Clinical Trials

To evaluate the SAEs in patients with COPD, the same methodology was utilized as previously described for asthma SAEs (Section 4.1).

We explored the data from all US repeat dose studies containing salmeterol. This assessment included 12 phase III and IV studies with salmeterol, involving 4344 adult subjects. The duration of these studies ranged from four to 24 weeks and efficacy endpoints included measures of lung function (i.e., FEV₁), symptoms, nighttime awakenings, rescue albuterol use, and health-related quality of life. Safety endpoints included collection of adverse events and exacerbations.

The following treatment groups were evaluated: salmeterol 50mcg BID, placebo, salmeterol 50mcg BID plus FP, and FP alone. The salmeterol group represents patients randomized to salmeterol as monotherapy. In this group, patients may or may not have been using concurrent ICS therapy. The salmeterol plus FP group represents patients randomized to salmeterol administered with FP in a single device. For this *post hoc* analysis of SAEs, all coding terms that fell within the general categories of respiratory-, cardiovascular-, and metabolic-related were included.

Serious adverse events in relation to cardiovascular and respiratory systems are presented in Table 6.1a. The incidence of SAEs in the metabolic body system was low relative to events in the respiratory and cardiovascular systems (0 to ≤0.28% across groups) and is not reported.

Table 6.1a Number of Subjects Reporting Serious Adverse Events by Cardiovascular and Respiratory Systems

	Salmeterol* (n=2418)	Placebo (n=861)	Salmeterol plus FP† (n=709)	FP (n=356)
Cardiovascular, n (%)	26 (1.08%)	14 (1.63%)	6 (0.85%)	3 (0.84%)
Respiratory, n (%)	45 (1.86%)	13 (1.51%)	9 (1.27%)	16 (4.49%)

* salmeterol=all studies where patients were randomized to salmeterol 50mcg BID

† salmeterol plus FP=all studies where patients were randomized to salmeterol 50mcg BID and FP

There were 6 deaths reported in the 4344 patients enrolled in these trials. One respiratory-related death (pneumonia) occurred in a patient receiving placebo.

Respiratory-related SAEs that occurred in ≥ 5 patients in any group are reported in Table 6.1b.

Table 6.1b Respiratory Serious Adverse Events Reported by ≥ 5 Subjects

SAE	Salmeterol* (n=2418)	Placebo (n=861)	Salmeterol plus FP† (n=709)	FP (n=356)
COPD, n (%)	5 (0.21%)	3 (0.35%)	3 (0.42%)	9 (2.53%)
COPD exacerbation, n (%)	23 (0.95%)	4 (0.46%)	2 (0.28%)	0
Pneumonia, n (%)	10 (0.41%)	4 (0.46%)	3 (0.42%)	7 (1.97%)

* salmeterol=all studies where patients were randomized to salmeterol 50mcg BID

† salmeterol plus FP=all studies where patients were randomized to salmeterol 50mcg BID and FP

6.2. Pooled Analysis of Cardiovascular Safety Data

A pooled analysis of cardiovascular safety data from seven studies of salmeterol in patients with COPD has been published.⁵³ This analysis showed no increased risk of cardiovascular adverse events for salmeterol compared with placebo (RR, 1.03; 95%CI 0.8-1.3, p=0.838).

6.3. Observational Studies in COPD

Observational studies in COPD have shown that salmeterol use was associated with a lower risk of hospitalization and a trend toward prolonged survival compared with short-acting bronchodilators (e.g., ipratropium, albuterol).^{54,55,56,57}

6.4. Summary

Currently available clinical data do not suggest that there is an association with beta₂-agonist use and serious adverse outcomes in patients with COPD.

7. POST-MARKETING EXPERIENCE FROM WORLDWIDE SPONTANEOUS ADVERSE EVENT REPORTS

As part of the ongoing safety evaluation of any marketed drug, spontaneous adverse event reports are evaluated on a periodic basis. Data from spontaneous reporting can be used to generate hypotheses concerning potential safety signals. However, spontaneous data are reported voluntarily from an unknown population size with lack of accurate information on the denominator (actual number of patients on the drug) and the numerator (the actual number of events). Reporting patterns are influenced by stage of the product life cycle in the market, characteristics of the patient population treated, publicity around the drug or the drug class and familiarity of healthcare professionals in using the product, as well as national medical practices. Furthermore, spontaneous adverse event reports are received from all sources including reports from patients without medical verification and often lack sufficient information pertinent to the medical evaluation of the case. Due to these inherent limitations of spontaneous reporting it is not possible to draw firm conclusions from these data.

Spontaneous data should not be viewed in isolation and should be interpreted in the context of data from randomized control trials and observational studies.

This review includes post-marketing exposure of salmeterol and all spontaneous reports of all cause death and respiratory-related reports (where known) occurring from first approval of salmeterol (1990) through March 31, 2005, and salmeterol administered with FP in a single device (1998) through April 30, 2005.

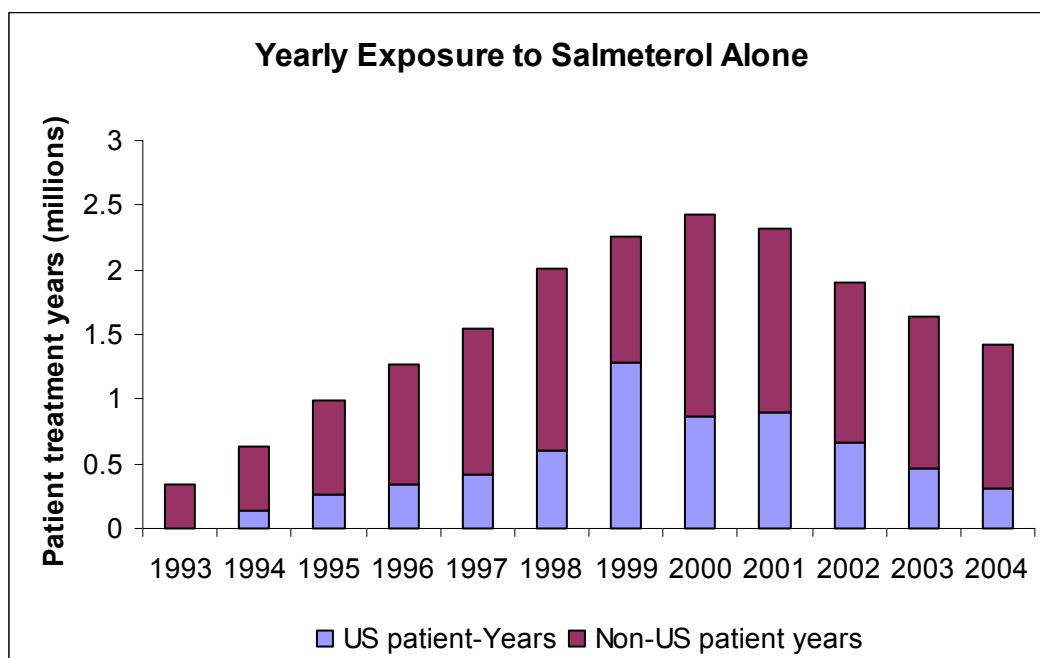
In New Zealand, reports of fatal outcome were solicited under a national monitoring program and are discussed separately.

7.1. Post-marketing Exposure

7.1.1. Post-marketing Exposure to Salmeterol Alone

It is estimated that there have been 24.3 million patient-years of exposure worldwide, to all formulations of salmeterol as a single medication until March 31, 2005. Yearly exposure estimated from sales data were received from Intercontinental Medical Statistics (IMS) and are summarized below in [Figure 7.1.1](#).

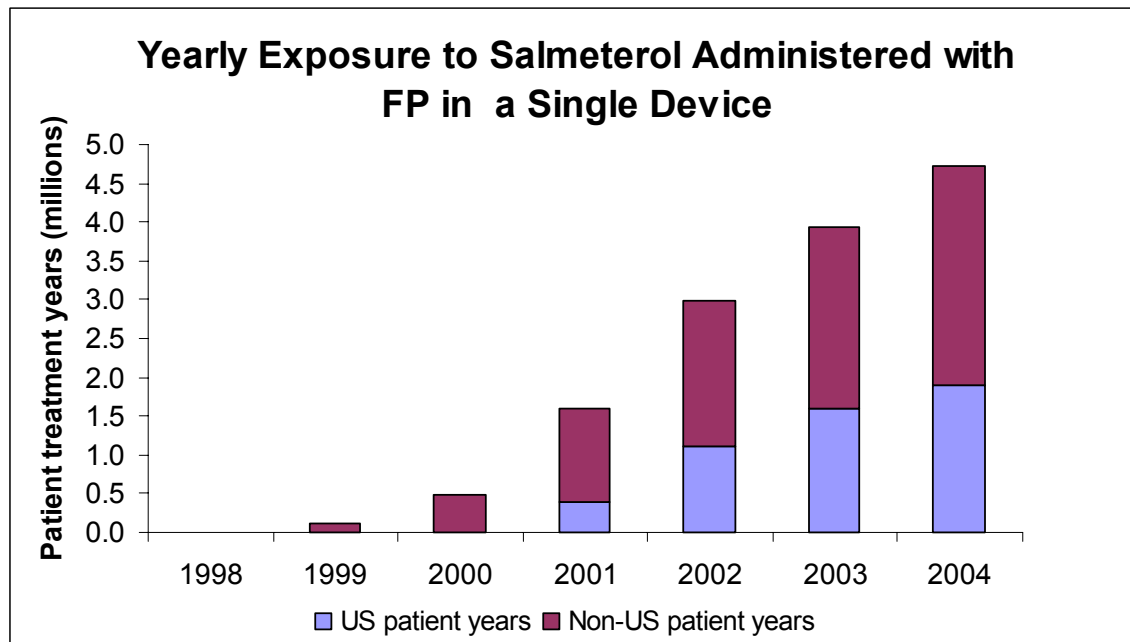
Figure 7.1.1 Yearly Exposure to Salmeterol



7.1.2. Post-marketing Exposure to Salmeterol Administered with FP in a Single Device

It is estimated that there have been 20.9 million patient-years of exposure worldwide, to all formulations of salmeterol administered with FP in a single device through April 30, 2005. Yearly exposure estimated from sales data were received from Intercontinental Medical Statistics (IMS) and are illustrated in [Figure 7.1.2](#) below.

Figure 7.1.2 Yearly Exposure to Salmeterol Administered with FP in a Single Device



7.1.3. Summary of Post-marketing Exposure to Salmeterol

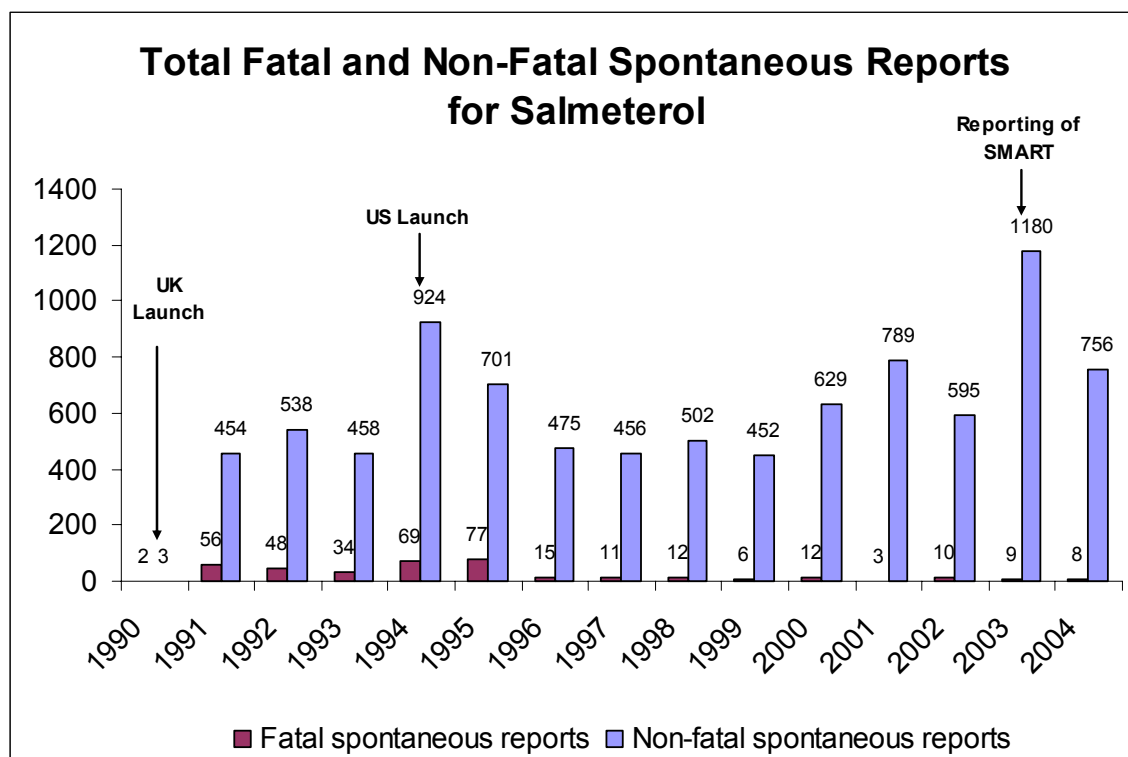
Overall patient exposure to the salmeterol molecule has continued to increase yearly since 1990 and cumulatively is estimated at over 45 million patient years. Most recently, the total exposure is driven by the use of salmeterol administered with FP in a single device.

7.2. Spontaneous Reports

7.2.1. All Spontaneous Reports for Salmeterol

Figure 7.2.1 shows the total number of global spontaneous reports of all events (fatal and non-fatal) for salmeterol since the first approval in 1990. The greatest number of spontaneous reports occurred in the year of the US launch (1994) and following the reporting of SMART (2003). This pattern is reflective of the expected pattern of events following the launch of a novel product, and suggests reporting patterns may be influenced by the introduction of a drug and publicity surrounding it.

Figure 7.2.1 Total Spontaneous Reports and Total Fatal Reports Received for Salmeterol



Excluding fatal events reported in New Zealand, there were 378 spontaneously reported cases with a fatal outcome. From launch to 1995, fatal reports accounted for 10-13% per year of the total number of spontaneous reports received for salmeterol. From 1996-2004, fatal reports decreased to 1-3% (approximately 15 cases per year) of the total number of spontaneous reports received for salmeterol. When the cause of death was reported or could be assessed from the case information, 58% were identified as respiratory-related events, and 18% as cardiac-related events. In the majority of the remaining reports, the cause of death was unknown.

Review of all fatal reports showed that the majority of cases were confounded predominately by disease severity, either alone or in combination with additional confounders, such as co-morbidity, advanced age, infection and medication errors.

7.2.1.1. Fatal Cases Originating from New Zealand

A total of 250 salmeterol cases with a fatal outcome, were reported from New Zealand, the vast majority (96%) of which originated from the Intensive Medicine Monitoring Programme (IMMP).

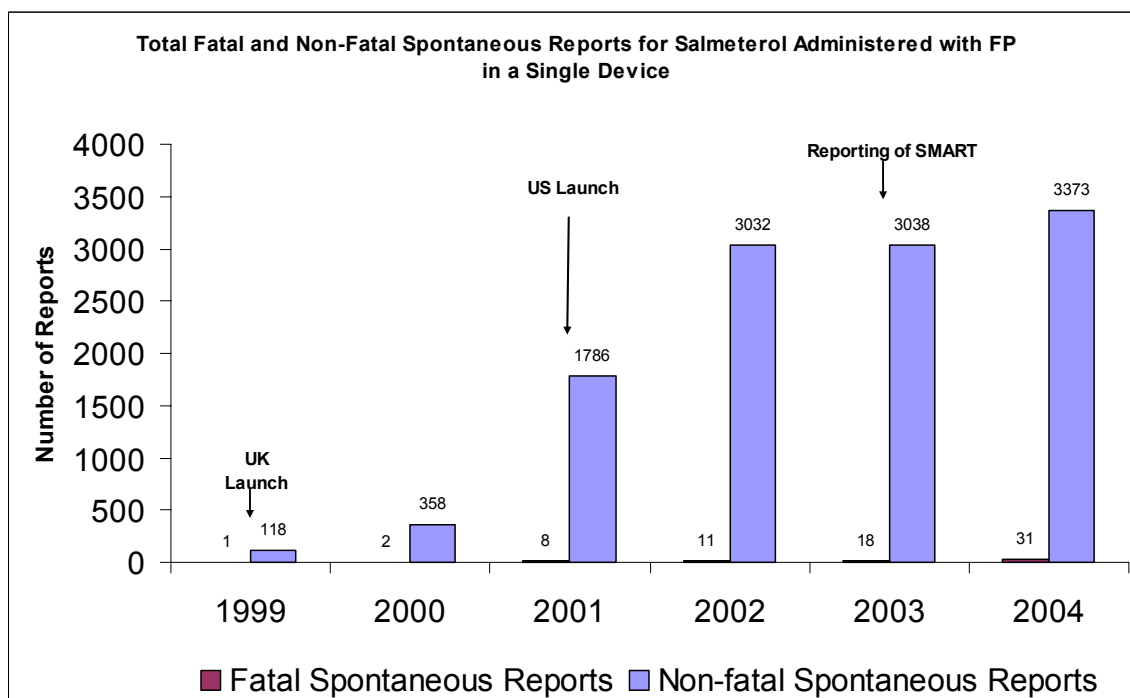
The IMMP was a government subsidized program, in which patients need to meet certain criteria for eligibility for treatment with salmeterol, including poorly controlled or uncontrolled disease state for at least 3 months and ongoing treatment with a total daily dose of 1500mcg beclomethasone or 750mcg FP.

Analysis of these reports revealed a distinctive reporting pattern due to the nature of patients permitted to receive salmeterol in the IMMP. Reports were influenced by patients with severe asthma and older patients (82% involved patients aged 60 years or above) with significant multi-morbidities.

7.2.2. All Spontaneous Reports for Salmeterol Administered with FP in a Single Device

Figure 7.2.2 shows, the total number of global spontaneous reports of all events (fatal and non-fatal) for salmeterol administered with FP in a single device since the first approval in 1998. The absolute number of reports continues to increase since the introduction of salmeterol administered with FP in a single device; however, in view of increasing total patient exposure, the relative number of reports is decreasing.

Figure 7.2.2 Total Spontaneous Reports and Total Fatal Reports Received for Salmeterol Administered with FP in a Single Dose



A total of 78 spontaneous cases with a fatal outcome have been reported with salmeterol administered with FP in a single device. In any given year, less than 1% of all spontaneously reported cases reports had a fatal outcome. Where the cause of death was reported, 37% were identified as respiratory-related events, 23% as cardiac-related events and the remaining 40% could not be assessed from the case information.

7.2.3. Summary of Spontaneous Reports with Salmeterol-Containing Products

A review of spontaneous reports, including fatal reports identified 5 major confounders: respiratory disease severity, indication (e.g., COPD), advanced age, multi-morbidity and

polypharmacy. In addition, issues relating to treatment compliance were noted (e.g., using salmeterol inappropriately as rescue medication).

The confounders observed from the review of GlaxoSmithKline's spontaneous adverse event database are in accordance with the published data in so far as age, indication, disease severity and co-morbidity were the most significant and consistently identified covariates of mortality in asthma and COPD literature.^{58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76}

In summary, the reporting of spontaneous events peaked with approvals of salmeterol in the UK and US and with publicity around SMART. In general, the absolute number of spontaneously reported events (including fatal events) is low and has not increased relative to exposure to salmeterol. Because of the nature of spontaneously reported events and the confounders discussed above, a definitive link between the use of salmeterol and spontaneously reported adverse events cannot be ascertained.

7.3. Disproportionality Analyses for Salmeterol and Salmeterol Administered with FP in a Single Device

Disproportionality analysis is an emerging drug safety surveillance tool used by the pharmaceutical industry and FDA to compare the frequency of spontaneously reported adverse events for a specific drug compared to the frequency derived from spontaneously reported adverse events from all other drugs. The analysis does not provide estimates of the incidence of adverse events.

7.3.1. Background and Methods

Disproportionality analysis was used with two spontaneous reporting databases to compute relative reporting frequencies of life-threatening respiratory-related adverse events and fatal outcomes with salmeterol and salmeterol administered with FP in a single device.

Relative reporting frequencies provide context that is lacking with simple reporting frequencies (i.e., the observed number of reports divided by an estimate of exposure) by relating the reporting frequency of a given drug-event pair to the reporting frequencies of all drugs and all events in the database. Relative reporting frequencies do not provide measures of the incidence of adverse events. A high relative reporting frequency does not necessarily indicate the presence of a causal relationship between a drug and an event; similarly, a low relative reporting frequency does not guarantee the absence of a causal relationship. It should be noted that relative reporting frequencies may reflect biases due to differential reporting; examples include publicity, label changes, or association of an adverse event with another drug in the same or similar pharmacological class. Despite these limitations, these methods provide a systematic and quantitative approach to understanding the reporting frequencies of spontaneously reported adverse events.

The disproportionality method used for this analysis was Multi-item Gamma Poisson Shrinker (MGPS).^{77,78} For each drug-event pair observed in a database, MGPS computes the internal expected counts using a stratified, full independence model and derives the empirical Bayes geometric mean (EBGM) and associated 2-sided 90% confidence intervals (lower and upper limits denoted EB05 and EB95, respectively).

EBGM values, sometimes referred to as “signal scores”, are the adjusted ratios of observed to expected counts after Bayesian shrinkage and thus represent the relative reporting frequencies for each drug-event pair.

An EBGM value close to 1 is interpreted to mean that the observed reporting frequency is close to the expected frequency, whereas an EBGM value of 5 is interpreted to mean that the drug-event pair has been reported 5 times more frequently than predicted by the full independence model. Similarly, an EBGM value less than 1 is seen when a drug-event pair is reported less frequently than expected. When MGPS is used for signal detection, $EB05 \geq 2$ is sometimes specified as a threshold for defining a safety signal.⁷⁹ MGPS is internally stratified by age, sex, and year of report to minimize the detection of apparent drug-event associations that may have been influenced by one of these variables (e.g., the case where a certain drug is commonly used in elderly patients and there may be confounding due to an adverse event that is common in elderly patients).

The first database analyzed was the Operating Companies Event Accession and Notification System (OCEANS), GlaxoSmithKline’s global adverse event database. OCEANS contains all spontaneous reports (more than 500,000) received by GlaxoSmithKline and its heritage organizations from as early as 1960 through April 30, 2005. The OCEANS dataset used for this analysis comprised all non-vaccine spontaneous reports, excluding reports from New Zealand (see Section 7.2.2). The second database analyzed was the public-release version of FDA’s post-marketing safety database, AERS (Adverse Event Reporting System). AERS is a surveillance system that relies on voluntary reporting of adverse events to FDA by healthcare professionals and consumers, as well as required reporting by pharmaceutical manufacturers. AERS includes spontaneous reports from US sources; serious and unlabeled spontaneous reports from non-US sources; and serious, unlabeled, and attributable post-marketing clinical trial reports from all sources. As of December 2004, AERS contained approximately 2.6 million reports. The AERS dataset used for this analysis was provided by Lincoln Technologies via WebVDME (v. 5.0) and contains reports received by FDA from 1968 through the end of 2004.

The data were analyzed cumulatively from the introduction of salmeterol in 1990. Since the rate of spontaneous reporting of adverse events associated with salmeterol has changed over time, the data are reported for years prior to 1995, post 1995, and for the total time that salmeterol has been available. In the AERS database, only the event “fatal outcome” could be evaluated for these two time periods. This is due to the fact that in 1997 there was a change in the AERS coding dictionary, which limits the comparability of the data across the AE terms during these time periods.

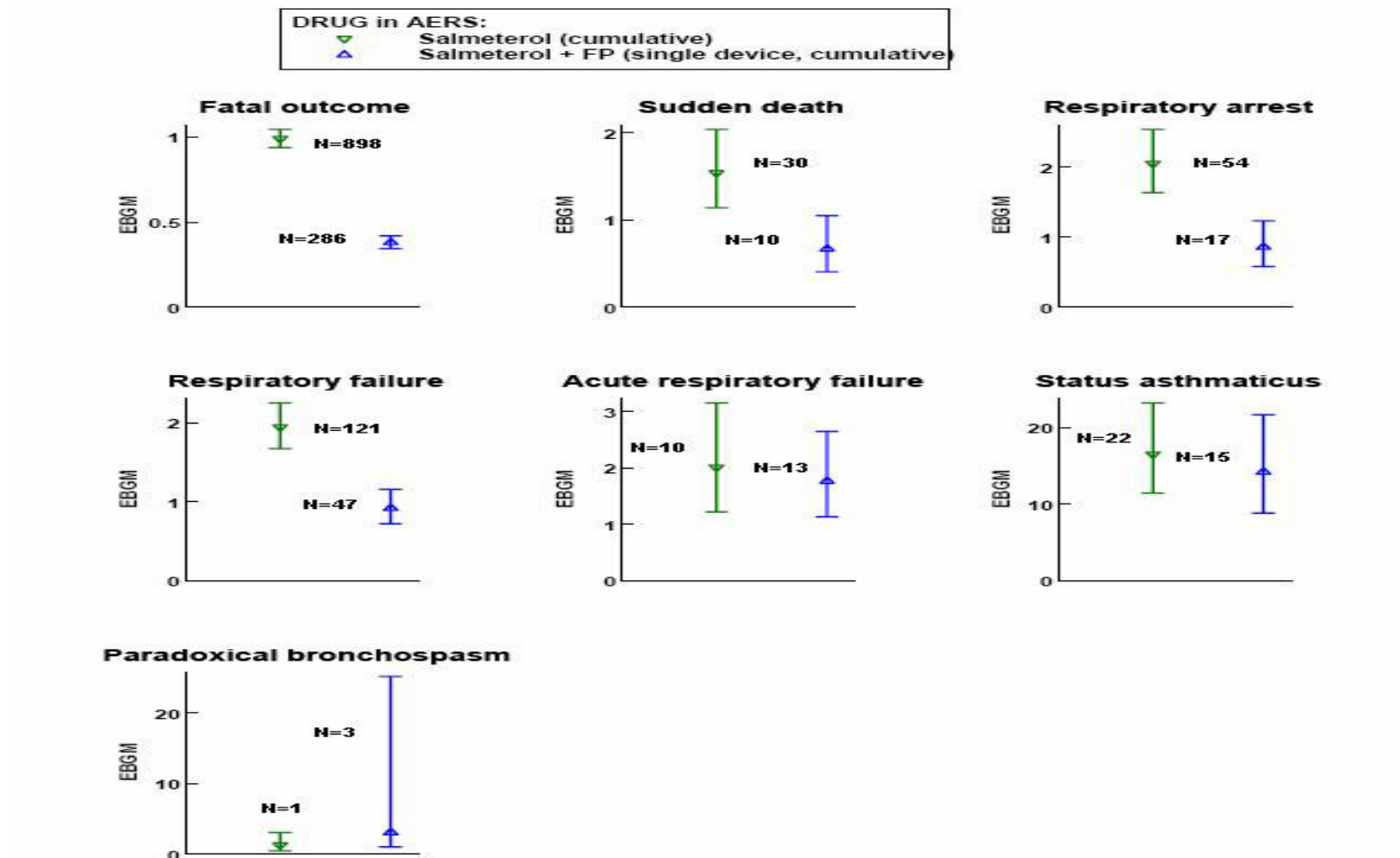
7.3.2. Results

The EBGM values and their lower and upper confidence bounds (EB05 and EB95) are shown for each adverse event term in Figures 7.5.2.1a and 7.5.2.1b as well as Figures 7.5.2.2a and 7.5.2.2b.

7.3.2.1. Cumulative Reporting of Life-Threatening Respiratory-Related Events and Fatal Outcomes

In AERS, the EBGM values for salmeterol were ≤ 2 for the following events: fatal outcome, respiratory arrest, respiratory failure, acute respiratory failure, paradoxical bronchospasm, and sudden death. For salmeterol administered with FP in a single device, EBGM values were even lower (<1) for respiratory failure, sudden death, fatal outcome and respiratory arrest. Higher EBGM values were observed for status asthmaticus (16.6 and 14.3 for salmeterol and salmeterol administered with FP in a single device, respectively).

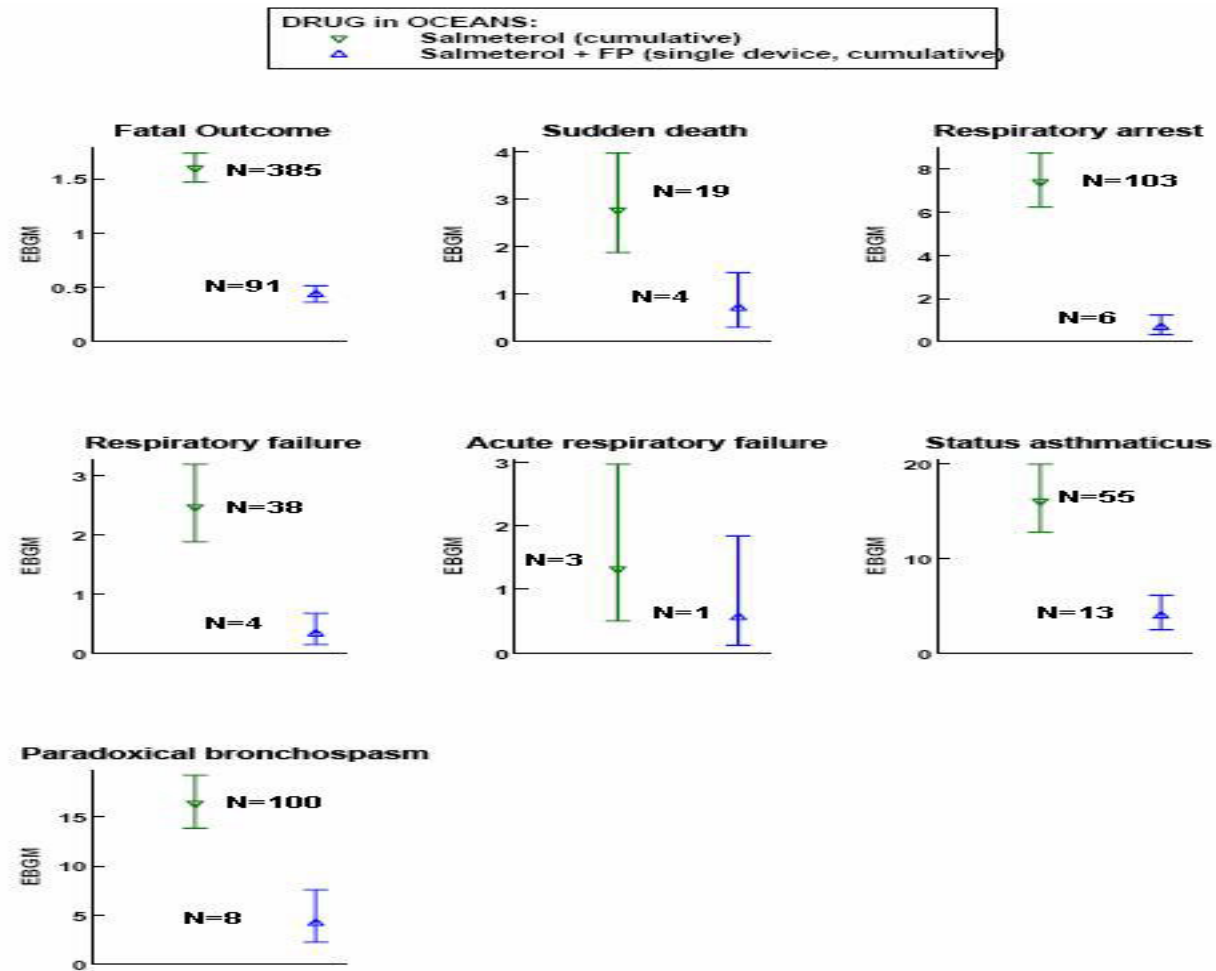
Figure 7.5.2.1a AERS: Cumulative EBGm (EB05, EB95) Values for Salmeterol Alone and Salmeterol Administered with FP in a Single Device



Signal scores were somewhat higher in OCEANS than in AERS, although the reporting patterns were similar. For salmeterol, the EBGM values were <2 for fatal outcome and acute respiratory failure and between 2 and 3 for respiratory failure and sudden death. For all events, signal scores were lower for salmeterol administered with FP in a single device than for salmeterol alone. EBGM values for salmeterol administered with FP in a single device were low (<1) for the following adverse events: respiratory failure, acute respiratory failure, sudden death, fatal outcome, and respiratory arrest). Higher EBGM values in OCEANS were seen for paradoxical bronchospasm and status asthmaticus.

Figure 7.5.2.1b

OCEANS: Cumulative EBGm (EB05, EB95) Values for Salmeterol and Salmeterol Administered with FP in a Single Device



7.3.2.2. Reporting Patterns Over Time

Figures 7.5.2.2a and 7.5.2.2b display EBGM values for salmeterol and the events of interest during two distinct time periods: the early marketing period and the current marketing period. EBGM values from AERS for “fatal outcome” were low in both time periods (Figure 7.5.2.2a). In the OCEANS database, EBGM values are lower in the current marketing period compared to the early marketing period for four events: fatal outcome, sudden death, respiratory arrest, and respiratory failure (Figure 7.5.2.2b). EBGM values for status asthmaticus were similar in the two time periods, whereas reporting of paradoxical bronchospasm was higher in the later time period.

Although differences in reporting frequencies for individual terms were noted between the AERS and OCEANS databases, the overall patterns described above were seen in both post-marketing databases examined. These results may reflect differences in the composition of the databases. AERS is large and diverse, but is focused on US reporting, whereas OCEANS is a smaller and less diverse database that includes worldwide data on GlaxoSmithKline products

Figure 7.5.2.2a AERS: EBGM (EB05, EB95) Values for Salmeterol Over Time (Launch Through End 1995 and 1996 Through End 2004)

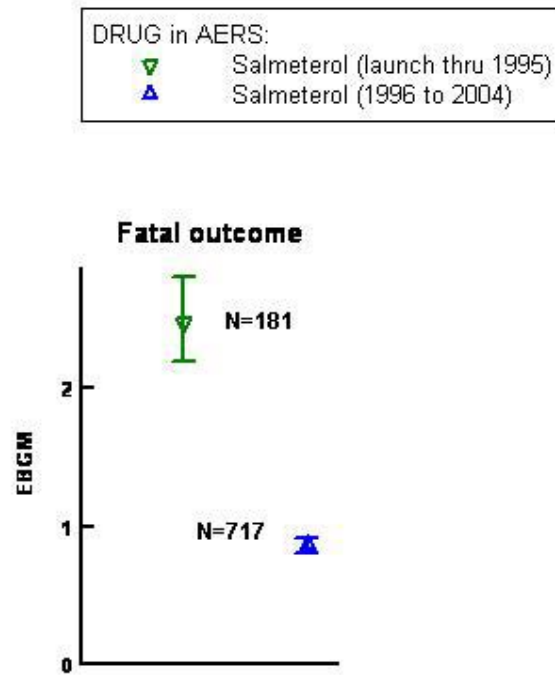
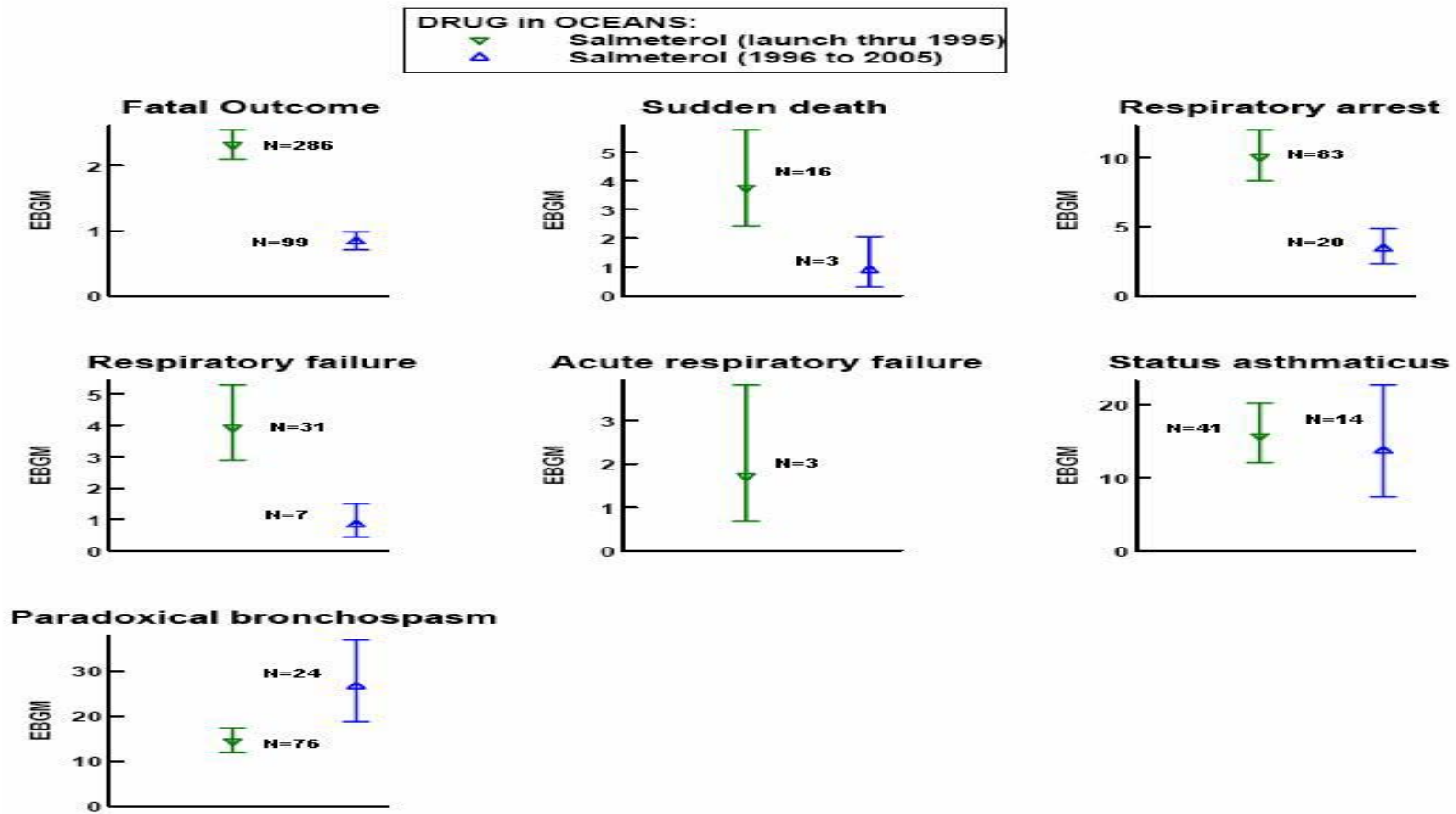


Figure 7.5.2.2b OCEANS: EBGIM (EB05, EB95) Values for Salmeterol Over Time
(Launch Through End 1995 and 1996 Through End 2004)



7.3.3. Summary of Disproportionality Analyses

Disproportionality analyses of two post-marketing databases were performed to evaluate relative reporting frequencies of life-threatening respiratory-related events and fatal outcomes with salmeterol alone and salmeterol administered with FP in a single device. These analyses showed that fatal outcomes have been reported relatively infrequently. In general, life-threatening respiratory-related adverse events have been reported relatively infrequently with the exceptions of status asthmaticus and paradoxical bronchospasm. Relative reporting frequencies for fatal outcomes and for the majority of the life-threatening respiratory-related events examined have declined from the early marketing period to the current marketing period for salmeterol alone. Relative reporting frequencies for fatal outcomes and for the majority of the life-threatening respiratory-related events examined are lower with salmeterol administered with FP in a single device than with salmeterol alone. Notwithstanding the change in reporting frequencies over time, the product information for salmeterol alone and salmeterol administered with FP in a single device continues to include information relating to serious and life-threatening asthma-related events.

8. SAFETY INFORMATION FROM CURRENT PRESCRIBING INFORMATION

The prescribing information for both **SEREVENT** and **ADVAIR** provides detailed information related to appropriate use of these products. In order to describe the chronology of changes to the prescribing information, we have provided the warnings within the prescribing information that were included both prior to and following the reporting of SMART.

8.1. Warnings Prior to the Results of SMART

The warnings stated below were contained in the prescribing information for **SEREVENT** prior to the results of SMART.

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 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 as well as warn them that increasing inhaled beta₂-agonist use is a signal of deteriorating asthma.

SEREVENT DISKUS IS NOT A SUBSTITUTE FOR INHALED OR ORAL CORTICOSTEROIDS. Corticosteroids should not be stopped or reduced when **SEREVENT DISKUS** is initiated.

DO Not Introduce SEREVENT DISKUS 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 or simply failed to relieve the deteriorating asthma.

Do Not Use SEREVENT DISKUS 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).

Watch for Increasing Use of Inhaled, Short-Acting Beta₂-Agonists, Which Is a Marker of Deteriorating Asthma or COPD: 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.**

Do Not Use SEREVENT DISKUS as a Substitute for Oral or Inhaled Corticosteroids: The use of beta-adrenergic agonist bronchodilators alone may not be adequate to control asthma in many patients. Early consideration should be given to adding anti-inflammatory agents, e.g., 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. Patients who already require oral or inhaled corticosteroids for treatment of asthma should be continued on a suitable dose 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).

Do Not Exceed Recommended Dosage: 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.

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 with a short-acting, inhaled bronchodilator; SEREVENT

DISKUS should be discontinued immediately; and alternative therapy should be instituted.

Immediate Hypersensitivity Reactions: Immediate hypersensitivity reactions may occur after administration of SEREVENT DISKUS, as demonstrated by cases of urticaria, angioedema, rash, and bronchospasm.

Upper Airway Symptoms: Symptoms of laryngeal spasm, irritation, or swelling, such as stridor and choking, have been reported in patients receiving SEREVENT DISKUS.

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.

8.2. Additional Safety Information Following the Results of SMART

Following the results of SMART, the following additional information was added to the prescribing information:

BOXED 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 death in patients receiving salmeterol (13 deaths out of 13,176 patients treated for 28 weeks) versus those on placebo (3 of 13,179) (see WARNINGS and CLINICAL TRIALS: Asthma: *Salmeterol Multi-center Asthma Research Trial*).

WARNINGS

DATA FROM A LARGE PLACEBO-CONTROLLED SAFETY STUDY THAT WAS STOPPED EARLY SUGGEST THAT SALMETEROL MAY BE ASSOCIATED WITH RARE SERIOUS ASTHMA EPISODES OR ASTHMA-RELATED DEATHS. Data from this study, called the Salmeterol Multi-center Asthma Research Trial (SMART), further suggest that the risk might be greater in African American patients. These results led to stopping the study prematurely (see CLINICAL TRIALS: Asthma: *Salmeterol Multi-center Asthma Research Trial*). The data from the SMART study are not adequate to determine whether concurrent use of inhaled corticosteroids provides protection from this risk. Given the similar basic mechanisms of action of beta₂-agonists, it is possible that the findings seen in the SMART study may be consistent with a class effect.

Finding similar to the SMART study findings were reported in a prior 16-week clinical study performed in the United Kingdom, the Salmeterol Nationwide Surveillance (SNS) study. In the SNS study, the incidence of asthma-related death was numerically, though not statistically, greater in patients with asthma treated with salmeterol (42 mcg twice daily) versus albuterol (180 mcg 4 times daily) added to usual asthma therapy.

Clinical Trials

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. The primary endpoint was the combined number of respiratory-related deaths or respiratory-related life-threatening experiences (intubation and mechanical ventilation). Secondary endpoints included combined asthma-related deaths or life-threatening experiences and asthma-related deaths. A planned interim analysis was conducted when approximately half of the intended number of patients had been enrolled (N = 26,355).

Due to the low rate of primary events in the study, the findings of the planned interim analysis were not conclusive. However, analyses of secondary endpoints suggested that patients receiving salmeterol may be at increased risk for some of these events compared to patients receiving placebo. The analysis for the total population showed a relative risk of 1.40 (95% CI 0.91, 2.14) for the primary endpoint in the salmeterol group relative to the placebo group (50 out of 13,176 vs. 36 out of 13,179, respectively). In the total population, a higher number of asthma-related deaths (13 vs. 3, RR 4.37, 95% CI 1.25, 15.34) and combined asthma-related deaths or life-threatening experiences (37 vs. 22, RR 1.71, 95% CI 1.01, 2.89) occurred in patients treated with salmeterol than those treated with placebo. The analysis of the African American subgroup showed a relative risk of 4.10 (95% CI 1.54, 10.90) for the primary endpoint in patients treated with salmeterol relative to those treated with placebo (20 out of 2,366 vs. 5 out of 2,319, respectively). In African Americans, a higher number of asthma-related deaths (7 vs. 1, RR 7.26, 95% CI 0.89, 58.94) and combined asthma-related deaths or life-threatening experiences (19 vs. 4, RR 4.92, 95% CI 1.68, 14.45) occurred in patients treated with salmeterol than those treated with placebo. Analysis of the Caucasian population showed a relative risk of 1.05 (95% CI 0.62, 1.76) for the primary endpoint for those treated with salmeterol relative to those treated with placebo (29 out of 9,281 vs. 28 out of 9,361, respectively). In Caucasians, a higher number of asthma-related deaths (6 vs. 1, RR 5.82, 95% CI 0.70, 48.37) occurred in patients treated with salmeterol than in patients treated with placebo. In Caucasians, the relative risk was 1.08 (17 vs. 16, 95% CI 0.55, 2.14) for combined asthma-related deaths or life-threatening experiences in patients treated with salmeterol relative to placebo. The numbers of patients from other ethnic groups were too small to draw any conclusions in these populations. Even though SMART did not reach predetermined stopping criteria for the total population, the study was stopped due to the findings in African American patients and difficulties in enrollment.

The prescribing information for **ADVAIR** contains similar information that is found in the **SEREVENT** prescribing information. Copies of prescribing information for **SEREVENT** and **ADVAIR** are provided in the [Sections 1.2 and 1.3 of the Appendix](#).

9. PHARMACOGENETICS OF BETA₂-AGONISTS

Pharmacogenetic research of beta₂-agonists has centered on the β₂-adrenergic receptor (β₂-AR), the cell surface receptor mediating the effects of all beta₂-agonists.⁸⁰ The β₂-adrenergic receptor is a 413 amino acid protein encoded by an intronless gene (*ADRB2*) located on chromosome 5q31-32m within a chromosomal region genetically linked to asthma susceptibility.^{81,82}

Sequencing of *ADRB2* has identified at least 19 single nucleotide polymorphisms (SNPs) within the coding and promoter region.^{83,84} To date, the most frequently studied *ADRB2* coding SNPs are characterized by substitutions of glycine for arginine at position 16 (Arg16Gly) and glutamine to glutamic acid at position 27 (Gln27Glu), both of which occur commonly in the population (minor allele frequency approximately 0.4-0.5).

Associations between *ADRB2* SNPs and therapeutic outcomes suggest that genetic variation can influence the response to a variety of beta₂-agonists; however, the clinical significance of these observations is not yet clear.^{85,86,87,88} Variations in individual study designs, heterogeneity across the patient populations studied, and limited sample sizes preclude consensus definitions of genotype-phenotype relationships from being reached.

Another potentially critical factor in unravelling pharmacogenetic associations centers on the pharmacologic properties of the beta₂-agonists administered. The predominance of literature has centered on the short-acting beta₂-agonist, albuterol, in asthma patients, but because pharmacologic properties of beta₂-agonists vary,⁸⁹ conclusions drawn from clinical studies that investigate associations between bronchodilation and *ADRB2* pharmacogenetics may not be comparable between short- and long- acting beta₂-agonists. In a single 24-week, cross-over study comparing use of short-acting beta₂-agonists with salmeterol evaluating patients by Arg16Gly genotype, lower exacerbation rates were reported for Arg/Arg patients receiving salmeterol compared with regular or as-needed albuterol use).⁸⁸ In addition, Taylor et al.⁸⁸ also demonstrated that while there was reduced peak flow over time with albuterol in the Arg/Arg genotype, there was no diminution of pulmonary function with the Arg/Arg genotype in patients receiving salmeterol.

Only limited pharmacogenetic information is available for beta₂-agonist pharmacogenetics when co-administered with ICS. No pharmacogenetic associations predictive of clinical response to salmeterol or salmeterol co-administered with FP have been identified in our exploratory retrospective analyses performed to date. In one such study, the *ADRB2* Arg16Gly SNP was evaluated in subjects with persistent asthma (n=183). Following 12-weeks of chronic dosing with salmeterol administered with FP in a single device, no differences in AM PEF were observed across Arg16Gly genotypes (Figure 9a).⁹⁰ In another study, Arg16Gly effects were not associated with changes in response to FEV₁ over 12 hours, regardless of baseline ICS therapy (Figure 9b).⁹¹

Figure 9a Change from Baseline in AM PEF During the 12-week Treatment Period and Run-Out

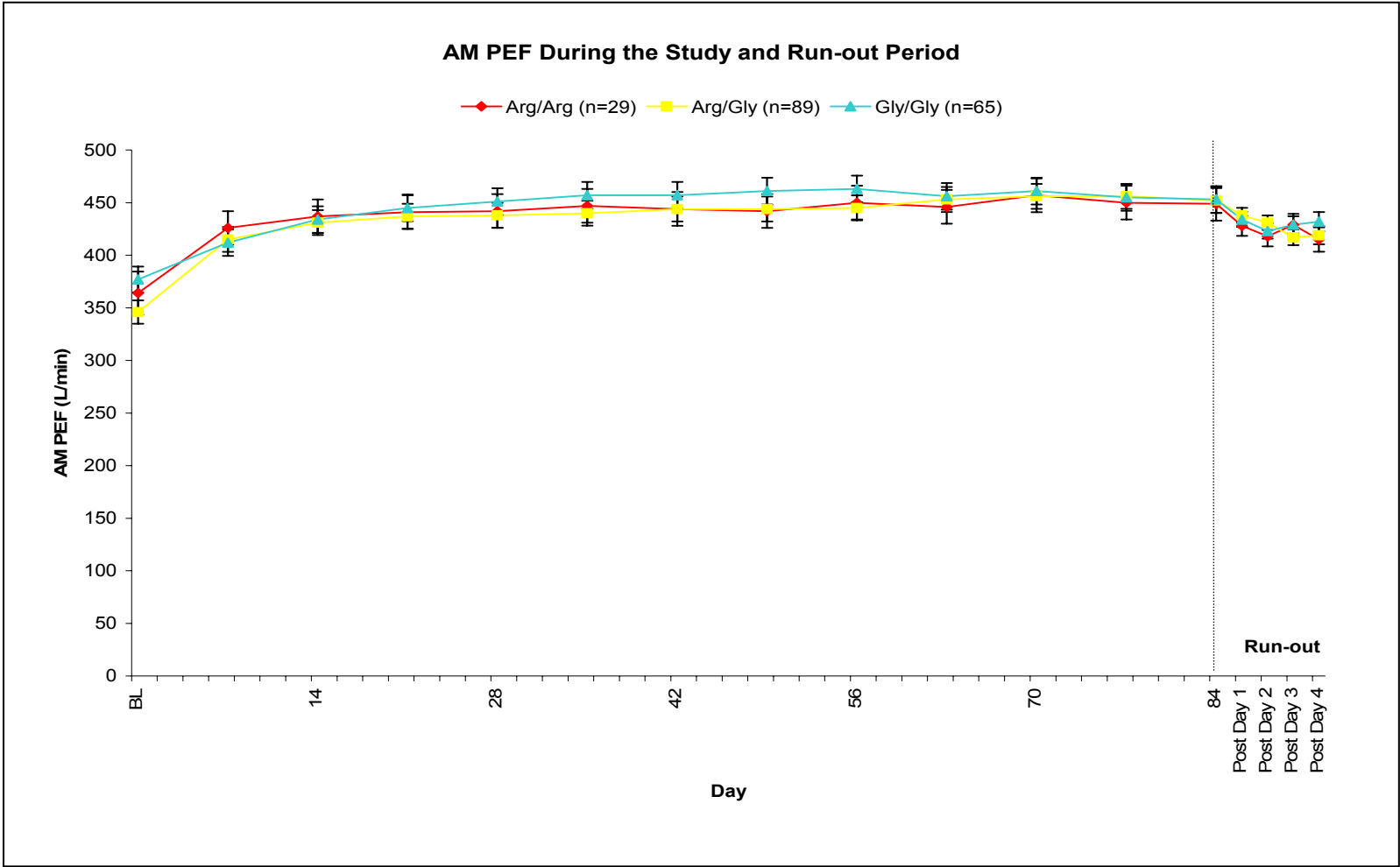
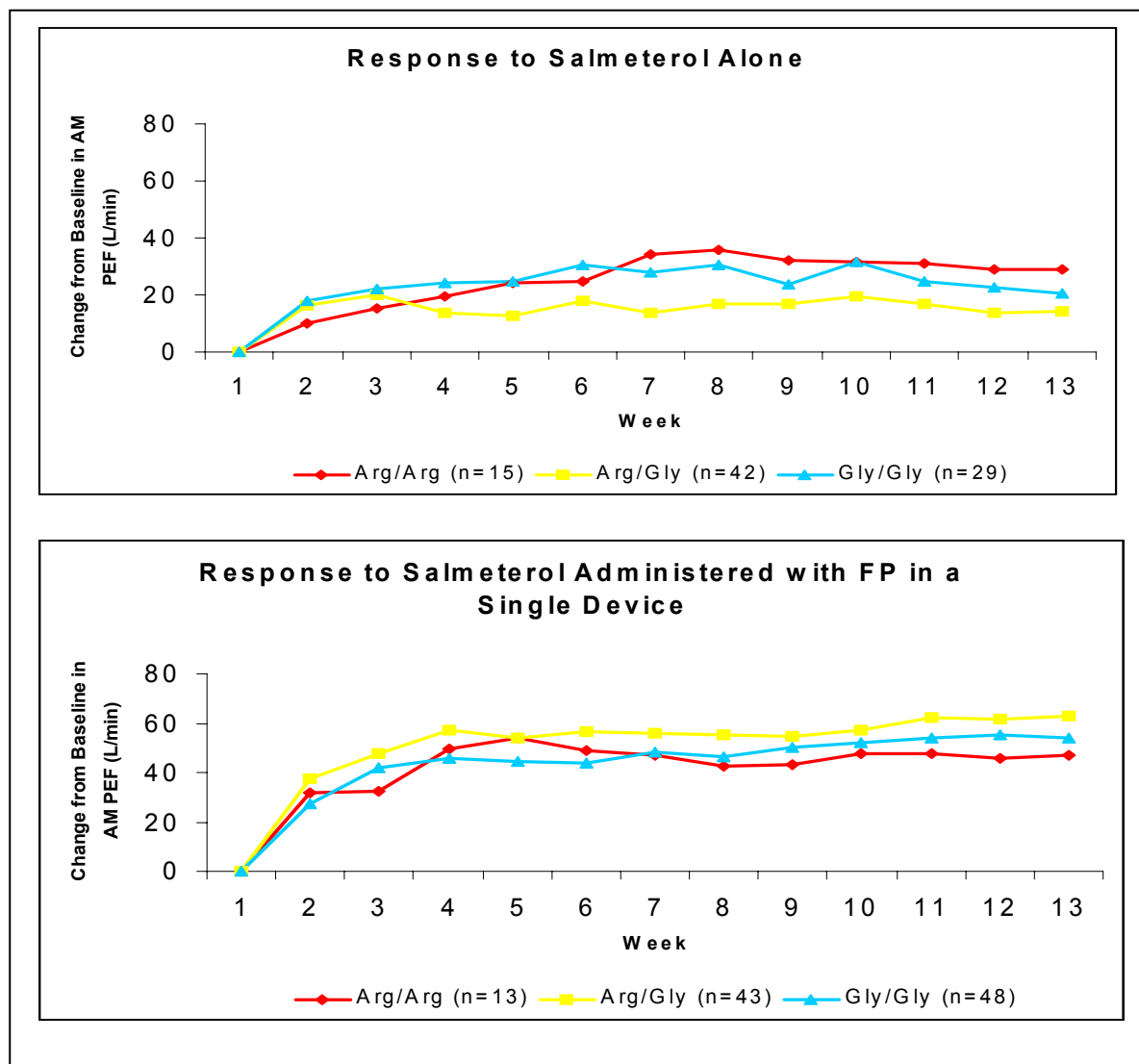


Figure 9b **Response of Salmeterol Alone and Salmeterol Administered with FP in a Single Device Following 12 Weeks of Therapy**



Beta₂-agonist pharmacogenetics in COPD patients are less well defined, especially given the difficulty of quantifying response phenotypes in this disease. Preliminary analyses have not identified pharmacogenetic associations.⁹²

10. ONGOING STUDIES

GlaxoSmithKline is committed to further research to evaluate the safety and efficacy of salmeterol. While no single trial design is sufficient for evaluating rare events such as mortality in patients with asthma this is not the case with COPD where regrettably, mortality is a relatively more common outcome. We believe that the currently ongoing asthma and COPD studies outlined below will provide additional valuable information regarding the safety and efficacy of salmeterol in patients with either asthma or COPD.

10.1. Randomized Controlled Trials

- **SFA103153:** This ongoing, randomized, double-blind, parallel group, 62-week study is examining the incidence of severe asthma-related events (asthma exacerbations) and other measures of overall asthma control (lung function, asthma symptoms, and short-acting beta₂-agonist use), measures of airway inflammatory control (i.e., bronchial hyperresponsiveness, exhaled nitric oxide) and safety in approximately 460 subjects of African descent (12-65 years of age with persistent asthma who are symptomatic while on inhaled corticosteroid therapy) when FP is administered with salmeterol in a single device compared with FP alone. Results are expected mid-2007.
- **SFA100062:** This ongoing randomized, parallel group, double-blind, comparative 38 week trial is examining lung function and other measures of asthma control in approximately 540 adults and adolescents, at least 12 years of age, with persistent asthma, who have either a B16-Arg/Arg, a B16-Gly/Gly or a B16-Arg/Gly *ADRB2* genotype and are treated with FP 100mcg plus salmeterol 50mcg administered in a single device or salmeterol 50mcg alone. Secondary measures include an evaluation of maximum albuterol dose responses (MADR) and haplotype analysis. Safety measurements include the incidence of clinical adverse events and exacerbations. Results are expected in early 2007.
- **SCO30003 (Towards a Revolution in COPD Health [TORCH])**⁹³: This ongoing, global, multi-center, randomized, double-blind, parallel group, placebo-controlled study is investigating the long-term effects of FP 500mcg plus salmeterol 50mcg in a single device, salmeterol 50mcg, FP 500mcg, or placebo on the survival of approximately 6200 subjects with chronic obstructive pulmonary disease (COPD) over 3 years of treatment. Results are expected mid-2006.

10.2. Observational Studies

- **EPI40215:** This study will use Medicaid data to examine racial variation and the association of asthma-related prescription medication use with asthma-related ER visits, hospitalizations, and deaths. This first phase (ongoing) will provide descriptive analysis of the asthmatic population, patterns of prescribing, and outcomes. If there are sufficient numbers of cases for analysis, this will be followed by a full study to analyze racial differences in the association between asthma outcomes and exposure to treatment, including salmeterol, and to test for effect modification by concomitant use of inhaled corticosteroids.

10.3. Exploratory Pharmacogenetic Analyses

- A collection of approximately 1000 subjects from the clinical trials with salmeterol, fluticasone or salmeterol plus FP has been assembled and will be extensively genotyped for polymorphisms in the beta₂-adrenergic receptor and glucocorticoid pathway. These genotypes will be used to evaluate any relationship between SNPs and haplotypes and responses to therapy with salmeterol.

11. BENEFIT-TO-RISK PROFILE

Asthma is estimated to affect 12% of the US population and the number of deaths due to asthma is approximately 5,000 annually. Published studies have suggested a progressive increase in asthma-related mortality rates from 1980 to the mid-1990's, with evidence of a decline from 1998-2001.²⁹ Some risk factors associated with asthma-related death include, excessive reliance of rescue medications, under use of anti-inflammatory asthma medications, disease severity, pollution, gender, age, substance abuse, delay in seeking care, and ethnic background.⁹⁴ The rate of asthma death in African Americans was approximately 2.5 fold that of Caucasians.²⁹ Although African Americans make up only 12% of the US population, they account for 24% of all asthma-related deaths.²⁹

While there is no cure for asthma, pharmacotherapy represents a key element for any asthma management program. Salmeterol represents an important contribution to the therapeutic armamentarium for the treatment of asthma and COPD. Salmeterol has been shown to improve lung function, symptom control, including nocturnal symptoms, and asthma-related quality of life and to reduce the use of rescue medication as compared with placebo. The effectiveness of salmeterol as a controller medication has been demonstrated in patients with asthma, whether they were treated concomitantly with inhaled corticosteroids or were receiving short-acting beta₂-agonists only.

Inflammation is now recognized as an important pathological feature of asthma and national and international guidelines recommend a step-wise approach to treatment starting with the recommendations for the use of anti-inflammatory controller medications (i.e., inhaled corticosteroids) for all patients with persistent asthma. In part, this recommendation is supported by large, observational studies, in which use of inhaled corticosteroids has been linked to reductions in the risk of hospitalization for asthma^{30,95,96,97}, near fatal asthma^{76,98} and asthma death.^{31,98}

For patients who remain symptomatic despite low-dose ICS therapy, the addition of a long-acting beta₂-agonist is the preferred next step in the asthma treatment algorithm. The evidence to support improved outcomes with inhaled corticosteroids plus long-acting beta₂-agonists compared with inhaled corticosteroids alone has evolved over time and has been established through numerous clinical trials showing improvements in lung function and symptoms, and reductions in albuterol use.^{8,9,10,11,12}

Data regarding an association between salmeterol use and serious asthma episodes or asthma-related death have been seen in SNS and SMART, but a cause and effect relationship or other explanation for the observed association cannot be established from these data. Nonetheless, the prescribing information for salmeterol-containing products provides detailed information about the possibility of these rare events and the substantial therapeutic benefits of salmeterol are firmly established based on clinical trial data.

The reporting of spontaneous events peaked with approvals of salmeterol in the UK and US and with publicity around SMART. In general, the absolute number of spontaneously reported events (including fatal events) is low and has not increased relative to exposure to salmeterol. In addition, large population-based studies have not shown an

association between salmeterol and rare serious asthma episodes or asthma-related death.

When a pharmacological mechanism has not been established, other factors not associated with the pharmacological effects of salmeterol may influence rare serious asthma episodes or asthma-related deaths. Patient factors, such as appropriate adherence to medications, limited access to medical care, delay in seeking medical care, and smoking are all associated with risk for rare, serious asthma episodes or asthma-related deaths. In addition, there are conflicting data to suggest that specific genetic variations may be associated with an altered pharmacological response to some β_2 -agonists.

In light of what remains unknown, GlaxoSmithKline remains committed to the ongoing surveillance of salmeterol and continues to gather additional valuable information regarding its safety and efficacy. Specifically, 1) a prospective clinical trial has been initiated to examine whether measures of safety, overall asthma control and airway inflammatory control are comparable in African American subjects with persistent asthma when salmeterol is used with FP compared with FP alone; and, 2) a prospective clinical trial has been initiated to identify whether genetic polymorphisms are associated with asthma outcomes; and, 3) an observational study has been initiated to evaluate if there is an association between salmeterol exposure and asthma morbidity and mortality in African American and Caucasian subjects with asthma. Finally, GlaxoSmithKline is also conducting a study to evaluate the potential effect of salmeterol on all-cause mortality in patients with COPD.

Based on a comprehensive review of the safety and efficacy of salmeterol, GlaxoSmithKline firmly believes that salmeterol continues to exhibit a favorable benefit-to-risk profile. Salmeterol offers an important therapeutic option for patients and clinicians and has been shown to improve the level of care in patients with asthma and COPD.

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1. APPENDIX

1.1. US Phase II to IV Multi-dose Studies Evaluating Salmeterol

	Study	Design	Age	Duration (weeks)	Formulation	Patients on salmeterol 50mcg BID (n)
1	SLG201	R, DB, PG	A	1	Aerosol	33
2	SLGA2004	R, DB, PG	A	4	Powder	141
3	SMS20010	R, DB, X	P	1	Aerosol	19
4	SMS20011	R, DB, X	P	1	Aerosol	20
5	SLD311	R, DB, PG	A	12	Aerosol	80
6	SLD312	R, DB, PG	A	12	Aerosol	69
7	SLD320	R, DB, PG	A	52	Aerosol	176
8	SLD390	R, DB, PG	P	12	Aerosol	102
9	SLG311	R, DB, PG	A	12	Aerosol	78
10	SLG312	R, DB, PG	A	12	Aerosol	106
11	SMS30076	R, DB, PG	P	4	Aerosol	113
12	SMS30077	R, DB, PG	P	4	Aerosol	31
13	FLTA3015	R, DB, PG	A	4	Aerosol	67
14	SLG400	R, DB, PG	A	52	Aerosol	149
15	SFCA3002	R, DB, PG	A	12	Powder	92
16	SFCA3003	R, DB, PG	A	12	Powder	88
17	SLG410	R, DB, PG	A	12	Aerosol	78
18	SLG411	R, DB, PG	A	12	Aerosol	84
19	SLGA3009	R, O	A	52	Powder	408
20	SLGA3010	R, DB, PG	A	12	Powder	159
21	SLGA3011	R, DB, PG	A	12	Powder	172
22	SLG3014	R, DB, PG	P	12	Powder	109
23	SAS30001	R, DB, PG	A	12	Aerosol	91
24	SAS30003	R, DB, PG	A	12	Aerosol	92
25	SAS30004	R, DB, PG	A	12	Aerosol	91
26	SAS30017	R, DB, PG	A	12	Powder	90
27	FLTA4021	R, DB, PG	A	12	Aerosol	118
28	FLTA4022	R, DB, PG	A	12	Aerosol	113
29	SLGA5001	R, DB, PG	A	12	Aerosol	126
30	SLGA5002	R, DB, PG	A	12	Aerosol	135
31	SLGA5003	R, DB, PG	A	12	Aerosol	140
32	SLGA5004	R, DB, PG	A	12	Aerosol	139
33	SLGA5005	R, DB, PG	A	12	Aerosol	137
34	SLGA5006	R, DB, PG	A	12	Aerosol	126
35	SLGA5007	R, DB, PG	A	12	Aerosol	123
36	SLGA5008	R, DB, PG	A	12	Aerosol	117
37	SLGA5013	R, DB, PG	A	26	Aerosol	103
38	SLGA5014	R, DB, PG	A	26	Aerosol	99
39	SLGA5015	R, DB, PG	A	26	Aerosol	110
40	SLGA5016	R, DB, PG	A	26	Aerosol	128
41	SLGA5017	R, DB, PG	A	26	Aerosol	239
42	SLGA5018	R, DB, PG	A	26	Aerosol	260
43	SLGA5019	R, DB, X	A	4	Aerosol	23
44	SLGA5020	R, DB, X	A	4	Aerosol	24
45	SLGA5021	R, DB, PG	A	24	Aerosol	246
46	SLGA5022	R, DB, PG	A	24	Aerosol	221
47	SLGA5024	R, DB, PG	A	4	Aerosol	156

	Study	Design	Age	Duration (weeks)	Formulation	Patients on salmeterol 50mcg BID (n)
48	SLGA5025	R, DB, PG	A	4	Aerosol	133
49	SMS40003	R, DB, PG	A	12	Powder	240
50	SMS40004	R, DB, PG	A	12	Powder	236
51	SAS40036	R, DB, PG	A	16	Powder	152
52	SAS40037	R, DB, PG	A	16	Powder	160
Total Subjects						6542

R=randomized, DB=double-blind, PG=parallel-group, X=cross-over, A=adult, P=pediatric, O=open-label

PREScribing INFORMATION

SEREVENT[®] DISKUS[®]

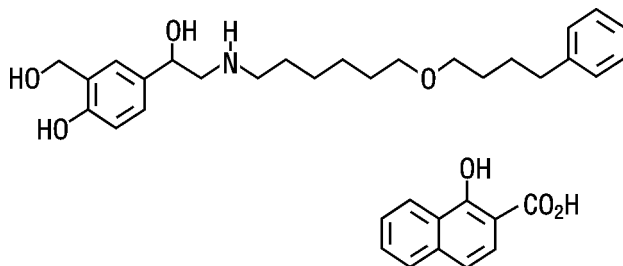
(salmeterol xinafoate inhalation powder)

FOR ORAL INHALATION ONLY

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 13,176 patients treated for 28 weeks) versus those on placebo (3 of 13,179) (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 to off-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 selective, 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 adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

In vitro tests show that 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 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 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.

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.

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). 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

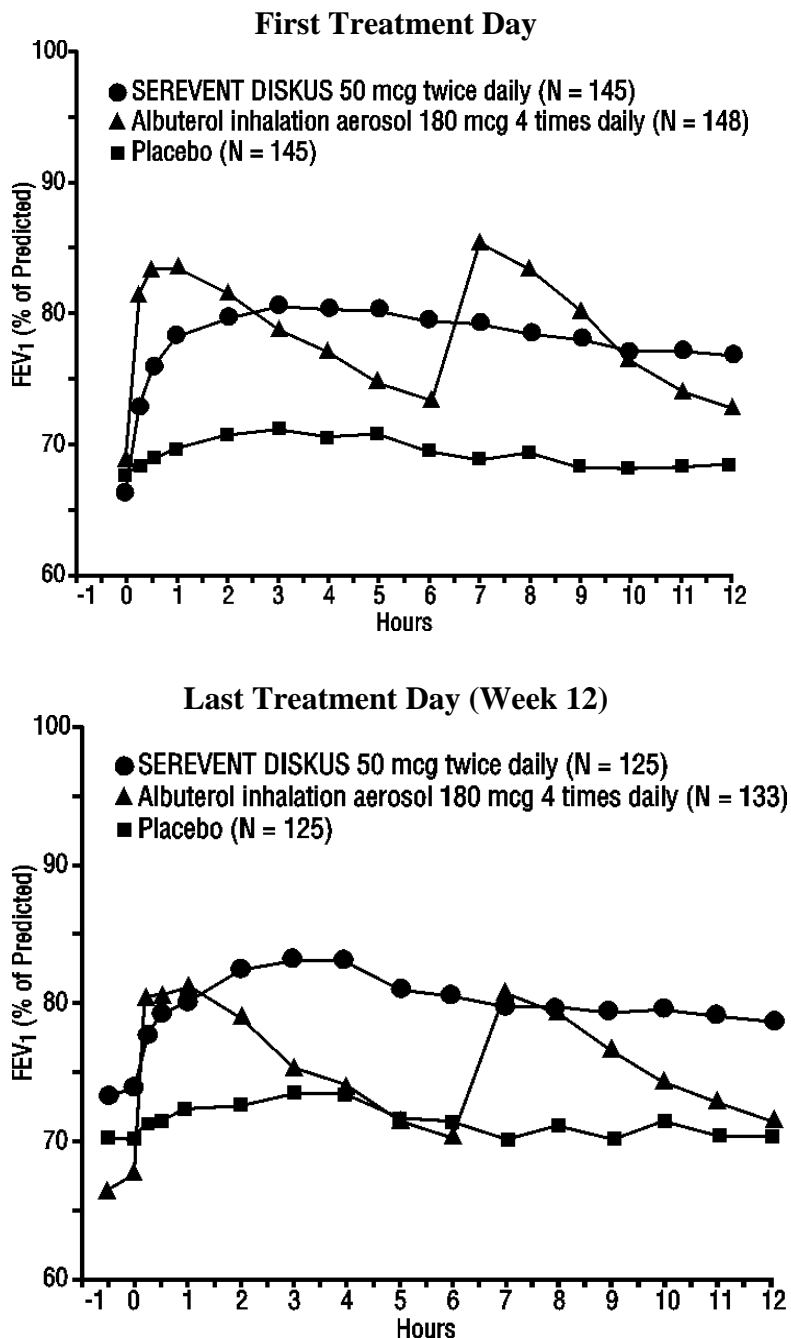


Table 1 shows the treatment effects seen during daily treatment with SEREVENT DISKUS for 12 weeks in adolescent and adult patients with mild-to-moderate asthma.

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 ($p < 0.001$).

Safe usage with 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	<u>% Fall in FEV₁</u>				
postdose	<10%	15	29	31	60
exercise	≥10%, <20%	3	6	11	21
challenge	≥20%	34	65	10	19
Mean maximal % fall in FEV ₁ (SE)		-25% (1.8)		-11% (1.9)	
8.5-Hour	<u>% Fall in FEV₁</u>				
postdose	<10%	12	23	26	50
exercise	≥10%, <20%	7	13	12	23
challenge	≥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. The primary endpoint was the combined number of respiratory-related deaths or respiratory-related life-threatening experiences (intubation and mechanical ventilation). Secondary endpoints included combined asthma-related deaths or life-threatening experiences and asthma-related deaths. A planned interim analysis was conducted when approximately half of the intended number of patients had been enrolled (N = 26,355).

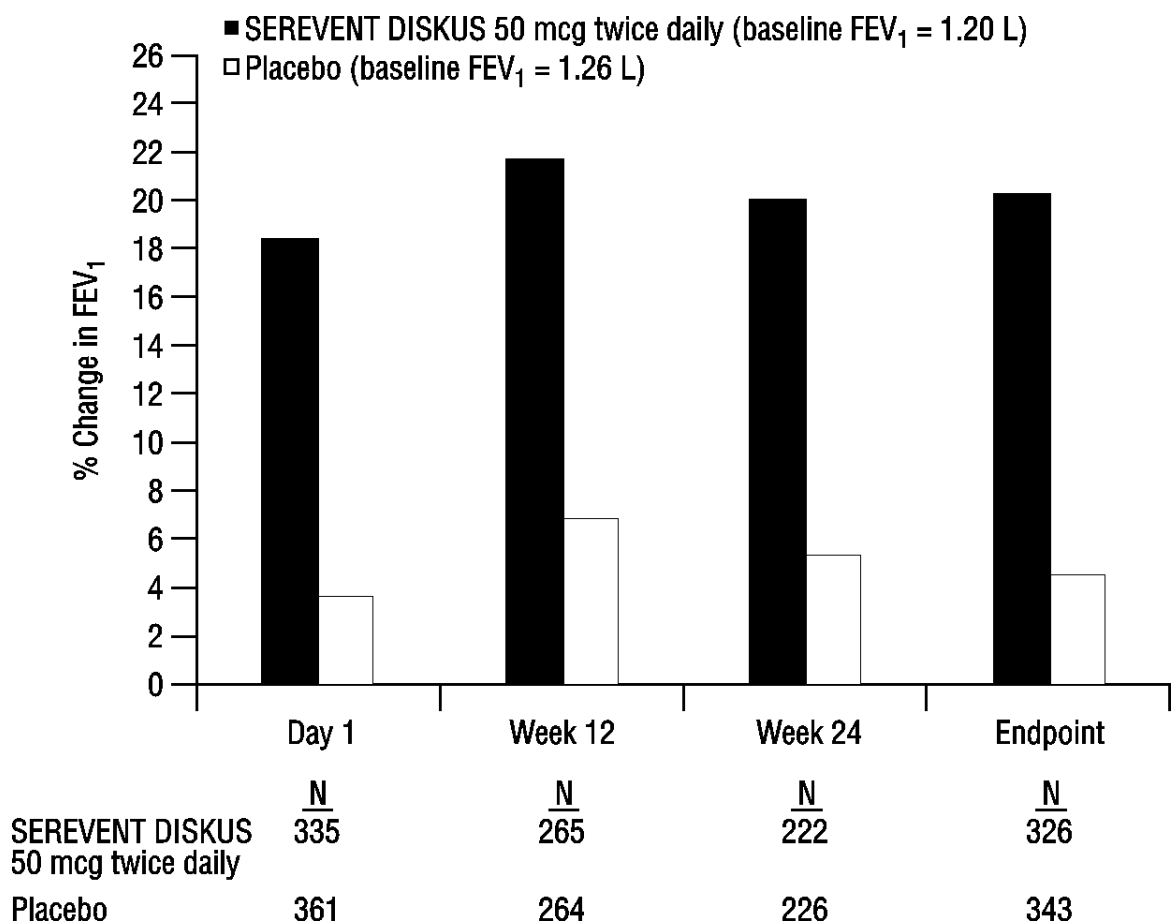
Due to the low rate of primary events in the study, the findings of the planned interim analysis were not conclusive. However, analyses of secondary endpoints suggested that patients receiving salmeterol may be at increased risk for some of these events compared to patients receiving placebo. The analysis for the total population showed a relative risk of 1.40 (95% CI 0.91, 2.14) for the primary endpoint in the salmeterol group relative to the placebo group (50 out of 13,176 vs. 36 out of 13,179, respectively). In the total population, a higher number of asthma-related deaths (13 vs. 3, RR 4.37, 95% CI 1.25, 15.34) and combined asthma-related deaths or life-

threatening experiences (37 vs. 22, RR 1.71, 95% CI 1.01, 2.89) occurred in patients treated with salmeterol than those treated with placebo. The analysis of the African American subgroup showed a relative risk of 4.10 (95% CI 1.54, 10.90) for the primary endpoint in patients treated with salmeterol relative to those treated with placebo (20 out of 2,366 vs. 5 out of 2,319, respectively). In African Americans, a higher number of asthma-related deaths (7 vs. 1, RR 7.26, 95% CI 0.89, 58.94) and combined asthma-related deaths or life-threatening experiences (19 vs. 4, RR 4.92, 95% CI 1.68, 14.45) occurred in patients treated with salmeterol than those treated with placebo. Analysis of the Caucasian population showed a relative risk of 1.05 (95% CI 0.62, 1.76) for the primary endpoint for those treated with salmeterol relative to those treated with placebo (29 out of 9,281 vs. 28 out of 9,361, respectively). In Caucasians, a higher number of asthma-related deaths (6 vs. 1, RR 5.82, 95% CI 0.70, 48.37) occurred in patients treated with salmeterol than in patients treated with placebo. In Caucasians, the relative risk was 1.08 (17 vs. 16, 95% CI 0.55, 2.14) for combined asthma-related deaths or life-threatening experiences in patients treated with salmeterol relative to placebo. The numbers of patients from other ethnic groups were too small to draw any conclusions in these populations. Even though SMART did not reach predetermined stopping criteria for the total population, the study was stopped due to the findings in African American patients and difficulties in enrollment.

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.

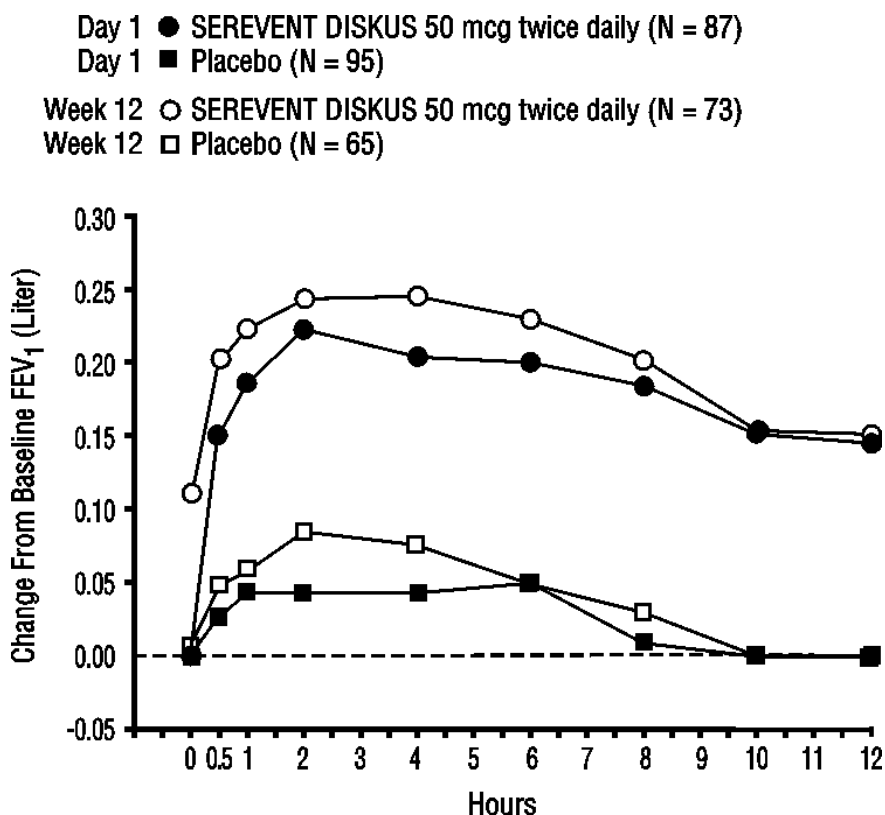
Figure 2 displays the integrated 2-hour postdose FEV₁ results from the 2 clinical trials. The percent change in FEV₁ refers to the change from baseline, defined as the predose value on Treatment Day 1. To account for patient withdrawals during the study, Endpoint (last evaluable FEV₁) data are provided. 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 2. 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 3](#), evidence of bronchodilatation was seen throughout the 12-hour period. [Figure 3](#) 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 3. 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, who require regular treatment with inhaled, short-acting beta₂-agonists. It is not indicated for patients whose asthma can be managed by 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.

SEREVENT DISKUS may be used alone or in combination with inhaled or systemic corticosteroid therapy.

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

DATA FROM A LARGE PLACEBO-CONTROLLED SAFETY STUDY THAT WAS STOPPED EARLY SUGGEST THAT SALMETEROL MAY BE ASSOCIATED WITH RARE SERIOUS ASTHMA EPISODES OR ASTHMA-RELATED DEATHS. Data from this study, called the Salmeterol Multi-center Asthma Research Trial (SMART), further suggest that the risk might be greater in African American patients. These results led to stopping the study prematurely (see CLINICAL TRIALS: Asthma: *Salmeterol Multi-center Asthma Research Trial*). The data from the SMART study are not adequate to determine whether concurrent use of inhaled corticosteroids provides protection from this risk. Given the similar basic mechanisms of action of beta₂-agonists, it is possible that the findings seen in the SMART study may be consistent with a class effect.

Findings similar to the SMART study findings were reported in a prior 16-week clinical study performed in the United Kingdom, the Salmeterol Nationwide Surveillance (SNS) study. In the SNS study, the incidence of asthma-related death was numerically, though not statistically, greater in patients with asthma treated with salmeterol (42 mcg twice daily) versus albuterol (180 mcg 4 times daily) added to usual asthma therapy.

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 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 as well as warn them that increasing inhaled beta₂-agonist use is a signal of deteriorating asthma.

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 Patient's Instructions for Use accompanying the product.)

1. Do Not Introduce SEREVENT DISKUS 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 or simply failed to relieve the deteriorating asthma.

2. Do Not Use SEREVENT DISKUS 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. Watch for Increasing Use of Inhaled, Short-Acting Beta₂-Agonists, Which Is a Marker of Deteriorating Asthma or COPD: 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. Do Not Use SEREVENT DISKUS as a Substitute for Oral or Inhaled Corticosteroids: The use of beta-adrenergic agonist bronchodilators alone may not be adequate to control asthma in many

patients. Early consideration should be given to adding anti-inflammatory agents, e.g., 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. Patients who already require oral or inhaled corticosteroids for treatment of asthma should be continued on a suitable dose 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).

5. Do Not Exceed Recommended Dosage: 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.

6. 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 with a short-acting, inhaled bronchodilator; SEREVENT DISKUS should be discontinued immediately; and alternative therapy should be instituted.

7. Immediate Hypersensitivity Reactions: Immediate hypersensitivity reactions may occur after administration of SEREVENT DISKUS, as demonstrated by cases of urticaria, angioedema, rash, and bronchospasm.

8. Upper Airway Symptoms: Symptoms of laryngeal spasm, irritation, or swelling, such as stridor and choking, have been reported in patients receiving SEREVENT DISKUS.

9. 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.

PRECAUTIONS

General: 1. Cardiovascular and Other 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.

2. 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 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. 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.
2. 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, you should instruct them not to exceed the recommended dose of 1 inhalation twice daily, morning and evening. You should instruct them to contact you or the pharmacist if they have questions.
3. 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).
4. Patients should not stop therapy with SEREVENT DISKUS for asthma or COPD without physician/provider guidance since symptoms may worsen after discontinuation.
5. • 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.

6. The physician should be notified immediately if any of the following situations occur, which may be a sign of seriously worsening asthma or COPD:
 - 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.
7. 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.
8. Patients should be cautioned regarding adverse effects associated with beta₂-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.
9. When patients are prescribed SEREVENT DISKUS, other medications for asthma and COPD should be used only as directed by the physician.
10. SEREVENT DISKUS should not be used with a spacer device.
11. Patients who are pregnant or nursing should contact the physician about the use of SEREVENT DISKUS.
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 Patient's Instructions for Use accompanying the product.

Drug Interactions: *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/m^2 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/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 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/m^2 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/m^2 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/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. 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

Adverse reactions to salmeterol are similar in nature to reactions to 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).

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 3 reports the incidence of adverse events in these 2 studies.

Table 3. 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 3 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 ≥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 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.

Table 4. 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 might otherwise 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 5), 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 5. 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 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 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.

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 no. 1), 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 or simply failed to relieve the deteriorating asthma.

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 Patient's Instructions for Use). The patient must not exhale into the DISKUS and the DISKUS should only be activated and used in a level, horizontal position.

Asthma: 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 and additional therapeutic options, such as inhaled or systemic corticosteroids, should be considered. 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 teal green, disposable 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 overwrap 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.



GlaxoSmithKline
Research Triangle Park, NC 27709

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PREScribing INFORMATION

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)

* As salmeterol xinafoate salt 72.5 mcg, equivalent to salmeterol base 50 mcg

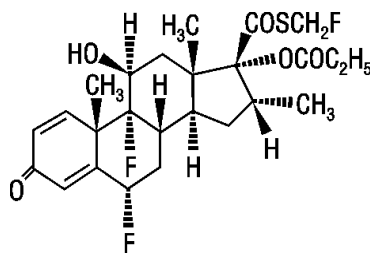
For Oral Inhalation Only

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 13,176 patients treated for 28 weeks) versus those on placebo (3 of 13,179) (see WARNINGS).

DESCRIPTION

ADVAIR DISKUS 100/50, ADVAIR DISKUS 250/50, and ADVAIR DISKUS 500/50 are combinations of fluticasone propionate and salmeterol xinafoate.

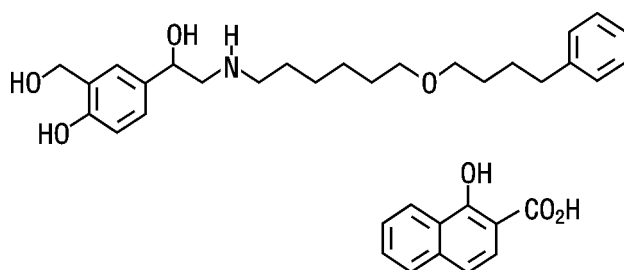
One active component of ADVAIR DISKUS is fluticasone propionate, a corticosteroid having the chemical name *S*-(fluoromethyl) 6 α ,9-difluoro-11 β ,17-dihydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carbothioate, 17-propionate and the following chemical structure:



Fluticasone propionate is a white to off-white powder with a molecular weight of 500.6, and the empirical formula is C₂₅H₃₁F₃O₅S. 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 to off-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 forced expiratory volume in 1 second [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.

CLINICAL PHARMACOLOGY

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, 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.

Inflammation is also a component in the pathogenesis of chronic obstructive pulmonary disease (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 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: ADVAIR DISKUS: Adult and Adolescent Patients 12 Years of Age and Older: Following administration of ADVAIR DISKUS to healthy adult subjects, peak plasma concentrations of fluticasone propionate were achieved in 1 to 2 hours and those of salmeterol were achieved in about 5 minutes.

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, and of salmeterol averaged 200 and 150 pg/mL, respectively, indicating no significant changes in systemic exposures of fluticasone propionate and salmeterol.

In a repeat-dose study, the highest recommended dose of ADVAIR DISKUS was administered to 45 adolescent and adult patients with asthma. One (1) inhalation twice daily of the following treatments was administered: ADVAIR DISKUS 500/50, fluticasone propionate powder 500 mcg and salmeterol powder 50 mcg given concurrently, or fluticasone propionate powder 500 mcg alone. Mean peak steady-state plasma concentrations of fluticasone propionate averaged 57, 73, and 70 pg/mL, respectively, indicating no significant changes in systemic exposure of fluticasone propionate. No plasma concentrations of salmeterol were measured in this repeat-dose study.

No significant changes in excretion of fluticasone propionate or salmeterol were observed. The terminal half-life of fluticasone propionate averaged 5.33 to 7.65 hours when ADVAIR DISKUS was administered, which is similar to that reported when fluticasone propionate was given concurrently with salmeterol or when fluticasone propionate was given alone (average, 5.30 to 6.91 hours). No terminal half-life of salmeterol was reported upon administration of ADVAIR DISKUS or salmeterol given concurrently with fluticasone propionate.

Pediatric Patients: In a clinical study conducted in patients with asthma aged 4 to 11 years, fluticasone propionate concentrations were obtained in 61 patients at 20 and 40 minutes after dosing with 50 and 100 mcg of fluticasone propionate inhalation powder twice daily using the DISKUS. Plasma concentrations were low and ranged from undetectable (about 80% of the plasma samples) to 88 pg/mL. Mean peak fluticasone propionate plasma concentrations at the 50- and 100-mcg dose levels were 5 and 8 pg/mL, respectively.

Special Populations: Formal pharmacokinetic studies using ADVAIR DISKUS have not been conducted to examine gender differences or in special populations, such as elderly patients or patients with hepatic or renal impairment.

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.

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. The systemic bioavailability of fluticasone propionate from the DISKUS device in healthy volunteers averages 18%.

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.

Peak steady-state fluticasone propionate plasma concentrations in subjects with COPD averaged 53 pg/mL (range, 19.3 to 159.3 pg/mL) after treatment with 250 mcg twice daily (N = 30) via the DISKUS device.

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 91%. 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: Hepatic Impairment: Since fluticasone propionate is predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of fluticasone propionate in plasma. Therefore, patients with hepatic disease should be closely monitored.

Gender: 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.

Age: 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.

Other: Formal pharmacokinetic studies using fluticasone propionate have not been conducted in other special populations.

Drug Interactions: Fluticasone propionate is a substrate of cytochrome P450 3A4. Coadministration of fluticasone propionate and the highly potent 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 plasma fluticasone propionate exposure resulted in a significant decrease (86%) in plasma cortisol area under the plasma concentration versus time curve (AUC).

Caution should be exercised when other potent 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 plasma 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 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 was detected in either urine or feces.

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.

Special Populations: Hepatic Impairment: Since salmeterol is predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of salmeterol in plasma. Therefore, patients with hepatic disease should be closely monitored.

Other: Formal pharmacokinetic studies using salmeterol base have not been conducted in other special populations.

Pharmacodynamics: ADVAIR DISKUS: Adult and Adolescent Patients: 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 hypothalamic-pituitary-adrenal (HPA) axis was also evaluated in these studies. 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: 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.

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 plasma 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.

Chronic Obstructive Pulmonary Disease: In clinical studies with ADVAIR DISKUS in patients with COPD associated with chronic bronchitis, 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 subjects (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 subjects had a prolonged QTc interval at baseline.

In a 24-week study, 130 patients with COPD associated with chronic bronchitis 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).

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.

Pediatric Patients: 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.

Fluticasone Propionate: Asthma: 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: In a 24-week study, the steady-state fluticasone propionate pharmacokinetics and serum cortisol levels were described in a subset of patients with COPD associated with chronic bronchitis (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 following at least 4 weeks of dosing. Serum cortisol concentrations following 250 and 500 mcg twice-daily dosing were 10% and 21% lower than placebo, indicating a dose-dependent increase in systemic exposure to fluticasone propionate.

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 (see PRECAUTIONS: General). 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.

Asthma: 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.

Chronic Obstructive Pulmonary Disease: In 24-week clinical studies in patients with COPD associated with chronic bronchitis, 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 subjects).

No significant differences with salmeterol 50 mcg alone or in combination with fluticasone propionate as ADVAIR DISKUS 500/50 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 = 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 (see ADVERSE REACTIONS: Chronic Obstructive Pulmonary Disease Associated With Chronic Bronchitis).

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: Adult and Adolescent Patients 12 Years of Age and Older: In clinical trials comparing ADVAIR DISKUS with the 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.

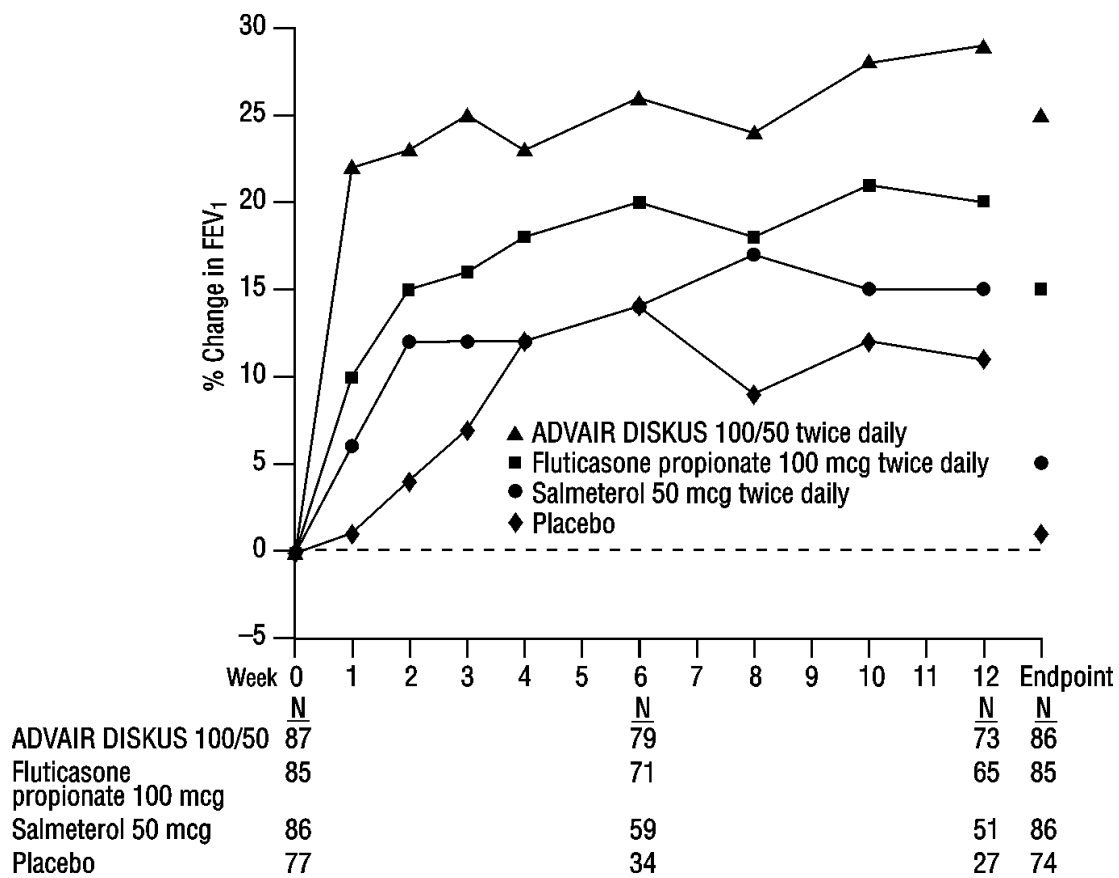
Predefined withdrawal criteria for lack of efficacy, an indicator of worsening asthma, were utilized for this placebo-controlled study. Worsening asthma was defined as a clinically important decrease in FEV₁ or peak expiratory flow (PEF), increase in use of VENTOLIN[®] (albuterol, USP) Inhalation Aerosol, 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 DISKUS 100/50 were withdrawn due to worsening asthma compared with fluticasone propionate, salmeterol, and placebo.

Table 1. 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 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 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 1. 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 2](#).

Table 2. 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 to 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.

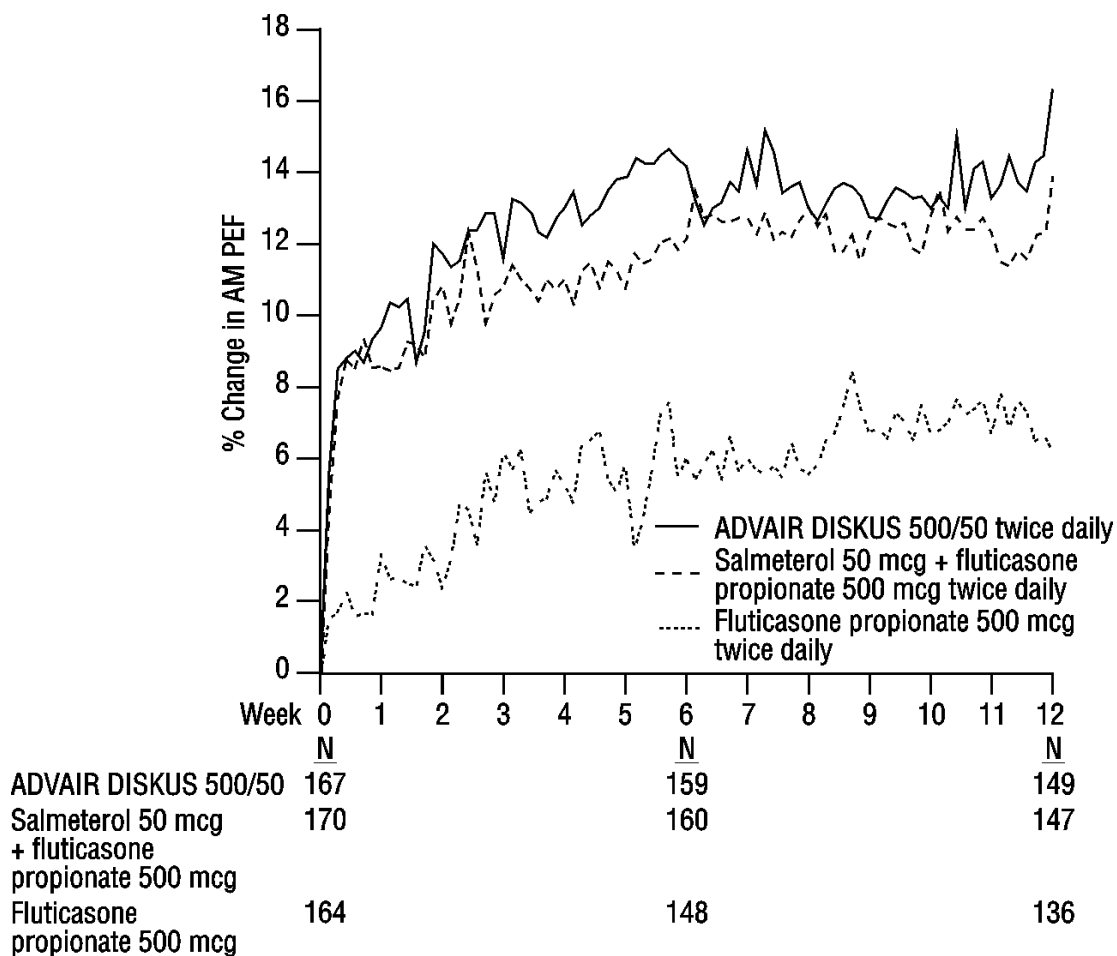
Efficacy results in this study were similar to those observed in Study 1. Patients receiving ADVAIR DISKUS 250/50 had significantly greater improvements in FEV₁ (0.48 L, 23%) compared with fluticasone propionate 250 mcg (0.25 L, 13%), salmeterol (0.05 L, 4%), and placebo (decrease of 0.11 L, decrease 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 to 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. As shown in Figure 2, 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.

Figure 2. Mean Percent Change From Baseline in Morning Peak Expiratory Flow in Patients With Asthma Previously Treated With Inhaled Corticosteroids (Study 3)



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 FEV₁) in most patients was seen within 30 to 60 minutes. Maximum improvement in FEV₁ generally occurred within 3 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 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 FEV₁ 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)

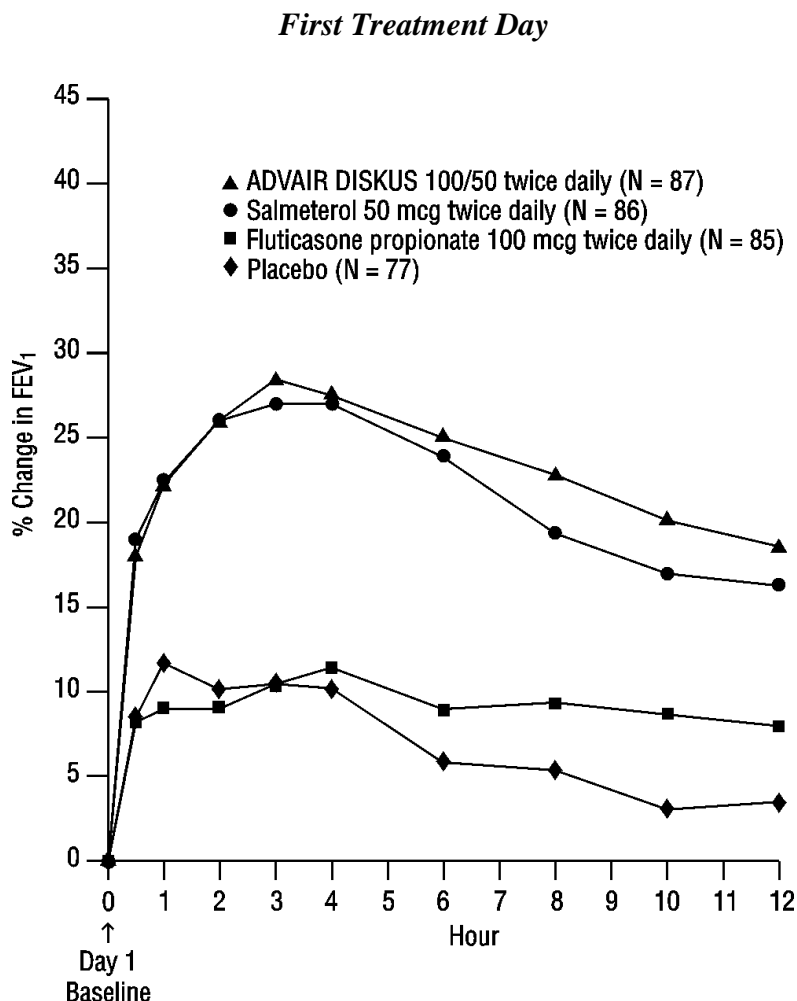
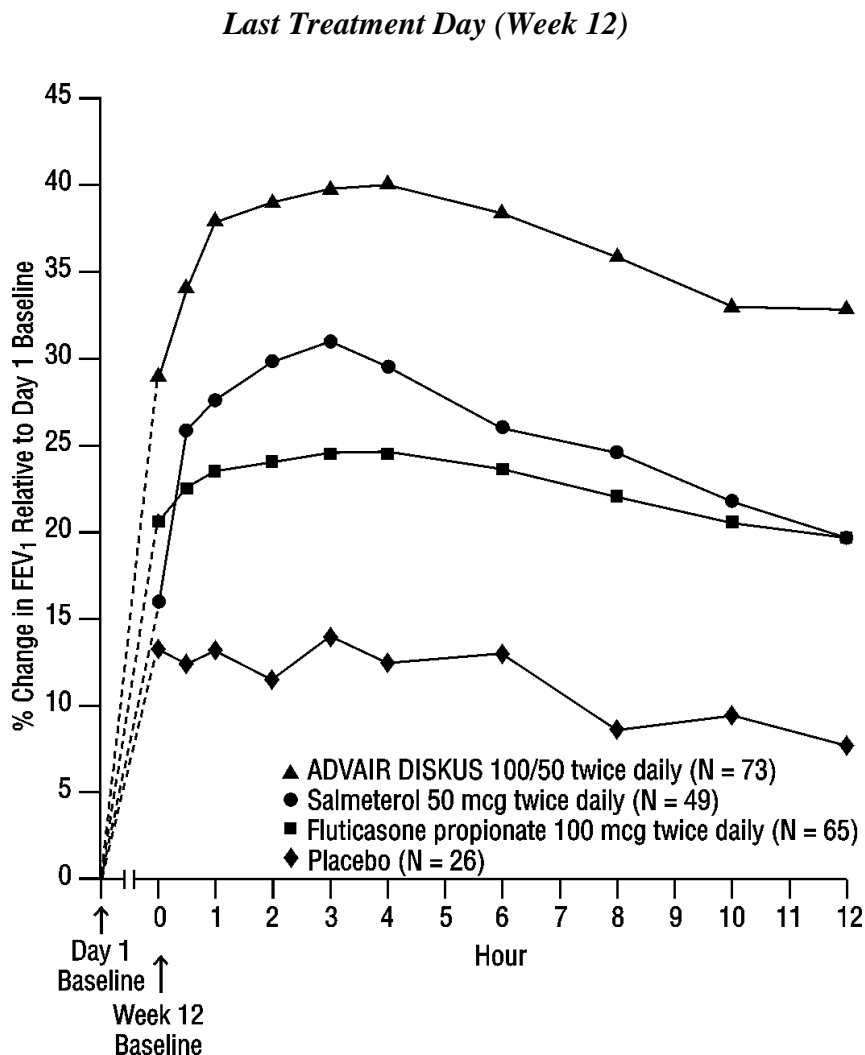


Figure 4. Percent Change in Serial 12-hour FEV₁ in Patients With Asthma Previously Using Either Inhaled Corticosteroids or Salmeterol (Study 1)



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.

Chronic Obstructive Pulmonary Disease Associated With Chronic Bronchitis: In a clinical trial evaluating twice-daily treatment with ADVAIR DISKUS 250/50 in patients with COPD associated with chronic bronchitis, improvements in lung function (as defined by predose and postdose FEV₁) were significantly greater with ADVAIR DISKUS than with fluticasone propionate 250 mcg, salmeterol 50 mcg, or placebo. The study was a randomized, double-blind, parallel-group, 24-week trial. All 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. 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.

Figures 5 and 6 display predose and 2-hour postdose FEV₁ results. 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).

A similar degree of improvement in lung function was also observed with ADVAIR DISKUS 500/50 twice daily.

Figure 5. Predose FEV₁: Mean Percent Change From Baseline in Patients With COPD Associated With Chronic Bronchitis

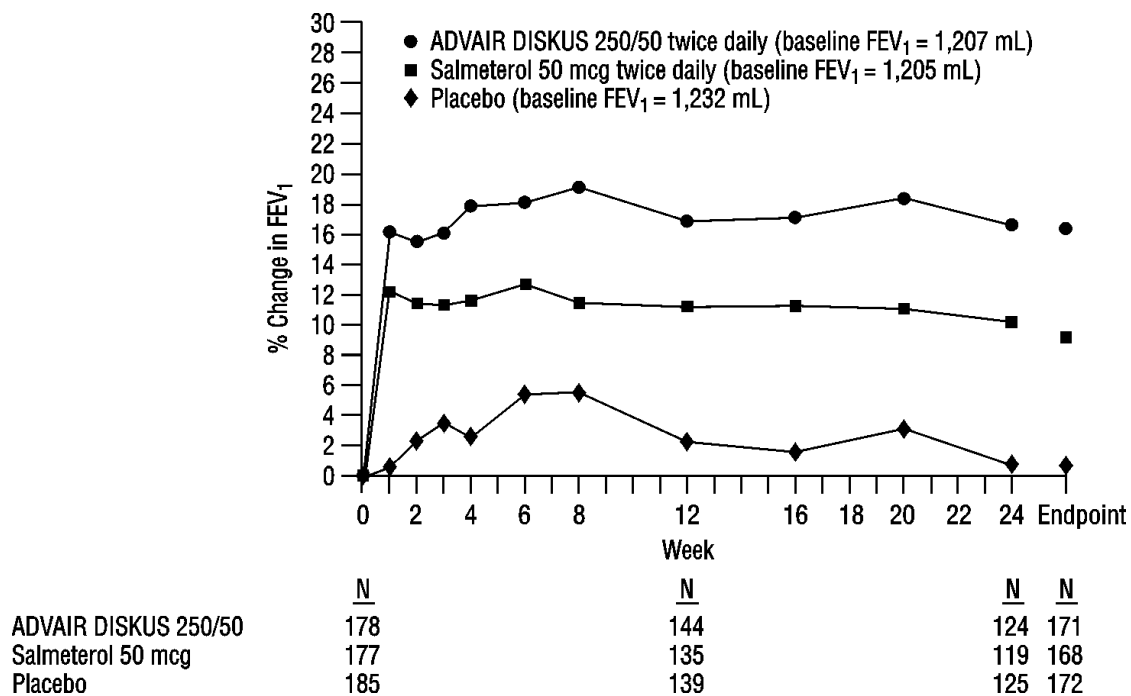
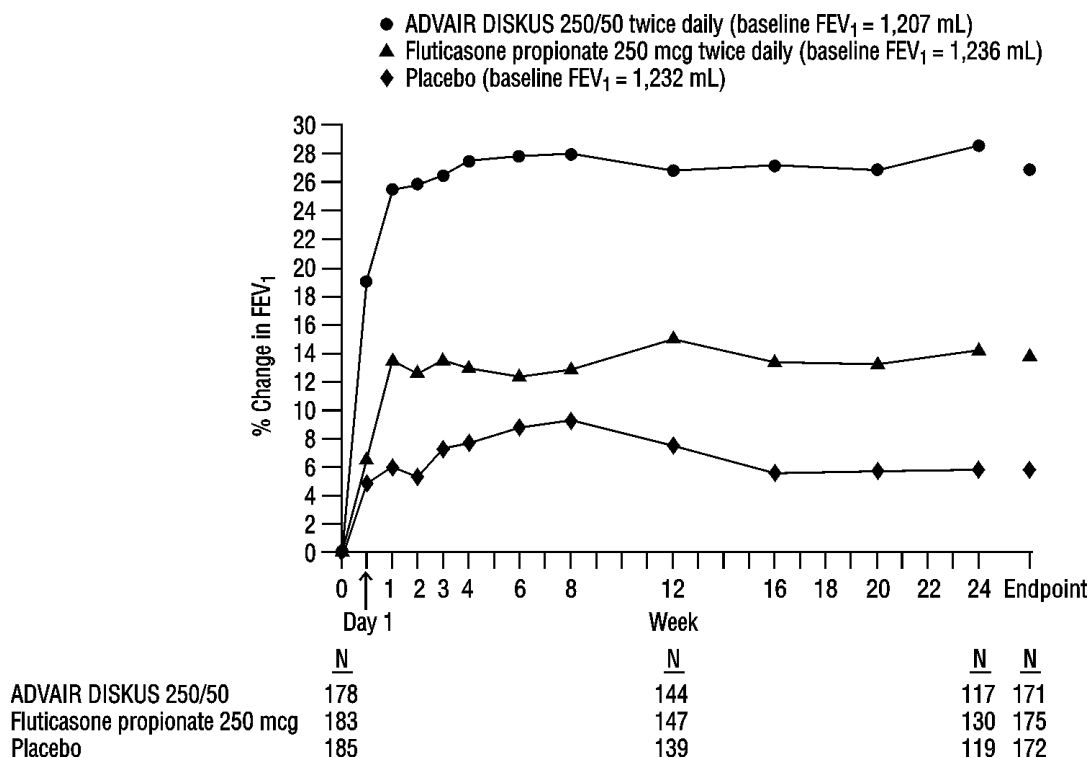


Figure 6. Two-Hour Postdose FEV₁: Mean Percent Changes From Baseline Over Time in Patients With COPD Associated With Chronic Bronchitis



Patients treated with ADVAIR DISKUS 250/50 or ADVAIR DISKUS 500/50 did not have a significant reduction in chronic bronchitis symptoms (as measured by the Chronic Bronchitis Symptom Questionnaire) or in COPD exacerbations compared to patients treated with placebo over the 24 weeks of therapy. The improvement in lung function with ADVAIR DISKUS 500/50 was similar to the improvement seen with ADVAIR DISKUS 250/50. Since there is evidence of more systemic exposure to fluticasone propionate from this higher dose and no documented advantage for efficacy, ADVAIR DISKUS 500/50 is not recommended for use in COPD.

The benefit of treatment of patients with COPD associated with chronic bronchitis with ADVAIR DISKUS 250/50 for periods longer than 6 months has not been evaluated.

INDICATIONS AND USAGE

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

ADVAIR DISKUS is NOT indicated for the relief of acute bronchospasm.

Chronic Obstructive Pulmonary Disease Associated With Chronic Bronchitis:

ADVAIR DISKUS 250/50 is indicated for the twice-daily maintenance treatment of airflow obstruction in patients with COPD associated with chronic bronchitis.

ADVAIR DISKUS 250/50 mcg twice daily is the only approved dosage for the treatment of COPD associated with chronic bronchitis. Higher doses, including ADVAIR DISKUS 500/50,

are not recommended (see DOSAGE AND ADMINISTRATION: Chronic Obstructive Pulmonary Disease Associated With Chronic Bronchitis).

The benefit of treating patients with COPD associated with chronic bronchitis with ADVAIR DISKUS 250/50 for periods longer than 6 months has not been evaluated. Patients who are treated with ADVAIR DISKUS 250/50 for COPD associated with chronic bronchitis for periods longer than 6 months should be reevaluated periodically to assess the continuing benefits and potential risks of treatment.

ADVAIR DISKUS is NOT indicated for the relief of acute bronchospasm.

CONTRAINDICATIONS

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

Hypersensitivity to any of the ingredients of these preparations contraindicates their use (see DESCRIPTION and ADVERSE REACTIONS: Observed During Clinical Practice: *Non-Site Specific*).

WARNINGS

DATA FROM A LARGE PLACEBO-CONTROLLED SAFETY STUDY THAT WAS STOPPED EARLY SUGGEST THAT SALMETEROL, A COMPONENT OF ADVAIR DISKUS, MAY BE ASSOCIATED WITH RARE SERIOUS ASTHMA EPISODES OR ASTHMA-RELATED DEATHS. Data from this study further suggest that the risk might be greater in African American patients. 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 to placebo when added to usual asthma therapy. The primary endpoint was the combined number of respiratory-related deaths or respiratory-related life-threatening experiences (intubation and mechanical ventilation). Secondary endpoints included combined asthma-related deaths or life-threatening experiences and asthma-related deaths.

A planned interim analysis was conducted when approximately half of the intended number of patients had been enrolled (N = 26,355). Due to the low rate of primary events in the study, the findings of the planned interim analysis were not conclusive. However, analyses of secondary endpoints suggested that patients receiving salmeterol may be at increased risk for some of these events compared to patients receiving placebo. The analysis for the total population showed a relative risk of 1.40 (95% CI 0.91, 2.14) for the primary endpoint in the salmeterol group relative to the placebo group (50 out of 13,176 vs. 36 out of 13,179, respectively). In the total population, a higher number of asthma-related deaths (13 vs. 3, RR 4.37, 95% CI 1.25, 15.34) and combined asthma-related deaths or life-threatening experiences (37 vs. 22, RR 1.71, 95% CI 1.01, 2.89) occurred in patients treated with salmeterol than those treated with placebo. The analysis of the African American subgroup showed a relative risk of 4.10 (95% CI 1.54, 10.90) for the primary endpoint in patients treated with salmeterol relative to those treated with placebo (20 out of 2,366

vs. 5 out of 2,319, respectively). In African Americans, a higher number of asthma-related deaths (7 vs. 1, RR 7.26, 95% CI 0.89, 58.94) and combined asthma-related deaths or life-threatening experiences (19 vs. 4, RR 4.92, 95% CI 1.68, 14.45) occurred in patients treated with salmeterol than those treated with placebo. Analysis of the Caucasian population showed a relative risk of 1.05 (95% CI 0.62, 1.76) for the primary endpoint for those treated with salmeterol relative to those treated with placebo (29 out of 9,281 vs. 28 out of 9,361, respectively). In Caucasians, a higher number of asthma-related deaths (6 vs. 1, RR 5.82, 95% CI 0.70, 48.37) occurred in patients treated with salmeterol than in patients treated with placebo. In Caucasians, the relative risk was 1.08 (17 vs. 16, 95% CI 0.55, 2.14) for combined asthma-related deaths or life-threatening experiences in patients treated with salmeterol relative to placebo. The numbers of patients from other ethnic groups were too small to draw any conclusions in these populations. Even though SMART did not reach predetermined stopping criteria for the total population, the study was stopped due to the findings in African American patients and difficulties in enrollment. The data from the SMART study are not adequate to determine whether concurrent use of inhaled corticosteroids, such as fluticasone propionate, a component of ADVAIR DISKUS, provides protection from this risk. Therefore, it is not known whether the findings seen with SEREVENT Inhalation Aerosol would apply to ADVAIR DISKUS. Given the similar basic mechanisms of action of beta₂-agonists, it is possible that the findings seen in the SMART study may be consistent with a class effect.

Findings similar to the SMART study findings were reported in a prior 16-week clinical study performed in the United Kingdom, the Salmeterol Nationwide Surveillance (SNS) study. In the SNS study, the incidence of asthma-related death was numerically, though not statistically, greater in patients with asthma treated with salmeterol (42 mcg twice daily) versus albuterol (180 mcg 4 times daily) added to usual asthma therapy.

1. ADVAIR DISKUS 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 physiological amounts of glucocorticoid 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.

2. ADVAIR DISKUS 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 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, 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 or simply failed to relieve the deteriorating asthma.

3. Drug Interaction With Ritonavir: A drug interaction study in healthy subjects has shown that ritonavir (a highly potent 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* 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.

4. Do Not Use ADVAIR DISKUS to Treat Acute Symptoms: An inhaled, short-acting beta₂-agonist, not ADVAIR DISKUS, should be used to relieve acute symptoms of 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 shortness of breath that occurs acutely, 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. For patients taking ADVAIR DISKUS, inhaled, short-acting beta₂-agonists should only be used for symptomatic relief of acute symptoms of shortness of breath (see PRECAUTIONS: Information for Patients).

5. Watch for Increasing Use of Inhaled, Short-Acting Beta₂-Agonists, Which Is a Marker of Deteriorating Asthma: Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient's inhaled, short-acting beta₂-agonist becomes less effective, the patient needs more inhalations than usual, or the patient develops a significant decrease in lung function, 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 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.

6. Do Not Use an Inhaled, Long-Acting Beta₂-Agonist in Conjunction With ADVAIR DISKUS: Patients who are receiving ADVAIR DISKUS twice daily should not use additional salmeterol or other inhaled, long-acting beta₂-agonists (e.g., formoterol) for prevention of exercise-induced bronchospasm (EIB) or the maintenance treatment of asthma or the maintenance treatment of bronchospasm associated with COPD. Additional benefit would not be gained from using supplemental salmeterol or formoterol for prevention of EIB since ADVAIR DISKUS already contains an inhaled, long-acting beta₂-agonist.

7. Do Not Exceed Recommended Dosage: ADVAIR 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.

8. Paradoxical Bronchospasm: As with other inhaled asthma and COPD 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.

9. Immediate Hypersensitivity Reactions: Immediate hypersensitivity reactions may occur after administration of ADVAIR DISKUS, as demonstrated by cases of urticaria, angioedema, rash, and bronchospasm.

10. 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 DISKUS.

11. Cardiovascular Disorders: 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.

12. Discontinuation of Systemic Corticosteroids: Transfer of patients from systemic corticosteroid therapy to ADVAIR DISKUS may unmask conditions previously suppressed by the systemic corticosteroid therapy, e.g., rhinitis, conjunctivitis, eczema, arthritis, and eosinophilic conditions.

13. 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.

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 DISKUS, and may require discontinuation of ADVAIR DISKUS. ADVAIR DISKUS, 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 electrocardiograms (ECGs) have been seen infrequently in individual patients in controlled clinical studies with ADVAIR DISKUS 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 DISKUS.

Metabolic and Other Effects: Long-term use of orally inhaled corticosteroids may affect normal bone metabolism, resulting in a loss of bone mineral density (BMD). A 2-year study of 160 patients (females 18 to 40 and males 18 to 50 years of age) with asthma receiving chlorofluorocarbon-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

region L1 through L4. Long-term treatment effects of fluticasone propionate on BMD in the COPD population have not been studied.

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 DISKUS may pose an additional risk. Since patients with COPD often have multiple risk factors for reduced BMD, assessment of BMD is recommended, including prior to instituting ADVAIR DISKUS 250/50 and periodically thereafter. If significant reductions in BMD are seen and ADVAIR DISKUS 250/50 is still considered medically important for that patient's COPD therapy, use of medication to treat or prevent osteoporosis should be strongly considered. ADVAIR DISKUS 250/50 mcg twice daily is the only approved dosage for the treatment of COPD associated with chronic bronchitis, and higher doses, including ADVAIR DISKUS 500/50, are not recommended.

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, regular eye examinations should be considered.

Lower respiratory tract infections, including pneumonia, have been reported following the inhaled administration of corticosteroids, including fluticasone propionate and ADVAIR DISKUS.

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 DISKUS 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 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.

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. The effects of long-term treatment of children and adolescents with inhaled corticosteroids, including fluticasone propionate, on final adult height are not known.

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 significance of these growth data is not certain. Physicians should closely follow the growth of children and adolescents taking corticosteroids by any route, and weigh the benefits of corticosteroid therapy against the possibility of growth suppression if growth appears slowed. Patients should be maintained on the lowest dose of inhaled corticosteroid that effectively controls their asthma.

The long-term effects of ADVAIR DISKUS 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 have received inhaled fluticasone propionate on a continuous basis for periods of 3 years or longer. In clinical studies in patients with asthma 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.

In clinical studies with ADVAIR DISKUS, 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 DISKUS, but at times therapy with ADVAIR DISKUS 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 DISKUS, 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*).

Chronic Obstructive Pulmonary Disease: ADVAIR DISKUS 250/50 twice daily is the only dosage recommended for the treatment of airflow obstruction in patients with COPD associated with chronic bronchitis. Higher doses, including ADVAIR DISKUS 500/50, are not recommended, as no additional improvement in lung function (defined by predose and postdose FEV₁) was observed in clinical trials and higher doses of corticosteroids increase the risk of systemic effects.

The benefit of treatment of patients with COPD associated with chronic bronchitis with ADVAIR DISKUS 250/50 for periods longer than 6 months has not been evaluated. Patients who are treated with ADVAIR DISKUS 250/50 for COPD associated with chronic bronchitis for periods longer than 6 months should be reevaluated periodically to assess the continuing benefits and potential risks of treatment.

Information for Patients: Patients being treated with ADVAIR 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 inhalation device appropriately and how it should be used in relation to other asthma or COPD medications they are taking. Patients should be given the following information:

1. Patients should use ADVAIR DISKUS at regular intervals as directed. Results of clinical trials indicate 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.

2. Most patients are able to taste or feel a dose delivered from ADVAIR DISKUS. However, whether or not patients are able to sense delivery of a dose, you should instruct them not to exceed the recommended dose of 1 inhalation each morning and evening, approximately 12 hours apart. You should instruct them to contact you or the pharmacist if they have questions.
3. The bronchodilation from a single dose of ADVAIR DISKUS may last up to 12 hours or longer. The recommended dosage (1 inhalation twice daily, morning and evening) should not be exceeded. Patients who are receiving ADVAIR DISKUS 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 or the maintenance treatment of bronchospasm in COPD.
4. ADVAIR DISKUS 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). ADVAIR DISKUS is not meant to relieve acute asthma symptoms or exacerbations of COPD.
5. Patients should not stop therapy with ADVAIR DISKUS without physician/provider guidance since symptoms may recur after discontinuation.
6. The physician should be notified immediately if any of the following situations occur, which may be a sign of seriously worsening asthma:
 - decreasing effectiveness of inhaled, short-acting beta₂-agonists;
 - need for more inhalations than usual of inhaled, short-acting beta₂-agonists;
 - significant decrease in lung function as outlined by the physician.
7. Patients should be cautioned regarding common adverse effects associated with beta₂-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.
8. Patients who are at an increased risk for decreased BMD should be advised that the use of corticosteroids may pose an additional risk and should be told to monitor and, where appropriate, seek treatment for this condition.
9. Long-term use of inhaled corticosteroids, including fluticasone propionate, a component of ADVAIR DISKUS, may increase the risk of some eye problems (cataracts or glaucoma). Regular eye examinations should be considered.
10. When patients are prescribed ADVAIR DISKUS, other medications for asthma and COPD should be used only as directed by their physicians.
11. ADVAIR DISKUS should not be used with a spacer device.
12. Patients who are pregnant or nursing should contact their physicians about the use of ADVAIR DISKUS.
13. Effective and safe use of ADVAIR 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.
- After inhalation, rinse the mouth with water without swallowing.
- Never wash the mouthpiece or any part of the DISKUS. KEEP IT DRY.
- Always keep the DISKUS in a dry place.
- Discard **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.

14. Patients should be warned to avoid exposure to chickenpox or measles and, if they are exposed, to consult their physicians without delay.

15. For the proper use of ADVAIR DISKUS and to attain maximum improvement, the patient should read and carefully follow the Patient’s Instructions for Use accompanying the product.

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.

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 taking FLONASE® (fluticasone propionate) Nasal Spray, 50 mcg concurrently (N = 46) and those who were not (N = 130).

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.

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 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 is a substrate of cytochrome P450 3A4. A drug interaction study with fluticasone propionate aqueous nasal spray in healthy subjects has shown that ritonavir (a highly potent 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 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 plasma fluticasone propionate exposure, a reduction in plasma cortisol AUC, and no effect on urinary excretion of cortisol. Caution should be exercised when ADVAIR DISKUS is coadministered with ketoconazole and other known potent cytochrome P450 3A4 inhibitors.

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, respectively, the maximum recommended daily inhalation dose in adults and children on a mcg/m² basis) for 78 weeks or in rats at inhalation doses up to 57 mcg/kg (less than and approximately equivalent to, respectively, the maximum recommended daily inhalation dose in adults and children 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 daily inhalation dose in adults on a mcg/m² basis). Prostate weight was significantly reduced at a subcutaneous dose of 50 mcg/kg.

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 maximum recommended daily inhalation dose in adults and children based on comparison of the plasma area under the curves [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. 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 and 25 times, respectively, the maximum recommended daily inhalation dose in adults and children on a mg/m² basis). No tumors were seen at 0.21 mg/kg (approximately 15 and 8 times, respectively, the maximum recommended daily inhalation dose in adults and 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: ADVAIR DISKUS: 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 to toxicity data from the components administered separately. In mice combining 150 mcg/kg subcutaneously of fluticasone propionate (less than the maximum recommended daily inhalation dose in adults on a mcg/m² basis) with 10 mg/kg orally of salmeterol (approximately 410 times the maximum recommended daily inhalation dose in adults on a mg/m² basis) was teratogenic. Cleft palate, fetal death, increased implantation loss and delayed ossification were 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 daily inhalation dose in adults on a mcg/m² basis) and up to 1.4 mg/kg orally of salmeterol (approximately 55 times the maximum recommended daily inhalation dose in adults on a mcg/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 daily inhalation dose in adults on a mcg/m² basis) and up to 1 mg/kg of salmeterol (approximately 80 times the maximum recommended daily inhalation dose in adults on a mcg/m² basis). Combining 100 mcg/kg subcutaneously of fluticasone propionate (equivalent to the maximum recommended daily inhalation dose in adults on a mcg/m² basis) with 10 mg/kg orally of salmeterol (approximately 810 times the maximum recommended daily inhalation dose in adults on a mcg/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 DISKUS in pregnant women. ADVAIR DISKUS 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 (less than or equivalent to the maximum recommended daily inhalation dose in adults on a mcg/m² 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 maximum recommended daily inhalation dose in adults 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 daily inhalation dose in adults 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).

Fluticasone propionate crossed the placenta following administration of a subcutaneous dose of 100 mcg/kg to mice (less than the maximum recommended daily inhalation dose in adults on a mcg/m² basis), administration of a subcutaneous or an oral dose of 100 mcg/kg to rats (approximately equivalent to the maximum recommended daily inhalation dose in adults on a mcg/m² basis), and administration of an oral dose of 300 mcg/kg to rabbits (approximately 5 times the maximum recommended daily inhalation dose in adults on a mcg/m² basis).

There are no adequate and well-controlled studies in pregnant women. Fluticasone propionate 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 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 salmeterol in pregnant women. Salmeterol 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 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.

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 10 mcg/kg tritiated fluticasone propionate (less than the maximum recommended daily inhalation dose in adults on a mcg/m² basis) 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.

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 CLINICAL

TRIALS: Asthma: *Pediatric Patients* and ADVERSE REACTIONS: Asthma: *Pediatric Patients*). The safety and effectiveness of ADVAIR DISKUS in children with asthma under 4 years of age have not been established.

Controlled clinical studies have shown that orally inhaled corticosteroids 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 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.

Inhaled corticosteroids, including fluticasone propionate, a component of ADVAIR DISKUS, may cause a reduction in growth velocity in children and adolescents (see PRECAUTIONS: General: *Metabolic and Other Effects*). The growth of pediatric patients receiving orally inhaled corticosteroids, including ADVAIR DISKUS, 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. 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: Asthma).

Geriatric Use: Of the total number of patients in clinical studies of ADVAIR DISKUS for asthma, 44 were 65 years of age or older and 3 were 75 years of age or older. Of the total number of patients in a clinical study of ADVAIR DISKUS 250/50 for COPD, 85 were 65 years of age or older and 31 were 75 years of age or older. For both diseases, 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 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.

ADVERSE REACTIONS

Asthma: Adult and Adolescent Patients 12 Years of Age and Older: The incidence of common adverse events in [Table 3](#) 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.

Table 3. Overall Adverse Events With $\geq 3\%$ Incidence in US Controlled Clinical Trials With ADVAIR DISKUS in 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
Average duration of exposure (days)	77.3	78.7	72.4	70.1	60.1	42.3

[Table 3](#) includes all events (whether considered drug-related or nondrug-related by the investigator) that occurred at a rate of 3% or greater in either of the groups receiving ADVAIR DISKUS and were more common than in the placebo group. In considering these data, differences in average duration of exposure should be taken into account. Rare cases of immediate and delayed hypersensitivity reactions, including rash and other rare events of angioedema and bronchospasm, have been reported.

These adverse reactions were mostly mild to moderate in severity.

Other adverse events that occurred in the groups receiving ADVAIR DISKUS in these studies with an incidence of 1% to 3% and that occurred at a greater incidence than with placebo were:

Blood and Lymphatic: Lymphatic signs and symptoms.

Cardiovascular: Palpitations.

Drug Interaction, Overdose, and Trauma: Muscle injuries, fractures, wounds and lacerations, contusions and hematomas, burns.

Ear, Nose, and Throat: Rhinorrhea/postnasal drip; ear, nose, and throat infections; ear signs and symptoms; nasal signs and symptoms; nasal sinus disorders; rhinitis; sneezing; nasal irritation; blood in nasal mucosa.

Eye: Keratitis and conjunctivitis, viral eye infections, eye redness.

Gastrointestinal: Dental discomfort and pain, gastrointestinal signs and symptoms, gastrointestinal infections, gastroenteritis, gastrointestinal disorders, oral ulcerations, oral erythema and rashes, constipation, appendicitis, oral discomfort and pain.

Hepatobiliary Tract and Pancreas: Abnormal liver function tests.

Lower Respiratory: Lower respiratory signs and symptoms, pneumonia, lower respiratory infections.

Musculoskeletal: Arthralgia and articular rheumatism; muscle stiffness, tightness, and rigidity; bone and cartilage disorders.

Neurology: Sleep disorders, tremors, hypnagogic effects, compressed nerve syndromes.

Non-Site Specific: Allergies and allergic reactions, congestion, viral infections, pain, chest symptoms, fluid retention, bacterial infections, wheeze and hives, unusual taste.

Skin: Viral skin infections, urticaria, skin flakiness and acquired ichthyosis, disorders of sweat and sebum, sweating.

The incidence of common adverse 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 was similar to the incidences reported in [Table 3](#).

Pediatric Patients: Pediatric Study: ADVAIR DISKUS 100/50 was well tolerated in clinical trials conducted in children with asthma aged 4 to 11 years. The incidence of common adverse events in [Table 4](#) is based upon a 12-week US study in 203 patients with asthma aged 4 to 11 years (74 females and 129 males) who were receiving inhaled corticosteroids at study entry

and were randomized to either ADVAIR DISKUS 100/50 or fluticasone propionate inhalation powder 100 mcg twice daily.

Table 4. Overall Adverse Events With $\geq 3\%$ Incidence With ADVAIR DISKUS 100/50 in Patients 4 to 11 Years of Age With Asthma

Adverse Event	ADVAIR DISKUS 100/50 (N = 101) %	Fluticasone Propionate 100 mcg (N = 102) %
Ear, nose, & throat		
Upper respiratory tract infection	10	17
Throat irritation	8	7
Ear, nose, & throat infections	4	<1
Epistaxis	4	<1
Pharyngitis/throat infection	3	2
Ear signs & symptoms	3	<1
Sinusitis	3	0
Neurology		
Headache	20	20
Gastrointestinal		
Gastrointestinal discomfort & pain	7	5
Nausea & vomiting	5	3
Candidiasis mouth/throat	4	<1
Non-site specific		
Fever	5	13
Chest symptoms	3	<1
Average duration of exposure (days)	74.8	78.8

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 ADVAIR DISKUS 100/50.

Chronic Obstructive Pulmonary Disease Associated With Chronic Bronchitis: The incidence of common adverse events in [Table 5](#) is based upon 1 placebo-controlled, 24-week, US clinical trial in patients with COPD associated with chronic bronchitis. 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 50 mcg, or placebo.

Table 5. Overall Adverse Events 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
Average duration of exposure (days)	141.3	138.5	136.1	131.6

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 ADVAIR DISKUS 250/50 and were more common than in the placebo group.

These adverse reactions were mostly mild to moderate in severity.

Other adverse events that occurred in the groups receiving ADVAIR DISKUS 250/50 with an incidence of 1% to 3% and that occurred at a greater incidence than with placebo were:

Cardiovascular: Syncope.

Drug Interaction, Overdose, and Trauma: Postoperative complications.

Ear, Nose, and Throat: Ear, nose, and throat infections; ear signs and symptoms; laryngitis; nasal congestion/blockage; nasal sinus disorders; pharyngitis/throat infection.

Endocrine and Metabolic: Hypothyroidism.

Eye: Dry eyes, eye infections.

Gastrointestinal: Constipation, gastrointestinal signs and symptoms, oral lesions.

Hepatobiliary Tract and Pancreas: Abnormal liver function tests.

Lower Respiratory: Breathing disorders, lower respiratory signs and symptoms.

Non-Site Specific: Bacterial infections, candidiasis unspecified site, edema and swelling, nonspecific conditions, viral infections.

Psychiatry: Situational disorders.

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 DISKUS, fluticasone propionate, and/or salmeterol or a combination of these factors.

In extensive US and worldwide postmarketing experience with salmeterol, a component of ADVAIR DISKUS, 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 no. 2), 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 or simply failed to relieve the deteriorating asthma.

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

Ear, Nose, and Throat: Aphonia, earache, facial and oropharyngeal edema, paranasal sinus pain, throat soreness.

Endocrine and Metabolic: Cushing syndrome, Cushingoid features, growth velocity reduction in children/adolescents, hypercorticism, hyperglycemia, weight gain, osteoporosis.

Eye: Cataracts, glaucoma.

Gastrointestinal: Abdominal pain, dyspepsia, xerostomia.

Musculoskeletal: Back pain, cramps, muscle spasm, myositis.

Neurology: Paresthesia, restlessness.

Non-Site Specific: Immediate and delayed hypersensitivity reaction (including very rare anaphylactic reaction), pallor. Very rare anaphylactic reaction in patients with severe milk protein allergy.

Psychiatry: Agitation, aggression, depression.

Respiratory: Chest congestion; chest tightness; dyspnea; immediate bronchospasm; influenza; paradoxical bronchospasm; tracheitis; wheezing; reports of upper respiratory symptoms of laryngeal spasm, irritation, or swelling such as stridor or choking.

Skin: Contact dermatitis, contusions, ecchymoses, photodermatitis.

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 DISKUS, 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 DISKUS 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 DISKUS: No deaths occurred in rats given an inhaled single-dose combination of salmeterol 3.6 mg/kg (approximately 290 and 140 times, respectively, the maximum recommended daily inhalation dose in adults and children on a mg/m² basis) and 1.9 mg/kg of fluticasone propionate (approximately 15 and 35 times, respectively, the maximum recommended daily inhalation dose in adults and children 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 inhalation aerosol was well tolerated. Fluticasone propionate given by inhalation aerosol at doses 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 (>4,100 and >9,600 times, respectively, the maximum recommended daily inhalation dose in adults and children on a mg/m² basis). In rats the subcutaneous median lethal dose was >1,000 mg/kg (>8,100 and >19,200 times, respectively, the maximum recommended daily inhalation dose in adults and children 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 240 and 110 times, respectively, the maximum recommended daily inhalation dose in adults and children on a mg/m² basis) and in dogs at an inhalation dose of 0.7 mg/kg (approximately 190 and 90 times, respectively, the maximum recommended daily inhalation dose in adults and children 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, respectively, the maximum recommended daily inhalation dose in adults and children on a mg/m² basis) and in rats at 1,000 mg/kg (approximately 81,000 and 38,000 times, respectively, the maximum recommended daily inhalation dose in adults and children on a mg/m² basis).

DOSAGE AND ADMINISTRATION

ADVAIR DISKUS should be administered by the orally inhaled route only (see Patient's Instructions for Use). After inhalation, the patient should rinse the mouth with water without swallowing. ADVAIR DISKUS should not be used for transferring patients from systemic corticosteroid therapy.

Asthma: ADVAIR DISKUS is available in 3 strengths, ADVAIR DISKUS 100/50, ADVAIR DISKUS 250/50, and ADVAIR DISKUS 500/50, containing 100, 250, and 500 mcg of fluticasone propionate, respectively, and 50 mcg of salmeterol per inhalation.

ADVAIR DISKUS should be administered twice daily every day. More frequent administration (more than twice daily) 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. The safety and efficacy of ADVAIR DISKUS 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 DISKUS 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.

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' current asthma therapy.

- For patients who are not currently on an inhaled corticosteroid, whose disease severity warrants treatment with 2 maintenance therapies, including patients on non-corticosteroid maintenance therapy, the recommended starting dosage is ADVAIR DISKUS 100/50 twice daily.
- For patients on an inhaled corticosteroid, Table 6 provides the recommended starting dosage. 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.

Table 6. Recommended Dosages of ADVAIR DISKUS for Patients With Asthma Aged 12 Years and Older Taking Inhaled Corticosteroids

Current Daily Dose of Inhaled Corticosteroid		Recommended Strength and Dosing Schedule of ADVAIR DISKUS
Beclomethasone dipropionate	≤420 mcg	100/50 twice daily
	462-840 mcg	250/50 twice daily
Budesonide	≤400 mcg	100/50 twice daily
	800-1,200 mcg	250/50 twice daily
	1,600 mcg*	500/50 twice daily
Flunisolide	≤1,000 mcg	100/50 twice daily
	1,250-2,000 mcg	250/50 twice daily
Fluticasone propionate inhalation aerosol	≤176 mcg	100/50 twice daily
	440 mcg	250/50 twice daily
	660-880 mcg*	500/50 twice daily
Fluticasone propionate inhalation powder	≤200 mcg	100/50 twice daily
	500 mcg	250/50 twice daily
	1,000 mcg*	500/50 twice daily
Triamcinolone acetonide	≤1,000 mcg	100/50 twice daily
	1,100-1,600 mcg	250/50 twice daily

* ADVAIR DISKUS should not be used for transferring patients from systemic corticosteroid therapy.

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, or initiating oral corticosteroids, should be considered.

Pediatric Patients: For patients 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).

Chronic Obstructive Pulmonary Disease Associated With Chronic Bronchitis: The dosage for adults is 1 inhalation (250/50 mcg) twice daily (morning and evening, approximately 12 hours apart).

ADVAIR DISKUS 250/50 mcg twice daily is the only approved dosage for the treatment of COPD associated with chronic bronchitis. Higher doses, including ADVAIR DISKUS 500/50, are not recommended, as no additional improvement in lung function was observed in clinical trials and higher doses of corticosteroids increase the risk of systemic effects.

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

Patients who are receiving ADVAIR DISKUS twice daily should not use additional salmeterol or other inhaled, long-acting beta₂-agonists (e.g., formoterol) for the maintenance treatment of COPD or for any other reason.

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

Directions for Use: Illustrated Patient's Instructions for Use accompany each package of ADVAIR DISKUS.

HOW SUPPLIED

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 purple, disposable DISKUS inhalation 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 purple, disposable DISKUS inhalation 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 purple, disposable DISKUS inhalation 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.



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