

GLAXOSMITHKLINE

Sponsor Briefing Information

**ADVAIR DISKUS® (fluticasone propionate/salmeterol inhalation powder)
100/50 mcg, 250/50 mcg and 500/50 mcg**

**ADVAIR® HFA (fluticasone propionate/salmeterol) Inhalation Aerosol
45mcg/21mcg, 115mcg/21mcg, 230mcg/21mcg**

SEREVENT® (salmeterol xinafoate) Inhalation Aerosol

SEREVENT® DISKUS® (salmeterol xinafoate inhalation powder)

**Benefit Risk Assessment of Salmeterol for the Treatment of Asthma in
Adults and Children**

**FDA Joint Pulmonary/Allergy Drugs, Drug Safety and Risk Management,
and Pediatric Advisory Committees**

December 10 - 11, 2008

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EXECUTIVE SUMMARY

Overall Summary

The combination of salmeterol with an ICS provides unsurpassed asthma control to patients by improving lung function, preventing daytime and nighttime symptoms and decreasing the use of rescue medications. A review of over 20 years of clinical experience has demonstrated that there is no increased risk of serious asthma-related events when salmeterol is used appropriately with an ICS.

For ADVAIR, there was no evidence of increased risk for asthma-related death, asthma-related hospitalization, asthma-related intubation and all cause death in any database. Therefore, no regulatory action is necessary for this product.

However, when salmeterol is used in the absence of an ICS or when an ICS is not taken appropriately, an increase in serious asthma-related events have been observed.

Therefore, GSK has submitted a labeling supplement to reinforce the importance of maintaining concurrent ICS therapy while being treated with SEREVENT DISKUS. GSK believes the continued availability of SEREVENT DISKUS for the treatment of asthma ensures access to this effective medicine in patients where the fixed-dose combination may be unavailable, for patients who require an inhaled corticosteroid other than fluticasone propionate, or for the prescriber who needs the additional flexibility of ICS doses beyond those available in the fixed dose combination product.

Introduction

This briefing package is intended to provide the members and consultants of the joint Advisory Committee with information pertinent to the evaluation of the benefits and potential risks of the long-acting beta₂-agonist, salmeterol xinafoate, in the treatment of adults and children with asthma. This comprehensive review incorporates data from all GSK-sponsored randomized clinical trials, from all observational studies that met pre-defined criteria, and from spontaneously reported adverse events for salmeterol, either administered as SEREVENT or in combination with an inhaled corticosteroid (fluticasone propionate) as ADVAIR.

A signal of potential increased risk of serious asthma-related outcomes observed with salmeterol under conditions of use characteristic of its early years of clinical development and marketing appears to be mitigated by changes in medical practice that resulted in long-acting beta₂-agonists and ICS being administered concurrently. Overall, the proportion of patients dispensed SEREVENT without a concomitant ICS or other controller medication decreased from 31.2% during 1994 to 1996 to 1.2% during 2005 to 2007. By 2005 to 2007, 97% of patients received salmeterol as ADVAIR.

Results of analyses of ADVAIR from three diverse types of databases (randomized controlled trials, observational studies, and spontaneously reported adverse events from FDA's Adverse Event Reporting System [AERS] database) consistently demonstrated no signal of an increased risk of serious asthma-related outcomes with salmeterol and fluticasone propionate administered as a fixed dose regimen. Contemporary use of

salmeterol (SEREVENT) administered with concurrent ICS in separate inhalers does not appear to be associated with an increased risk of serious asthma-related outcomes.

In addition to no association of increased serious asthma-related outcomes when salmeterol is used appropriately with ICS, randomized, controlled trials have shown that concurrent use of salmeterol and ICS was highly efficacious by controlling and preventing the symptoms of asthma in both adults and children, which when left uncontrolled, alters or prevents normal daily activities. Results from randomized controlled trials also found that concurrent use salmeterol and ICS statistically significantly reduced exacerbations requiring systemic corticosteroids and observational studies of large claims databases demonstrated statistically significant reductions in emergency department visits and hospitalizations.

Thus, the efficacy and safety data demonstrate that the benefit to risk profile of salmeterol is distinctly favorable when used according to asthma treatment guidelines and prescribing information. Appropriate concurrent use of salmeterol with ICS, whether as ADVAIR or SEREVENT plus ICS, has significantly advanced the care and well-being of patients with asthma and remains a preferred treatment option based on evidence-based asthma treatment guidelines.

Burden of Asthma

Asthma is estimated to affect 300 million individuals worldwide, including 22 million in the US. Asthma outcomes have improved over the past decade, but the burden of this disease remains substantial. Asthma-related deaths have been decreasing since the mid-1990s, but asthma is still responsible for approximately 250,000 worldwide deaths annually with approximately 3,500 of them in the US. In 2005, there were 488,594 hospitalizations, 12.8 million physician office visits, 1.3 million hospital outpatient department visits, and 1.8 million emergency department visits due to asthma in the US. Additionally, uncontrolled asthma is considered responsible for 13 million lost school days and 14.5 million lost work days [[American Lung Association](#), 2007; [Minino](#), 2007]. Asthma can have a significant impact on patients' lives; more than 70% of patients with asthma surveyed reported that the worst aspects of having asthma were the interference in their daily lives and the panic they felt when their asthma symptoms increased [[Partridge](#), 2006]. While there is no cure for asthma, effective medications are vital to continue the improvements achieved in the standard of care of asthma over the past decade.

Asthma is currently recognized as a chronic inflammatory disorder of the airways characterized by pathological changes related to both inflammation and airway smooth muscle bronchoconstriction. Beta₂-agonists treat primarily the bronchospastic component of asthma, whereas inhaled corticosteroids (ICS) treat the inflammatory component. Since the late 1990s, based on a large body of clinical data, asthma treatment guidelines and educational programs have stressed the importance of treating all patients with persistent asthma with an ICS to control the underlying inflammatory process that is characteristic of asthma. Thus, according to contemporary standards of care, a long-acting beta₂-agonist (LABA), such as salmeterol xinafoate, is recommended to be used as concurrent therapy with an ICS for persistent asthma. The changes in asthma treatment

practice over time, including the pattern of usage of available therapies, have had a significant positive effect on the care and well-being of patients with asthma.

Regulatory History and Studies Influencing SEREVENT and ADVAIR Labeling

Salmeterol (as SEREVENT) has been available worldwide since 1990 and in ADVAIR (salmeterol in combination with fluticasone propionate [FP]) since 1998.

Shortly after the approval of SEREVENT in the UK, the SEREVENT Nationwide Surveillance (SNS) study was conducted between 1990 and 1992. The incidence of asthma-related death was numerically, though not statistically, greater in patients taking salmeterol compared with the patients receiving albuterol four times a day. The findings from SNS were available at the time of FDA approval of SEREVENT Inhalation Aerosol in 1994.

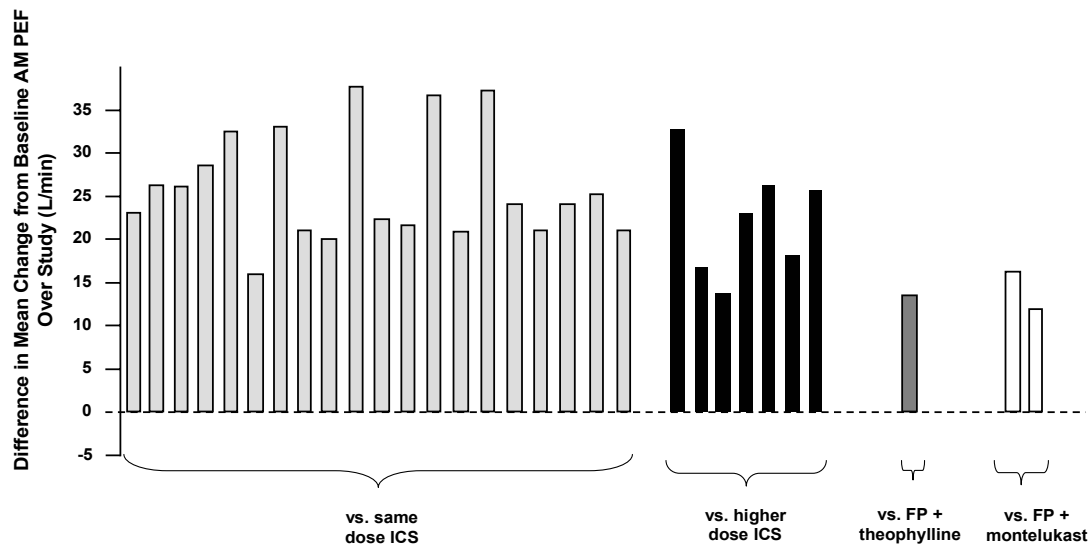
In response to the results of SNS and spontaneous adverse event reports associated with the use of beta₂-agonists, GSK in consultation with the FDA agreed to conduct a large, prospective clinical trial to obtain safety surveillance information. SMART (Salmeterol Multicenter Asthma Research Trial) was conducted in order to further characterize the safety of salmeterol. SMART was initiated in 1996 and terminated in January 2003. SMART showed a statistically significant increase in asthma-related deaths in patients receiving salmeterol added to usual medical care (13 deaths out of 13,176 patients treated with salmeterol versus three deaths out of 13,179 patients on placebo). Following termination of the study, a boxed warning was incorporated into the labelling for SEREVENT and ADVAIR on 11 August 2003.

Both SNS and SMART were conducted when the role of inflammation in the pathophysiology of asthma was not widely appreciated and the use of concomitant ICS was less common in patients with persistent asthma. For example, less than half the patients receiving salmeterol in SMART (1996) were also receiving an ICS at baseline; however, in 2008, greater than 98% of all patients in the US receiving salmeterol for asthma are also receiving concurrent ICS.

Efficacy Summary from GSK-Sponsored Randomized Controlled Trials

A systematic review of GSK randomized controlled trials specifically designed to assess efficacy was conducted to summarize the efficacy and benefits of asthma control provided by salmeterol administered with ICS in adults and children. [Figure 1](#) shows the improvement in lung function from individual studies with treatment with salmeterol plus ICS (1) vs. ICS administered at the same/equipotent dose, (2) vs. ICS administered at a higher dose, or (3) vs. ICS plus theophylline or montelukast.

Figure 1 Benefit in Lung Function (AM PEF, L/min) for Salmeterol plus ICS Beyond that Seen With ICS (Adolescents and Adults)



Each bar represents the treatment difference in a single study

For all studies, treatment with salmeterol plus ICS resulted in greater benefits in lung function compared with ICS or ICS plus other treatment (e.g., montelukast). Similar results were seen for symptom-free days, rescue free days and quality of life in adults and children. Concurrent use of salmeterol and ICS was also shown to significantly reduce exacerbations requiring treatment with systemic corticosteroids. The totality of data support that the combination of salmeterol used concurrently with ICS is unsurpassed in the overall daily control of asthma.

Meta-Analysis of Safety Data from GSK Randomized Controlled Clinical Trials

GSK performed a comprehensive review of all GSK-sponsored randomized controlled trials of salmeterol for the treatment of persistent asthma. To evaluate the safety profile of salmeterol, a meta-analysis of 215 studies comprising 106,575 patients with over 39,000 patient years of exposure was performed. The meta-analysis evaluated asthma-related hospitalizations, asthma-related deaths, asthma-related intubations and all cause death when salmeterol was used alone and when salmeterol was used with an ICS. Risk difference was used as the primary measure and is expressed as the difference between treatments in the rate of patients experiencing an outcome per 10,000 patients.

When examining outcomes in patients using salmeterol, it is important to understand how the concurrent use of ICS can be administered to patients in clinical trials. There are three situations in a clinical trial during which a patient may have received ICS concurrently with salmeterol and the assurance of ICS use varies among each:

- Addition of salmeterol to background ICS (ICS_{BK}). At the screening visit, patients reported taking ICS prior to the study and were instructed to continue that ICS throughout the treatment period of the study. However, the ICS medication was not

dispensed as part of the protocol nor was there systematic reinforcement or any measure of continued adherence to the medication. This analysis population was designated as **Sal + ICS_{BK} vs. ICS_{BK}**.

- Introduction of both salmeterol and ICS as blinded study medications administered in separate inhaler devices (SI), administered as study drug (SD) as part of the study protocol. This analysis population was designated as **Sal + ICS_{SI} vs. ICS_{SD}**.
- Introduction of salmeterol and ICS (FP) as a blinded study medication in a single inhaler (ADVAIR). This analysis population was designated as **ADVAIR vs. ICS_{SD}**.

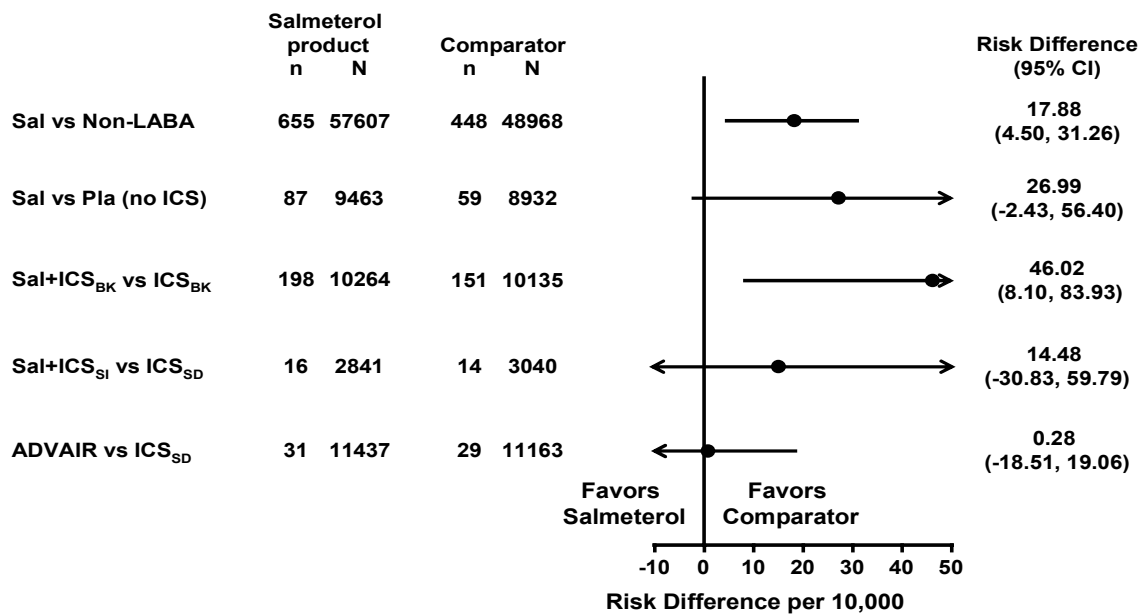
Asthma-Related Deaths

A total of 35 of the 106,575 patients in the meta-analysis database were reported to have had an asthma-related death. Thirty (30) of these cases were from SMART and SNS which together accounted for 86% of the asthma-related deaths. There were no asthma-related deaths in any patient (n=17,891) who received ADVAIR. Therefore, the data show that for studies where the concurrent use of salmeterol and ICS can be reasonably assured (e.g., ADVAIR and Sal + ICS_{SI}), there was no evidence of increased risk for asthma-related death or asthma-related hospitalization.

Asthma-Related Hospitalizations

Since asthma-related deaths are rare events, other more frequent outcomes, like asthma-related hospitalizations, may be used as a surrogate for asthma-related deaths. [Figure 2](#) displays the meta-analysis of the risk difference (RD) for patients with an asthma-related hospitalization.

Figure 2 Meta-Analysis: Risk Difference for Asthma-Related Hospitalization (0.5 Continuity Correction)



The RDs for asthma-related hospitalization were higher in patients who used salmeterol without an ICS and when ICS use was not controlled or dispensed by the protocol (i.e., salmeterol as blinded study drug added to background ICS [ICS_{BK}]). RD decreased when patients used both salmeterol and ICS as dispensed study drugs (Sal + ICS_{SI}). The lowest RD was observed when salmeterol was used concurrently with ICS in a fixed single inhaler (e.g., ADVAIR), demonstrating that ADVAIR was not associated with an increased risk for asthma-related hospitalizations. Thus, as was described above for asthma-related death, salmeterol used with ICS was not associated with increase risk of asthma-related hospitalization.

When a comprehensive review of comparable data from pediatric and African American patients was performed, similar results were observed. Thus, this comprehensive review suggests that when salmeterol and ICS are used concurrently as part of an appropriate therapeutic management plan, there is no signal of increased risk of asthma-related hospitalizations. This is likely due to increased prescribing of ICS and enhanced compliance to ICS therapy as a result of a better understanding of the appropriate treatment of asthma.

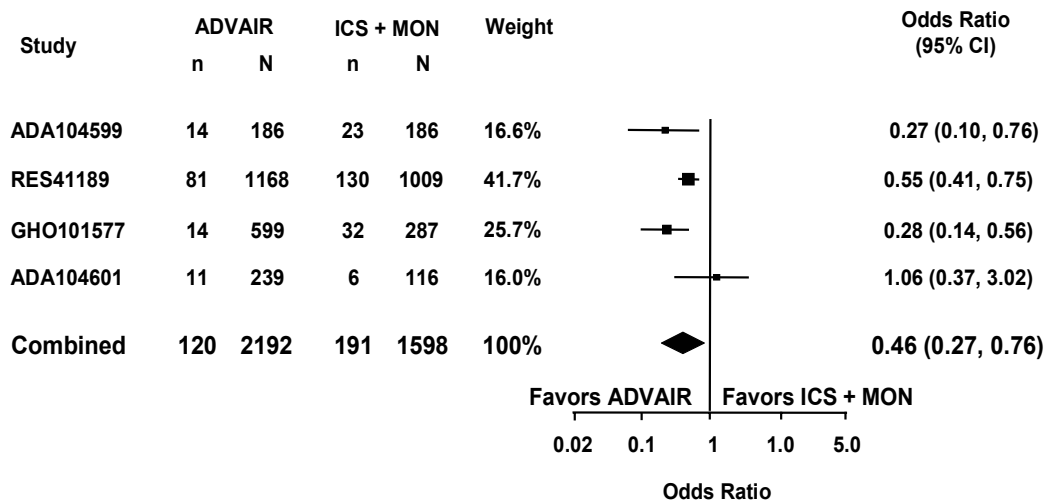
Observational Studies Evaluating Salmeterol and Serious Asthma-Related Outcomes

Observational studies provide important information on the patterns of salmeterol use and safety-related events among the broad range of patients treated in clinical practice. Since 2001, the vast majority of patients were dispensed salmeterol as ADVAIR (single inhaler containing salmeterol and fluticasone propionate).

A review of all published studies and unpublished GSK studies identified a total of six case-control or cohort studies of salmeterol and severe respiratory-related events. In all six studies (cohort and case control) in the US and UK, SEREVENT use was not associated with an increased risk of asthma-related mortality or serious asthma morbidity after adjusting for potential confounding by severity. Further, results from a meta-analysis of observational studies encompassing automated healthcare data from over 80,000 patients aged 18 and older across regions and health plans in the US showed that ADVAIR use was associated with a statistically significant reduction in asthma-related hospitalization and emergency room visits compared with ICS use. Similar beneficial trends in reductions in serious asthma events associated with ADVAIR vs. ICS as well as an alternative treatment regimen (ADVAIR vs. ICS plus montelukast) were observed from six pediatric studies across various populations including over 43,500 children treated in real-world clinical practice.

Four pediatric studies compared the risk of a patient experiencing an asthma-related emergency department (ED) or hospitalization endpoint for ADVAIR vs. ICS plus montelukast, including a total of 3,790 patients with 2,192 ADVAIR users and 1,598 ICS plus montelukast users (Figure 3).

Figure 3 Odds Ratio for Asthma-Related Combined ED/Hospitalizations: ADVAIR vs. ICS Plus Montelukast, Pediatric Studies

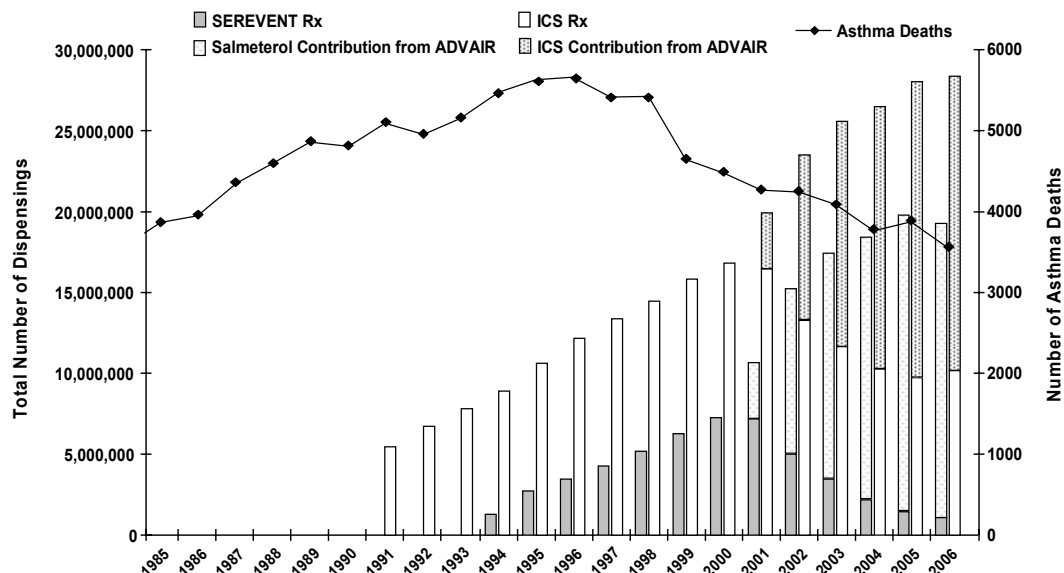


This meta-analysis showed that ADVAIR was associated with a statistically significantly lower risk of an asthma-related emergency department or hospitalization visit compared to ICS plus montelukast, illustrating that other treatment options may not provide greater benefit than ADVAIR in children.

Finally, when examining trends in the US population data from 2001 to 2007 (post-ADVAIR approval), salmeterol exposure more than doubled while the rate of asthma-related serious morbidity requiring hospital admission was relatively stable and asthma-related mortality declined [CDC, 2007]. The CDC-reported asthma-related mortality

rates (Figure 4) were plotted against the retail pharmacy dispensing totals for salmeterol-containing products (SEREVENT and ADVAIR) by year.

Figure 4 Number of Asthma Deaths Relative to ICS- and Salmeterol-Containing Dispensings, US, 1991 to 2006



The number of asthma deaths have decreased by 34% between 1998 and 2006, while, at the same time, dispensing of salmeterol-containing products (primarily ADVAIR since 2002) has increased from approximately 5.2 million to 19.2 million dispensings.

Results from multiple, large, observational studies did not confirm the signal of potential increased risk of severe asthma morbidity and mortality from early clinical trials with SEREVENT. On the contrary, the observational data suggest a beneficial role for salmeterol when used concurrently with ICS in decreasing the risk of severe asthma morbidity. With ADVAIR, a statistically significant reduction of an asthma-related hospitalization/ED visit was seen in adults and children compared with ICS and additionally in children compared with ICS plus montelukast.

Analysis of Worldwide Post-Marketing Experience from Spontaneous Adverse Event Reports

The results of disproportionality analyses (DPA; a statistical approach which evaluates whether an outcome is reported in excess relative to other marketed products) of the FDA's database for spontaneously reported adverse events for SEREVENT corroborates the signal from early randomized controlled trials that SEREVENT may be associated with an increase in serious asthma-related outcomes under conditions of use characteristic of the early marketing period. DPA confirms results from later clinical trials and observational data which showed no signal in more recent years. This shift in outcomes with SEREVENT is likely due to greater use and adherence with concurrent ICS in the latter marketing period.

Likewise, the results of DPA for ADVAIR also confirmed the results from randomized controlled trials and observational studies that ADVAIR is not associated with any increase in serious asthma-related outcomes.

Benefit-to-Risk Profile

While efficacy is substantial and justifies appropriate use of salmeterol in the treatment of asthma, concerns have been raised about a signal of potential increased risk of serious asthma outcomes, specifically asthma-related deaths and hospitalizations. This signal was seen primarily in two studies: one study in the early 1990s conducted in the UK (SNS) and one study conducted primarily in the late 1990s in the US (SMART).

The signal of potential increased risk of serious asthma-related outcomes observed with salmeterol under conditions of use characteristic of its early years (i.e., salmeterol used without concurrent ICS or under conditions when salmeterol and ICS use could be dissociated) of clinical development and marketing has been mitigated now that the standard of care for all patients with asthma requires that salmeterol be used only with ICS. Under these contemporary conditions of use, no signal of increased risk is apparent in large databases from 1) randomized controlled trials, 2) observational studies, and 3) spontaneous event reporting. In addition, while the use of salmeterol-containing products has increased substantially over the last decade, available evidence actually points in the direction of a beneficial role for the contemporary use of salmeterol with concurrent ICS in decreasing the risk of severe asthma morbidity and mortality.

The combination of salmeterol with an ICS provides unsurpassed asthma control to patients by improving lung function, preventing daytime and nighttime symptoms and decreasing the use of rescue medications. A review of over 20 years of clinical experience has demonstrated that there is no increased risk of serious asthma-related events when salmeterol is used appropriately with an ICS.

For ADVAIR, there was no evidence of increased risk for asthma-related death, asthma-related hospitalization, asthma-related intubation or all cause death. Therefore no regulatory action is necessary for this product.

For SEREVENT, the signal of potential increased risk of serious asthma-related outcomes is only apparent when SEREVENT is used without concurrent ICS or in patients who are likely non-adherent with their prescribed ICS. Therefore, GSK has submitted a supplement to provide for revisions to the labeling for SEREVENT DISKUS. This supplement provides further information to inform health care professionals and patients on the appropriate use of SEREVENT DISKUS in the treatment of asthma. In particular, by changing the indication statement, the proposed label emphasizes the imperative of concurrent use of ICS in asthma patients treated with SEREVENT DISKUS. For patients, the Medication Guide was updated also to reinforce the importance of maintaining concurrent ICS therapy while being treated with SEREVENT DISKUS. GSK believes the continued availability of SEREVENT DISKUS for the treatment of asthma ensures access to this effective medicine in patients where the fixed-dose combination may be unavailable. For example, at the Veterans Administration and some major managed care organizations (i.e., Kaiser Permanente and United Healthcare,

representing over 28 million lives), the preferred use of the combination of a LABA and an ICS is via two separate inhalers . In addition, the continued availability of SEREVENT is important for patients who require an inhaled corticosteroid other than fluticasone propionate, or for the prescriber who needs the additional flexibility of ICS doses beyond those available in the fixed dose combination product.

In conclusion, appropriate concurrent use of salmeterol with ICS, whether as ADVAIR or SEREVENT plus ICS, has significantly advanced the care and well-being of patients with asthma and remains a preferred treatment option based on evidence-based asthma treatment guidelines. It is critical that these products continue to be available to maintain the high standard of care that is currently available to patients with asthma.

Abbreviations

AERS	Adverse Event Reporting System
AQLQ	Asthma Quality of Life Questionnaire
CFC	chlorofluorocarbon
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CTR	Clinical Trial Registry
DPA	disproportionality analysis
EBGM	empirical Bayes geometric mean
ECG	electrocardiograph
ED	emergency department
FEV ₁	forced expiratory flow in one second
FP	fluticasone propionate
GINA	Global Initiative for Asthma
GOAL	Gaining Optimal Asthma Control
HFA	hydrofluoroalkane
ICS	inhaled corticosteroid
ICS _{BK}	background ICS
LABA	long-acting beta ₂ -agonist
MDI	metered dose inhaler
MGPS	Multi-item Gamma Poisson Shrinker
MHRA	Medicines and Healthcare products Regulatory Agency
NAEPP	National Asthma Education and Prevention Program
NHLBI	National Heart, Lung and Blood Institute
OR	odds ratio
PEF	peak expiratory flow
Pla	placebo
RD	risk difference
SAE	serious adverse event
Sal	salmeterol
SD	study drug
SI	separate inhaler devices
SMART	Salmeterol Multicenter Asthma Research Trial
SNS	SEREVENT Nationwide Surveillance Study
TORCH	Toward a Revolution in COPD Health

1. BACKGROUND AND REGULATORY HISTORY

1.1. Introduction

The purpose of this briefing package is to provide the members and consultants of the joint Advisory Committee with information pertinent to the evaluation of the benefits and risks of the long-acting beta₂-agonist, salmeterol xinafoate, in the treatment of asthma. The benefit-to-risk profile for salmeterol is addressed separately for SEREVENT® DISKUS® (salmeterol xinafoate) Inhalation Powder, a single component inhaler, and ADVAIR®¹ (fluticasone propionate, an inhaled corticosteroid and salmeterol), a fixed-dose combination product. This review is the result of a recommendation from the Pediatric Advisory Committee that met on 28 November 2007. The meeting occurred as a result of the requirement under the Best Pharmaceuticals for Children Act to review safety data for the 1-year period following granting of pediatric exclusivity for salmeterol. The committee recommended a more thorough, formal review of the benefit-to-risk profile of salmeterol in the treatment of asthma in adults and children, including consideration of data for another long-acting beta₂-agonist, formoterol.

1.2. Salmeterol in the Treatment of Asthma

Salmeterol is an inhaled LABA. Beta₂-agonist bronchodilators exert their functional response by stimulating the beta-receptor on target tissue, activating a G-coupled protein complex which produces cAMP. The functional response of cAMP acts to relax constricted airway smooth muscle. Constricted airway smooth muscle is a common characteristic of asthma that results in breathing difficulties, including symptoms of dyspnea, cough, chest tightness, inability to perform exercise or normal physical activities, and frequent nighttime awakenings due to shortness of breath. Salmeterol 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.

Asthma is currently recognized as a chronic inflammatory disorder of the airways characterized by pathological changes related to both inflammation and airway smooth muscle bronchoconstriction. Beta₂-agonists treat primarily the bronchospastic component of asthma, whereas ICS treat the inflammatory component. During the development period of salmeterol, short-acting beta₂-agonists were labelled for routine use, four times daily (with additional short-acting beta₂-agonist as needed for symptoms) or only as an as-needed rescue medication. The development of salmeterol in the late 1980s followed a rational approach to improve on the limitations of short-acting beta₂-agonists, which have only a 4- to 6-hour duration of action. Use of concomitant ICS during this period was relatively less common in patients with persistent asthma, since the role of inflammation in the pathophysiology of asthma was not widely appreciated. Since the mid-1990s, based on a large body of clinical data, asthma treatment guidelines and educational programs have stressed the importance of treating all patients with

¹ Available as: ADVAIR DISKUS® (fluticasone propionate and salmeterol inhalation powder), 100/50, 250/50, 500/50 and ADVAIR® HFA (fluticasone propionate mcg and salmeterol) Inhalation Aerosol, 45/21, 115/21 230/21

persistent asthma with an ICS to control the underlying inflammatory process that plays a central role in asthma. Thus, current national and international treatment guidelines and standards of care have evolved to recommend that LABAs be used as concurrent therapy with an ICS for both children and adults with persistent asthma [NAEPP, 2007; GINA, 2007].

1.3. Salmeterol Regulatory History

Approval has been granted to market salmeterol in over 100 countries as either SEREVENT (formulated as CFC or HFA metered dose inhalers or DISKUS dry powder inhaler) or as part of a combination product, ADVAIR (formulated as an HFA metered dose inhaler or DISKUS dry powder inhaler). Table 1 provides the year of approval for the first market for each salmeterol-containing product, as well as the year FDA approval was granted.

Table 1 Salmeterol Containing Products Year of First Market and FDA Approval

Salmeterol Containing Product	Market Approval	Asthma			COPD
		Adult (≥12 years)	Pediatric (≥4 years)	EIB	
SEREVENT CFC-MDI	UK	1990	1993	–	1996
	US ¹	1994	–	1994	1998
SEREVENT non-CFC MDI	UK	2006	2006	–	2006
SEREVENT DISKUS	UK	1994	1994	–	1996
	US	1997	1998	1998	2002
ADVAIR DISKUS	Sweden	1998	1998	–	2003
	US	2000	2004	–	2003 2008 ²
ADVAIR HFA	UK	2000	2004	–	–
	US	2006	–	–	–

1. CFC MDI discontinued in the US in 2002

2. Reduction of COPD exacerbations

1.3.1. Studies Influencing Safety-Related Aspects of SEREVENT and ADVAIR Labeling

1.3.1.1. SEREVENT Nationwide Surveillance (SNS) Study

The SEREVENT Nationwide Surveillance (SNS) study was performed between 1990 and 1992, following the launch of salmeterol (CFC-MDI) in the UK. 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 ratio randomization (salmeterol:albuterol) in 25,180 patients (>12 years of age) with moderate to severe asthma who required regular bronchodilator treatment. Patients were asked to continue all other medications that they were taking prior to entry into the study. At baseline, 69% of patients in both groups

reported receiving ICS. 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 adverse events from all causes was similar (4.0% for salmeterol vs. 4.1% for albuterol). For overall withdrawals, there was no difference between groups; however, there were statistically significantly fewer asthma-related withdrawals in the salmeterol group (2.91%) vs. the albuterol group (3.79%; $p=0.002$).

The incidence of asthma-related death was numerically, though not statistically significantly greater in patients taking salmeterol compared with the albuterol group. The findings from the SNS study were available at the time of FDA approval of SEREVENT Inhalation Aerosol.

Following the approval of SEREVENT Inhalation Aerosol, and based on spontaneous adverse event reports associated with the use of beta₂-agonists, GSK, in consultation with the FDA, agreed to conduct a large, prospective observational, randomized clinical trial to obtain safety surveillance information. SMART (Salmeterol Multicenter Asthma Research Trial) was conducted in order to further characterize the safety of salmeterol.

1.3.1.2. Salmeterol Multicenter Asthma Research Trial (SMART)

SMART was a multi-center, randomized, double-blind, parallel-group, placebo-controlled study conducted over 28 weeks at 6,163 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. The study originally planned to study 30,000 patients and was adjusted to 60,000 patients following a blinded review of overall event rates.

The study consisted of a single clinic visit (Visit 1) during which eligibility status was determined, written informed consent and baseline information were obtained, study procedures were reviewed and eligible patients were randomized to treatment. During Visit 1, patients 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. At baseline, 47% of patients in both groups reported using ICS. Total duration of study participation was 28 weeks with an additional 6-month post-study period to collect any spontaneously reported serious adverse events.

SMART was initiated in 1996 and terminated in January 2003. SMART showed a statistically significant increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176 patients treated with salmeterol versus 3 deaths out of 13,179 patients on placebo).

1.3.1.3. Discussion of SNS and SMART

In SNS, physicians reviewing the data concluded that under-treatment with ICS was a causative factor in the majority of fatal events reported [Castle, 1993]. Likewise, in SMART, in patients receiving salmeterol without reported ICS use at baseline, nine asthma deaths were reported compared with none in the placebo group. Comparatively, four asthma deaths were reported for salmeterol patients reporting ICS use at baseline compared with three in placebo [Nelson, 2006]. Thus, under-use of ICS in SNS and SMART may be a confounder modifying the results of each study, and in turn illustrates why SNS and SMART do not inform well on the possible role of salmeterol in the serious asthma-related outcomes of interest when salmeterol is used appropriately with concurrent ICS.

It has been suggested that while inflammation in the lung is uncontrolled in the absence of or under-use of ICS, the perception of worsening symptoms can be reduced by bronchodilation with beta₂-agonist bronchodilators. This reduced perception of worsening asthma due to inflammation may cause a delay in seeking medical care during an acute asthma crisis [McIvor, 1998]. Delay in seeking medical care in asthma, as also noted in other chronic diseases such as hypertension and stroke, are known risk factors for increased risk of untoward serious asthma-related outcomes [Dracup, 1997; Schroeder, 2000]. Observational data in New Zealand of the Maori, a native population, showed a higher rate of asthma-death compared with the non-Maori population. This outcome was driven by over-use of short-acting beta₂-agonists and under-use of ICS. Once New Zealand instituted an asthma educational program emphasizing the daily use of ICS, the rate of asthma death in the Maori decreased and now approaches the general population of New Zealand [Pomare, 1991; Pomare, 1992; D'Souza, 1998].

It is also possible that SNS and SMART results are confounded by the loss of the susceptible population over the course of the studies. Uncontrolled and severe asthma are known risk factors for asthma-related hospitalization and death [Strunk, 2002]. In both SNS and SMART, statistically significantly more patients withdrew from the non-salmeterol comparison arms due to asthma symptoms. Withdrawals due to treatment failure may represent unbalanced removal of patients with unstable or severe asthma. It remains unknown whether these patients may have experienced the serious asthma-related outcomes of interest; however, the loss of the susceptible population of patients, while speculative, is possible.

1.3.2. Labeling Changes Based on the Findings from SMART

The labeling for both SEREVENT and the combination product, ADVAIR, have been revised on several occasions based on the findings of serious asthma outcomes observed in SMART [Nelson, 2006]. Following termination of the study, a boxed warning was incorporated into the labelling for SEREVENT and ADVAIR on 11 August 2003.

On 13 July 2005, the safety data of LABAs for the treatment of asthma were extensively reviewed by the Pulmonary and Allergy Drugs Advisory Committee. The committee unanimously supported the positive benefit-to-risk profile of salmeterol and formoterol and requested additional wording in the label to inform on rare but serious asthma-related outcomes that may be associated with SEREVENT and FORADIL (formoterol

fumarate). Updated product labeling was approved by FDA on 02 March 2006. This update included revisions to the boxed warning and the addition of Medication Guides for patients for SEREVENT DISKUS and ADVAIR DISKUS. On 19 June 2006, FDA approved new safety labeling and a Medication Guide for patients for FORADIL. SYMBICORT Inhalation Aerosol (budesonide; formoterol fumarate dihydrate) a combination product, was approved on 21 July 2006 and includes the warnings comparable to FORADIL.

On 28 November 2007, a Pediatric Advisory Committee meeting was held as a result of the requirement under the Best Pharmaceuticals for Children Act to review safety data for the 1-year period following granting of pediatric exclusivity for salmeterol. While no new safety signals were identified in the year after granting exclusivity for salmeterol, based on the FDA's analysis of pediatric data from SMART and studies of formoterol in pediatric patients, the committee recommended a more thorough, formal benefit-to-risk profile of LABAs in the treatment of asthma.

1.3.3. Conclusions from Recent UK Medicines and Healthcare Products Regulatory Agency (MHRA) LABA Review

The Medicines and Healthcare products Regulatory Agency (MHRA, the UK regulatory agency) also conducted a comprehensive review on the use of LABAs in the treatment of asthma and published their conclusions in January 2008. The MHRA reviewed the following: the pharmacology of the two currently available LABAs, salmeterol and formoterol, and the combination products, SERETIDE (ADVAIR) and SYMBICORT; the current position of research into the benefit to risk profile of the beta₂-adrenoreceptor genotype; the epidemiology of asthma in relation to the introduction of LABAs; and an overall assessment of the benefits and risks of LABAs in the treatment of asthma.

The conclusions from the review were [[MHRA](#), 2008]:

- *Epidemiological data show that since the introduction of LABA, there has been a decrease in asthma-related hospitalizations in adolescents and a decrease in asthma-related mortality in all ages.*
- *Data from randomized, controlled clinical trials do not suggest a similar safety signal to that shown in postmarketing studies (SNS and SMART), probably because of more consistent use of concomitant inhaled corticosteroids in randomized controlled settings. The data support the use of LABA in conjunction with inhaled corticosteroids in the treatment of moderate to severe asthma consistent with the guideline on the management of asthma from the British Thoracic Society and Scottish Intercollegiate Guidelines Network.*
- *To aid compliance with the concomitant use of inhaled corticosteroids and LABA, a combination inhaler should be used when appropriate.*

The MHRA is currently reviewing the role of LABAs in the treatment of asthma in children younger than 12 years of age, and GSK have provided all available data to assist with this review.

1.3.4. Current FDA LABA Review – December 2008

In January 2008, FDA initiated a series of requests of GSK for clinical trial information from controlled clinical trials evaluating salmeterol. The FDA requested identification of all double-blind, randomized, chronic dosing, controlled asthma clinical trials containing salmeterol from the entire development program. Within these trials, all serious adverse events (SAEs) were assessed and independently adjudicated to identify asthma-related hospitalizations, asthma-related-intubations, asthma-related deaths, and all cause deaths.

GSK provided responses to each request, with the final requested clinical data sets being submitted to FDA on 03 July 2008. The final database provided to FDA included over 200 studies representing over 100,000 patients. Over this period, GSK developed *a priori* statistical approaches to examine the associations (if any) of salmeterol and the outcomes of interest [[RM2008/00078/00](#)]. Included in this briefing document are the results of GSK's analyses of the serious outcomes indicated above, as part of the data requested by FDA. In addition, this document will review key efficacy data from GSK sponsored studies as well as observational studies, thus providing a comprehensive summary of the benefit to risk profile of salmeterol-containing products in the treatment of asthma.

Based on this comprehensive review of the safety of salmeterol-containing products, GSK submitted a supplement to provide for revisions to the labeling for SEREVENT DISKUS. This supplement provided further information to inform health care professionals and patients on the appropriate use of SEREVENT DISKUS in the treatment of asthma. In particular, by changing the indication statement, the proposed label emphasizes the imperative of concurrent use of ICS in asthma patients treated with SEREVENT DISKUS. Salmeterol, when used with an ICS either via separate inhalers or in a fixed-dose combination, provides unsurpassed therapeutic benefits to patients with asthma and the data presented in this document substantiate the positive benefit-to-risk profile.

2. BENEFIT OF LABA ADDED TO ICS FOR THE TREATMENT OF ASTHMA

2.1. Benefit of Adding LABA to ICS in the Treatment of Asthma: Published Evidence

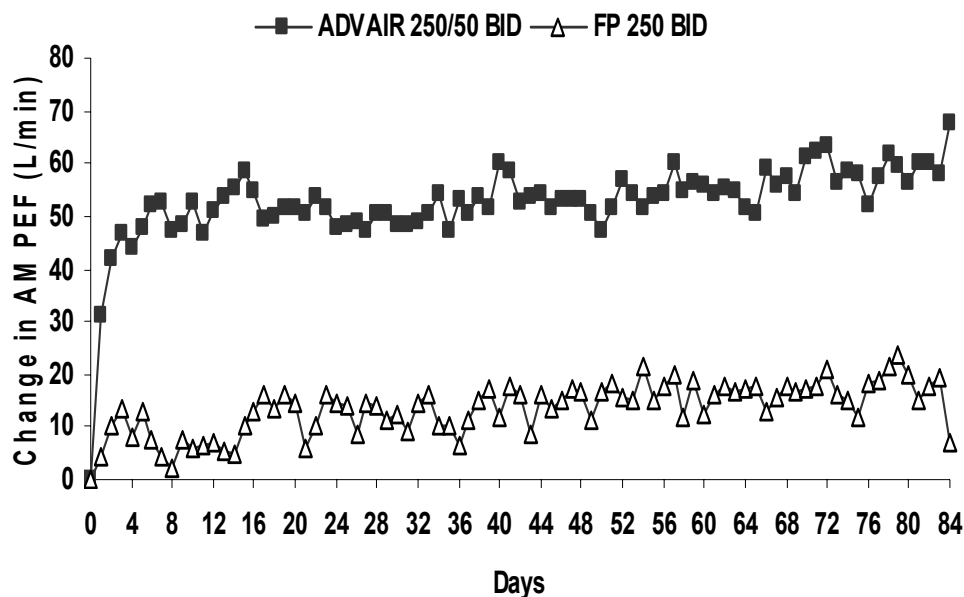
Current evidence-based national and international asthma treatment guidelines recommend use of ICS for all children and adults with persistent asthma. However, in both children and adults for whom ICS alone is not sufficient to control the symptoms of asthma, the guidelines recommend adding an inhaled LABA to ICS, or increasing the dose of ICS, or adding another medication (e.g., leukotriene modifier) as part of a stepwise treatment approach to gain control of asthma in all age groups [[NAEPP](#), 2007; [GINA](#), 2007]. Treatment guidelines also clearly state that the appropriate use of a LABA for the treatment of asthma is only with concomitant ICS [[NAEPP](#), 2007; [GINA](#), 2007].

In patients symptomatic on ICS alone, the addition of salmeterol to ICS has been repeatedly shown in controlled clinical studies to result in statistically significantly

greater improvements in lung function, symptoms, and rescue albuterol use compared with increasing the ICS dose alone [Greening, 1994; Woolcock, 1996; Condemi, 1999; Murray, 1999; Kelsen, 1999] or continuing the ICS at the same dose [Nathan, 2003; Pearlman, 2004; Nelson, 2003; van Noord, 2001; Kavuru, 2000; Shapiro, 2000; Aubier, 1999].

The greater benefit on lung function of adding salmeterol to an ICS is illustrated by the representative pivotal trial in Figure 5. In this study, patients were randomized to 12 weeks of twice-daily treatment with ADVAIR 250/50, FP 250mcg, salmeterol 50mcg, or placebo.

Figure 5 Improvement in Daily AM PEF (L/min): Study SFCA3003 [Shapiro, 2000]



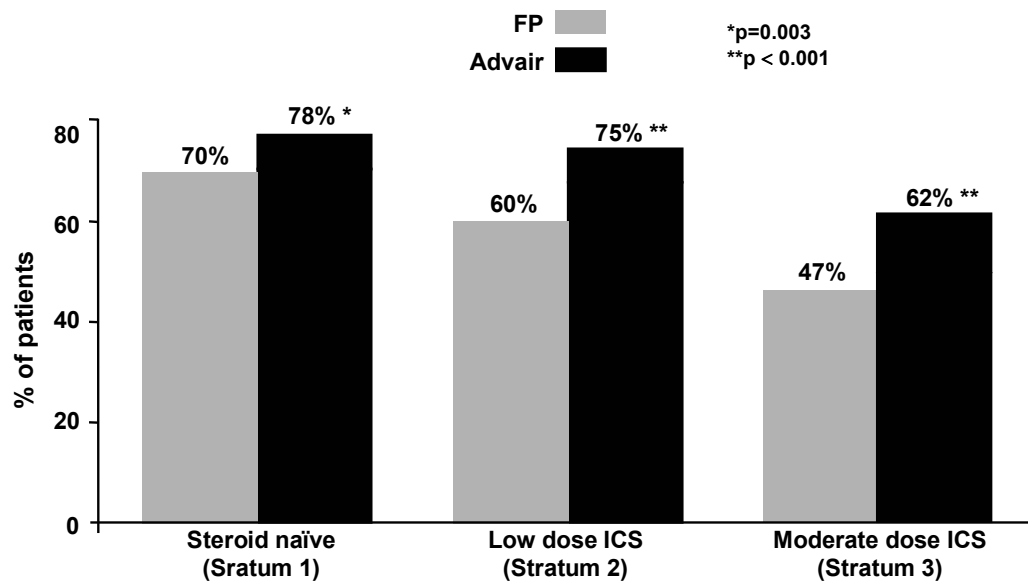
Treatment arms of salmeterol alone and placebo not shown

Treatment with ADVAIR 250/50 resulted in statistically significantly greater improvements in lung function (peak expiratory flow, PEF) compared with FP alone [Shapiro, 2000].

Guidelines for the management of asthma issued by the Global Initiative for Asthma (GINA/National Institutes of Health [NIH]) [GINA, 2002] state that the therapeutic aim should be to achieve overall asthma control in order to minimize the impact of asthma on the individual patients. Thus, a large double-blind, randomized, multi-national study of 3,416 patients (Gaining Optimal Asthma Control [GOAL]) [Bateman, 2004], compared ADVAIR and FP alone for one year and evaluated asthma control (well-controlled and total controlled asthma). Eligible patients were stratified by baseline therapy (ICS-naïve, low-dose ICS, or moderate-dose ICS) and initiated on either twice-daily ADVAIR 100/50 or FP 100mcg (ICS-naïve or low-dose ICS strata), or ADVAIR 250/50 or FP 250mcg (moderate-dose ICS stratum). Patients' therapy (ADVAIR or FP) was then titrated upwards with the aim to achieve total control of asthma. Figure 6 shows the proportion

of patients who achieved well-controlled asthma in each stratum over the one-year study period.

Figure 6 GOAL Study: Proportion of Patients Achieving Well-Controlled Asthma

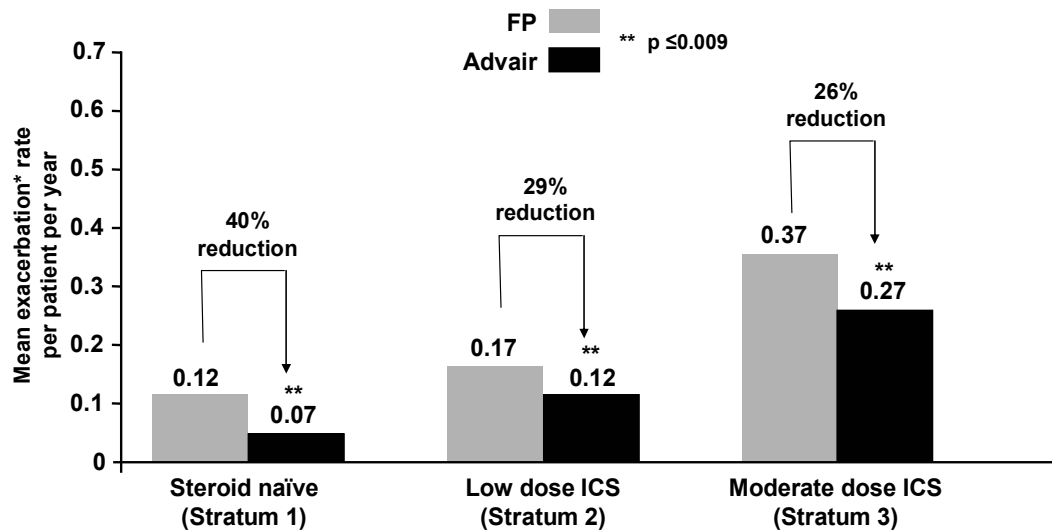


Results from this one-year study ([Figure 6](#)) showed that a statistically significantly greater proportion of patients (in each stratum) achieved well-controlled asthma on ADVAIR compared with FP.

The impact of asthma on patients' quality of life can be significant. In the GOAL study, the subjective impact of asthma on patients' perception of health was evaluated through use of a validated instrument called the Asthma Quality of Life Questionnaire (AQLQ) [[Juniper, 1992](#); [Juniper, 1994](#)]. After one year of treatment, statistically significantly more patients on ADVAIR achieved clinically meaningful improvements (≥ 0.5) in quality of life from baseline compared with FP [[Bateman, 2007](#)].

The 2007 NIH asthma treatment guidelines also state a key goal of therapy is to prevent reoccurring exacerbations of asthma and minimize ED visits and hospitalizations. In the GOAL study, an exacerbation was defined as a worsening of asthma requiring oral corticosteroids or ED visits/hospitalization. Results are shown in [Figure 7](#).

Figure 7 Exacerbation Rates per Patient per Year Over Weeks 1-52 (GOAL Study)



* Exacerbations defined as requiring oral steroids or hospitalizations/emergency visits during the 52-week study

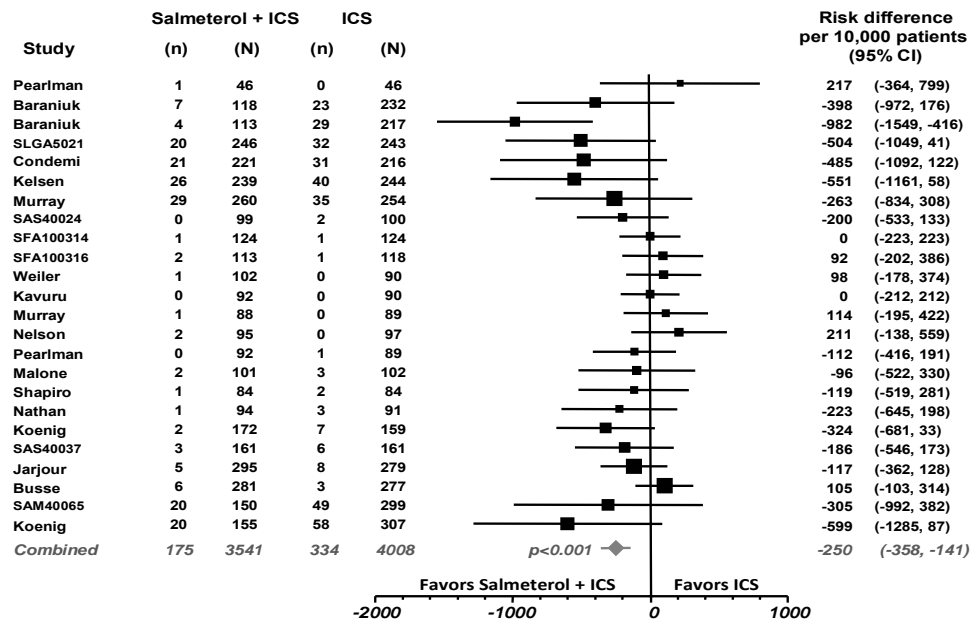
ADVAIR provided a statistically superior reduction in asthma exacerbation rates compared with FP for each stratum ($p \leq 0.009$) (Figure 7).

The treatment benefit of adding a LABA (salmeterol or formoterol) to ICS compared with ICS alone has also been demonstrated in four meta-analyses published by the Cochrane Group. These meta-analyses demonstrate a statistically significant benefit in measures of asthma control with the addition of a LABA to an ICS compared with: 1) ICS alone at a higher total daily dose [Greenstone, 2005], 2) ICS alone at the same total daily dose in both adult and pediatric patients on baseline ICS [Ni Chroinin, 2005] and 3) adult patients not on baseline ICS [Ni Chroinin, 2004] therapy. Additionally, a meta-analysis by Gibson and colleagues showed that ICS plus LABA produced statistically significantly greater improvements in a composite measure of asthma control compared with ICS at the same or higher total daily dose in adults [Gibson, 2007].

The treatment benefit of adding a LABA to ICS has also been shown in meta-analyses compared with ICS plus leukotriene modifier [Ducharme, 2006] and ICS plus theophylline [Tee, 2007].

Meta-analyses have also shown a statistically significant reduction of asthma exacerbations with ICS plus LABA compared with ICS alone. A recent meta-analysis of 24 US studies [Bateman, 2008] involving 7,549 participants, showed a 41% reduction in the percentage of patients experiencing a severe exacerbation with ICS plus salmeterol (4.9%) compared with ICS alone (8.3%) (Figure 8).

Figure 8 Decreased Relative Risk for Severe Asthma Exacerbations Requiring Oral Corticosteroids with Salmeterol + ICS Compared with ICS



Adapted from Bateman, et al. *Ann Intern Med* 2008;149:33-42.

The risk difference for a severe exacerbation requiring oral corticosteroids was statistically significantly in favor of patients using salmeterol plus ICS compared with ICS alone (250 fewer exacerbations per 10,000 patients).

Salmeterol has been extensively studied for over two decades. As described in this section, the large body of published evidence from individual studies and numerous meta-analyses consistently demonstrate the significant benefit of adding a LABA to ICS over and above treatment with ICS alone on measures of asthma control and quality of life, including asthma exacerbations. These findings clearly demonstrate the additional clinical benefit of ADVAIR treatment compared with FP alone.

2.2. Efficacy Analyses from GSK-Sponsored Clinical Trials

2.2.1. Introduction and Methods

This section presents the results of a systematic approach to summarize the benefits of salmeterol administered with ICS on lung function, asthma symptoms, rescue albuterol use, and quality of life from GSK-sponsored clinical trials. The results are presented separately for adolescents/adults and children.

For the efficacy analysis, a subset of all double-blind, randomized, parallel group, repeat-dose studies of salmeterol (including salmeterol-containing treatment arms, e.g., ADVAIR) were identified using pre-specified criteria. For example, only studies specifically designed and powered to establish the efficacy of salmeterol when used appropriately with concurrent ICS, and for which efficacy data were available in a

consistent format for comparison across studies were selected. A total of 33 studies (total N=14,506 for all treatments) met these criteria for inclusion; in 25 of these studies, salmeterol plus ICS was administered as ADVAIR. Since each of the studies selected was individually powered to evaluate efficacy and the studies were heterogeneous with regard to baseline asthma severity and baseline asthma medications, a meta-analysis was not performed. Rather, efficacy parameters were examined and reported individually for each study.

Further detail on the methods for inclusion and analysis of efficacy data from clinical trials with salmeterol plus ICS are contained in Attachment 1.

Results of the efficacy analyses were replicated in adults and children and showed a greater benefit of adding salmeterol to ICS compared with ICS or other treatment comparisons (e.g., ICS plus montelukast).

2.2.2. Efficacy Results

Key measures of asthma control from studies in adolescents and adults and from studies in children are presented in this section for the following:

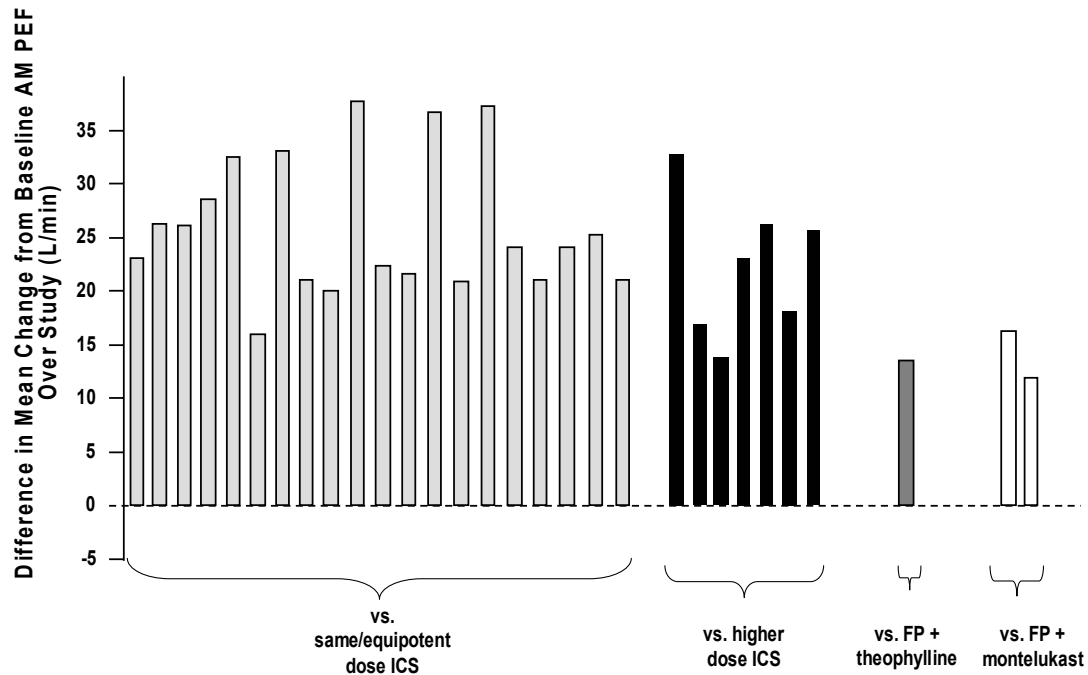
- Lung function (AM PEF)
- Symptom control:
 - Days with no asthma symptoms (symptom-free days)
 - Days with no use of albuterol for asthma symptoms (rescue-free days).
- Quality of Life (AQLQ)

2.2.2.1. Adolescents and adults

Lung function

Lung function is an important clinical endpoint, as decreased lung function in asthma has been associated with increased risk of exacerbations [[Kitch, 2004](#)]. Twenty-five (25) studies, 2 weeks to 52 weeks in duration, evaluated lung function (AM PEF) over the study duration of salmeterol plus ICS vs. ICS (same/equipotent dose or higher dose) or ICS plus add-on therapy (montelukast or theophylline). [Figure 9](#) shows the difference from individual studies between salmeterol plus ICS 1) vs. ICS at the same/equipotent dose, 2) vs. ICS administered at a higher dose, or 3) vs. ICS plus theophylline or montelukast in the mean change from baseline in AM PEF (L/min) over the study duration.

Figure 9 Benefit in Lung Function (AM PEF, L/min) for Salmeterol Plus ICS Beyond that Seen With ICS



Each bar represents a treatment difference in a single study.
A single study could contain more than one treatment comparison.

For all studies that measured PEF, treatment with salmeterol plus ICS resulted in consistently greater benefits in lung function beyond that seen with ICS. The beneficial treatment effect of salmeterol on lung function was preserved in both short-term and long-term studies. Across studies there was a 12L/min to nearly 40L/min average increase in AM PEF with the addition of salmeterol beyond that seen with ICS.

In addition, but not shown here, similar results were seen with FEV₁.

Asthma symptoms

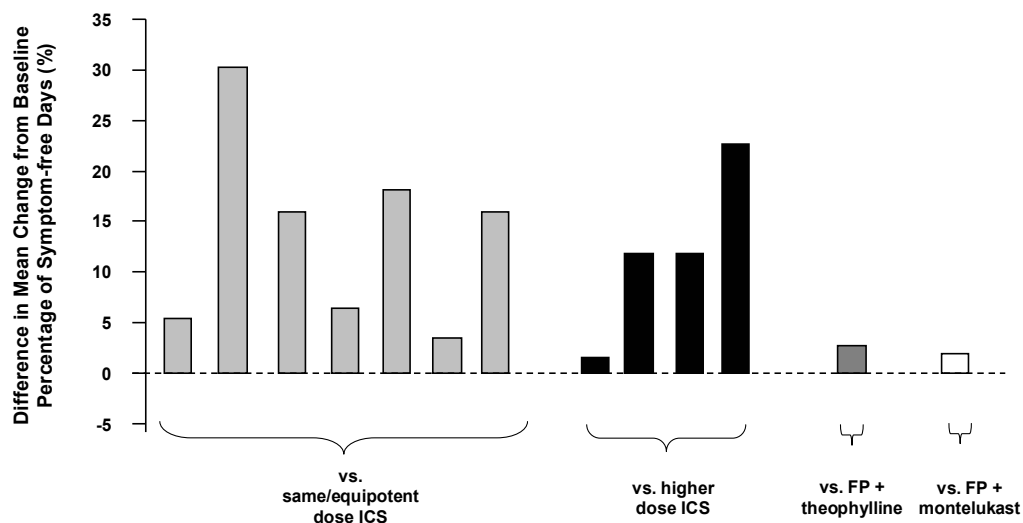
Asthma symptoms and albuterol use are important indicators of asthma control and can predict worsening asthma and the inability to perform normal daily activities. These are two of the most frequently used indicators by which physicians assess response to treatment and whether a change in asthma management is required [Diette, 2007].

The impact of asthma symptoms on patients' lives is substantial. In a large survey of patients ≥ 16 years of age with asthma prescribed regular maintenance therapy with ICS with or without LABA, more than 70% of patients reported the worst aspects of having asthma were the interference in their daily lives and the panic they felt when their asthma symptoms increased. Other concerns reported by approximately 50% of these patients were the embarrassment of having an asthma attack in front of others and the fear of having to go to the emergency room or hospital [Partridge, 2006].

Control of asthma symptoms is presented as two related efficacy endpoints: percent of days without asthma symptoms (symptom-free days) and percent of days with no use of albuterol for asthma symptoms (rescue-free days).

In a similar format to [Figure 9](#), [Figure 10](#) shows the difference from individual studies between salmeterol plus ICS 1) vs. ICS at the same/equipotent dose, 2) vs. ICS administered at a higher dose, or 3) vs. ICS plus theophylline or montelukast in the mean change from baseline in percent symptom-free days from 11 studies. Fewer studies collected symptom-free days in the same format; thus, the number of studies represented in [Figure 10](#) is less than the number shown for AM PEF ([Figure 9](#)).

Figure 10 Benefit in Symptom-Free Days (%) for Salmeterol Plus ICS Beyond that Seen With ICS

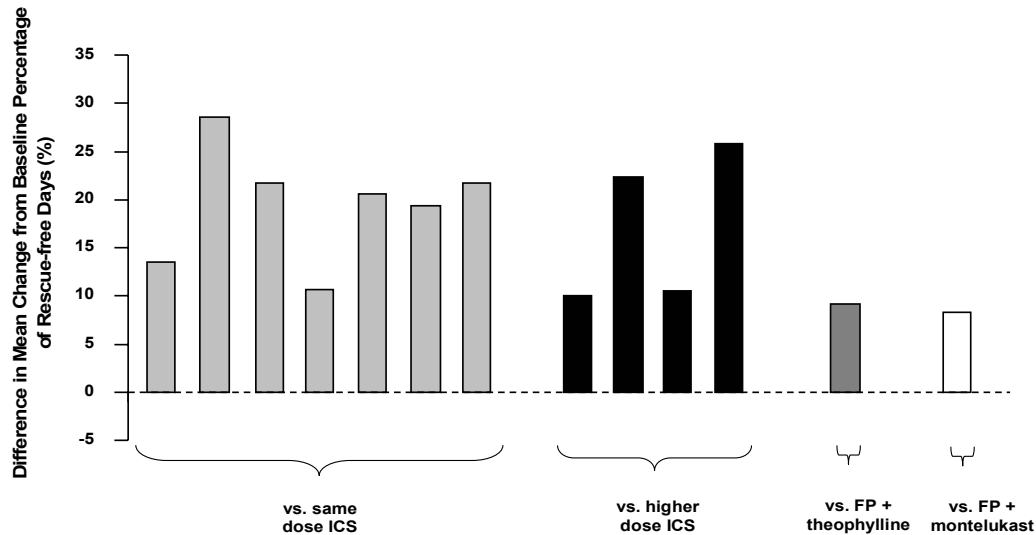


Each bar represents a treatment difference in a single study.
A single study could contain more than one treatment comparison.

For all studies that measured symptom-free days, treatment with salmeterol plus ICS resulted in consistently greater percentage of symptom-free days beyond that seen with ICS. The beneficial treatment effect on asthma symptoms was preserved in both short-term and long-term studies. Across studies there was a 2- to 30-percentage-point average increase in the proportion of days a patient was free from asthma symptoms with the addition of salmeterol beyond that seen with ICS.

[Figure 11](#) shows the difference for salmeterol plus ICS 1) vs. ICS at the same/equipotent dose, 2) vs. ICS administered at a higher dose, or 3) vs. ICS plus theophylline or montelukast in the mean change from baseline in percent rescue-free days in 11 studies. Fewer studies collected rescue-free days in the same format; thus, the number of studies represented in [Figure 11](#) is less than the number shown for AM PEF ([Figure 9](#)).

Figure 11 Benefit in Rescue-Free Days (%) for Salmeterol Plus ICS Beyond that Seen With ICS



Each bar represents a treatment difference in a single study.
A single study could contain more than one treatment comparison.

For all studies that measured rescue-free days, treatment with salmeterol plus ICS resulted in consistently greater benefits in rescue-free days beyond that seen with ICS. The beneficial treatment effect of salmeterol plus ICS on rescue albuterol use was preserved in both short-time and long-term studies. There was an 8- to 29-percentage-point average increase in the proportion of days a patient did not require rescue albuterol.

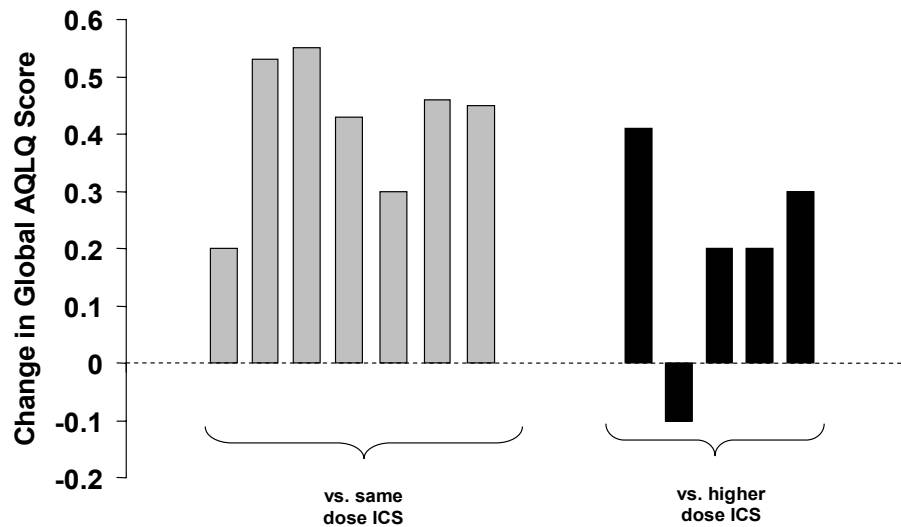
Asthma-related quality of life

The impact of asthma on patients' quality of life is substantial. Asthma limits patients' daily activities including sports and recreation, disturbs sleep, and causes patients to miss work and school. Patients' perception of asthma and its effects on daily living are important for the proper assessment and treatment of asthma [[Asthma in America](#), 1998].

Asthma-related quality of life is presented as the global AQLQ score, based on a 7-point scale where 1 = maximum impairment and 7 = no impairment.

In a similar format to [Figure 9](#), [Figure 12](#) shows the difference for salmeterol plus ICS 1) vs. ICS at the same/equipotent dose or 2) vs. ICS administered at a higher dose, in global AQLQ scores. The majority of these studies administered salmeterol plus ICS as ADVAIR. Fewer studies collected AQLQ; thus, the number of studies represented in [Figure 12](#) is less than the number shown for AM PEF ([Figure 9](#)).

Figure 12 Benefit in Asthma-Related Quality of Life (Global AQLQ Score) for Salmeterol Plus ICS Beyond that Seen With ICS



Each bar represents a treatment difference in a single study.
A single study could contain more than one treatment comparison.

Treatment with salmeterol plus ICS resulted in greater benefits in asthma-related quality of life beyond that seen with ICS for all studies administering salmeterol plus ICS as ADVAIR, and for all but one of the other comparisons. The beneficial treatment effect on quality of life was preserved in both short-term and long-term studies. Across the majority of studies, there was a 0.2 to a greater than 0.5 average additional increase in overall AQLQ score with the addition of salmeterol beyond that seen with ICS.

Summary of efficacy results for adolescents and adults

Overall, results of the efficacy analyses in adolescents and adults clearly showed the greater benefit of adding salmeterol to ICS in these studies, the majority of which administered ADVAIR, compared with ICS or other treatment comparisons (e.g., ICS plus montelukast).

2.2.2.2. Pediatrics

2.2.2.2.1. Introduction

In the US, 6.2 million children <18 years of age have current asthma [CDC, 2007; American Lung Association, 2007]. Children experience a higher incidence of asthma exacerbations resulting in hospitalization or emergency department (ED) visits compared with adults. In addition, asthma-related illness is the most common reason for missed school days among children; it is estimated that in 2003, in children ≤18 years age with one asthma attack in the previous year, there were 12.8 million missed school days [American Lung Association, 2007]. In 2004, the Centers for Disease Control (CDC) estimated 159,500 hospitalizations and 670,000 ED visits due to asthma in children under the age of 15 [CDC, 2007].

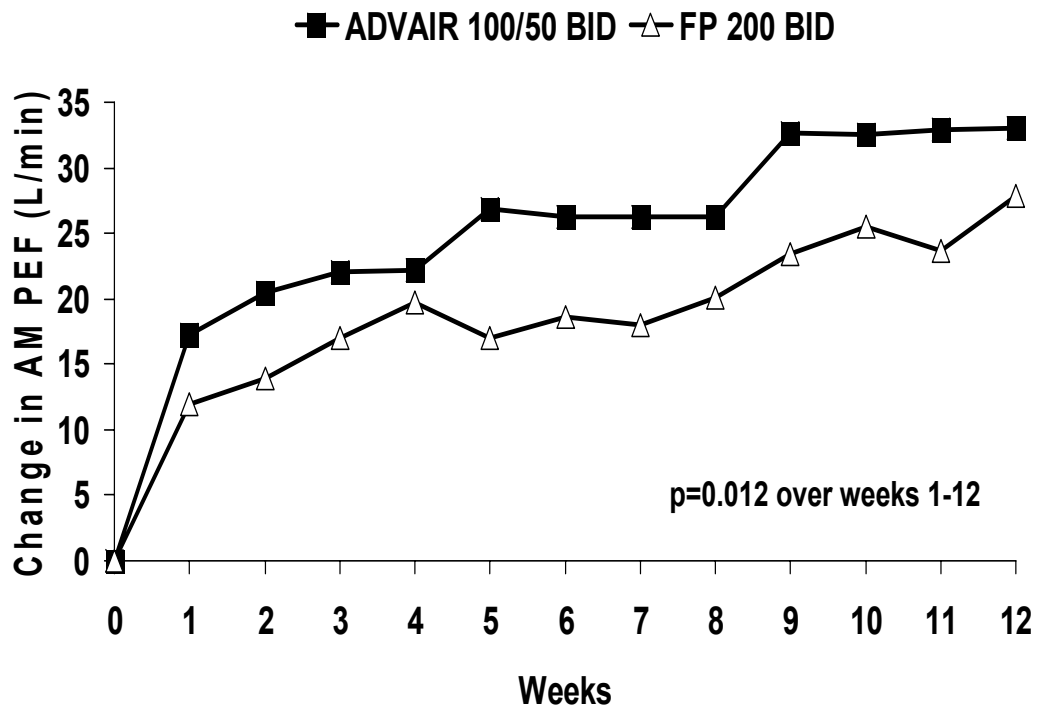
As with adults, asthma treatment guidelines recognize ICS as the cornerstone of therapy for persistent asthma in children with a stepwise approach to treatment recommended based upon the level of asthma control [NAEPP, 2007; GINA, 2007]. When ICS alone is not sufficient to control asthma in children, guidelines recommend increasing the ICS dose or addition of other controller therapy, including LABA or leukotriene modifier. In the US, higher doses of ICS (e.g., doses of FP >200mcg/day) are not approved for use in children; thus, although higher doses are used by medical practitioners despite the current label restrictions, minimizing the ICS dose used in children is desirable to avoid dose-dependent systemic effects of ICS. In addition, the dose-response to increasing the ICS dose in children may be limited [Masoli, 2004]. As an alternative in children symptomatic on ICS, one option is to add salmeterol by administering the combination product, ADVAIR, thus helping to ensure the lowest effective dose of ICS is used. ADVAIR DISKUS 100/50 is indicated for use in children 4 to 11 years of age who remain symptomatic on ICS.

Compared with adults, there are fewer studies in children designed to examine the efficacy profile of asthma medications. Pediatric studies also present unique challenges. Studies have confirmed that parents often underestimate their child's actual asthma symptoms [Fuhlbrigge, 2006]. While most experts agree that the triggers (i.e., exercise or viral insult) of asthma in pediatric patients are similar to adults, children with persistent asthma have more asymptomatic periods often with normal or near-normal lung function and greater variation in the severity of the disease compared with adults [Chipps, 2006; Fuhlbrigge, 2006].

The difficulty in demonstrating symptom improvement in children in clinical studies is illustrated by the results of well-designed clinical trials in well-established asthma medications in which statistically significant improvements were demonstrated for lung function but not asthma symptoms for montelukast relative to placebo [Knorr, 1998], FP relative to placebo [Levy, 2006], and formoterol plus budesonide relative to budesonide alone [Pohunek, 2006].

The beneficial effect on lung function of adding salmeterol to an ICS (FP) compared with increasing the FP dose in children in a recent study is shown in Figure 13. In this study, 303 children 4 to 11 years of age uncontrolled on FP 100mcg BID were randomized to 12 weeks of either twice-daily ADVAIR 100/50 or FP 200mcg.

Figure 13 Improvement in Daily AM PEF (L/min): Study SAM104926 [GSK CTR]



Both treatments improved lung function over time. Treatment with twice daily ADVAIR 100/50 resulted in statistically significantly greater improvements in lung function compared with twice daily FP 200mcg over the 12 weeks.

2.2.2.2.2. Summary of pediatric studies comparing ICS plus salmeterol as additional therapy vs. higher dose ICS alone

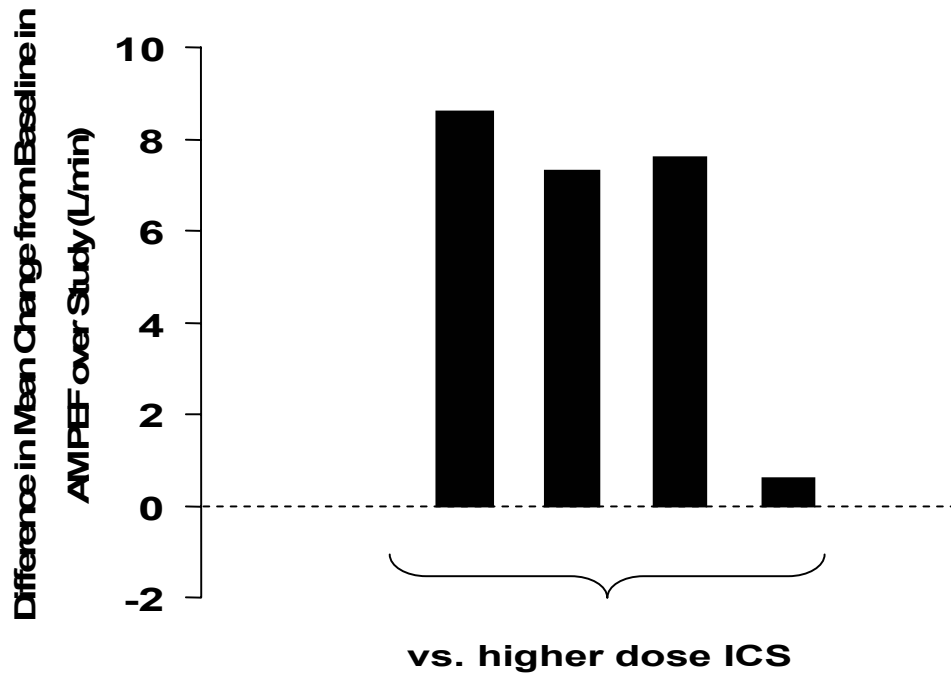
This section presents the results of efficacy outcomes across GSK pediatric studies which compared treatment arms of salmeterol plus ICS and a higher dose of ICS in patients symptomatic on ICS alone. These studies in pediatric patients address the clinical question of whether to add a LABA or increase the ICS dose when a child is not controlled on ICS alone.

The methods for study selection are described in Attachment 1.

A total of four pediatric studies in children 4 to 16 years of age were specifically designed to compare salmeterol plus ICS vs. higher-dose ICS therapy in children symptomatic on ICS alone. The duration of double-blind study treatment ranged from 8 to 54 weeks. Results of these comparisons for AM PEF, symptom-free days, and rescue-free days, are presented below. Asthma-related quality of life was not assessed in these studies.

Measures of pulmonary function in children are important indicators of asthma severity, with low values associated with exacerbations over time [Fuhlbrigge, 2001]. Figure 14 shows the difference from individual studies between salmeterol plus ICS vs. higher dose ICS in the mean change from baseline in AM PEF (L/min) over the study duration.

Figure 14 Benefit in Lung Function (AM PEF, L/min) for Salmeterol Plus ICS Beyond That Seen with Higher Dose ICS



Each bar represents a treatment difference in a single study

In all studies, treatment with salmeterol plus ICS resulted in greater improvement in AM PEF vs. higher dose ICS.

Asthma symptoms and albuterol use are important indicators of asthma control and quality of life in adults and children. The burden of asthma on children was illustrated by the results of a large survey of children 4 to 18 years of age (or their parents). The survey found that the majority (60%) of children reported asthma symptoms during the day in the previous 4 weeks, and 30% of children or their parents felt fearful as a result of their/their child's asthma. For 19% of children and 26% of parents surveyed, asthma symptoms including the inability to breathe or shortness of breath were considered the worst thing about their/their child's asthma [Children & Asthma in America, 2004].

For an individual patient, improvements in symptoms can be measured; however, as stated above, since children often have asymptomatic periods, it is more difficult to detect differences in asthma symptom-based endpoints in a population of children. Results of these comparisons for symptoms and rescue use are not presented graphically for the four pediatric studies comparing salmeterol plus ICS with a higher dose of ICS since these measures were not collected in the same manner. In these four studies, patients'

symptoms and use of rescue albuterol improved from baseline levels with salmeterol plus ICS and higher dose ICS; these improvements were statistically significantly greater with ADVAIR compared with higher dose ICS for one of the four studies, and showed small numerically greater improvements for the other three studies.

Given the challenge of documenting treatment effects in pediatric patients based on changes in symptoms and lung function, some researchers recommend examining reductions in exacerbations as an alternative measure of efficacy [Reddel, 1999]. While specifically designed randomized controlled trials evaluating exacerbations with SEREVENT and ADVAIR have not been conducted by GSK in pediatric populations, large observational studies have confirmed a statistically significantly lower risk of severe exacerbations resulting in ED visits and/or hospitalizations comparing ADVAIR vs. ICS and vs. ICS plus montelukast in children and are shown in Section 4.4.3.

Overall, studies in children demonstrated that salmeterol plus ICS provided a greater improvement in lung function compared with ICS. Modest improvements in symptoms and rescue albuterol use with ICS plus salmeterol were consistently observed relative to ICS. Concurrent use of salmeterol with ICS (e.g., ADVAIR DISKUS) is an efficacious treatment option for children and remains an important therapeutic option for children who remain symptomatic on an ICS.

2.2.3. Summary

Adding LABA to ICS in patients requiring additional asthma control is a well-accepted treatment strategy that has been proven through clinical development programs meeting FDA expectations and is endorsed by evidence-based national and international treatment guidelines. The consistent benefit of this treatment strategy was confirmed in the current analysis in multiple randomized, controlled clinical trials in adolescents and adults, in which treatment with salmeterol plus ICS was compared with ICS administered at the same or higher total daily dose or with add-on non-ICS therapy, confirms published data and provides additional support for this treatment option.

In children, efficacy data from randomized, controlled clinical trials demonstrated the greater benefit of adding salmeterol to ICS compared with higher dose ICS as shown for pulmonary function and other measures of asthma control. Higher doses of ICS are not approved for use in children, but are used by medical practitioners despite the current label restrictions. The concurrent use of salmeterol with an ICS as an alternative treatment option minimizes the ICS dose used and may avoid dose-dependent systemic effects of ICS.

3. SAFETY DATA FROM RANDOMIZED CONTROLLED CLINICAL TRIALS

3.1. Introduction

During the development period of salmeterol, asthma was considered primarily a disease of airway smooth muscle dysfunction and the standard of care for patients with persistent asthma often included only bronchodilators. Therefore, the development programs for

SEREVENT included patients with persistent asthma who often were not taking concurrent anti-inflammatory treatment, or if they were, it may have been as background medication rather than study drug and thus, was not regulated or reinforced by protocol. The results of the clinical programs showed that SEREVENT was an effective bronchodilator whether or not administered with an ICS (e.g., improving lung function and reducing daytime and night time symptoms and short-acting beta₂-agonist use).

Since the approval to market SEREVENT, evidence-based assessments of the pathophysiology of asthma have established that asthma is a disease of both inflammation and smooth muscle hyperreactivity [GINA, 1995; NHLBI, 1997]. In fact, the inflammatory component of asthma should be the primary target of asthma therapy. However, ICS alone do not fully control asthma for many patients, and the dose response curve for ICS is relatively flat [Szeffler, 2002]. For patients who remain symptomatic on anti-inflammatory medications such as ICS, adding LABA to ICS further improves control of asthma by treating the bronchospastic components of asthma which are not well controlled by ICS alone.

The benefits of concurrent use of LABA and ICS compared with equipotent or higher dose ICS alone have been consistently demonstrated in clinical trials and independent meta-analyses by examining improvements in asthma control and reductions in worsening asthma (i.e., exacerbations) in both children and adults [Greenstone, 2005; Ni Chroinin, 2005; Walters, 2007]. In addition, LABAs used concurrently with ICS have been shown to be more effective than other treatment options such as ICS used concurrently with leukotriene modifiers [Ducharme, 2006]. The most recent national [NAEPP, 2007] and international [GINA, 2007] asthma-treatment guidelines, based on systematic reviews of the literature, all recommend the use of LABA plus ICS as a preferred therapy for moderate or severe asthma based on the superior effectiveness of this combination compared with alternative treatment options in controlling asthma in both children and adults.

Prior to contemporary treatment guidelines that LABA should only be used concurrently with ICS, two separate large surveillance trials were conducted in which patients receiving SEREVENT experienced higher rates of rare, but serious adverse events, including asthma-related death. The outcomes from SNS [Castle, 1993] and SMART [Nelson, 2006] were primarily observed with SEREVENT in patients not receiving concurrent ICS or in patients under-treated with ICS. However, neither study was designed to address the role of ICS use with SEREVENT.

GSK performed a comprehensive review of randomized controlled trials of salmeterol for the treatment of persistent asthma. A meta-analysis was planned to address:

- The safety profile of salmeterol, when used appropriately with ICS both in a single inhaler and in separate inhalers, in accordance with current asthma treatment guidelines and standards of care.
- The safety profile of salmeterol when used without an ICS, which was common when salmeterol was first approved, but is not in accordance with current asthma treatment guidelines and standards of care.

3.1.1. Safety Database Scope and Exposure for All GSK Studies

The database for this meta-analysis contains all clinical studies of salmeterol sponsored by GSK which were randomized, double-blind, chronic dosing designs. The only types of studies not included were pharmacokinetic, pharmacodynamic, open-label or single-dose studies.

In these clinical trials, ICS could be administered in several different ways:

- Background ICS (ICS_{BK}) refers to patients who reported taking ICS prior to the study and were instructed to continue that ICS throughout the treatment period of the study. However, background ICS was not dispensed as part of the protocol nor was there systematic reinforcement or any measure of continued adherence to the medication.
- ICS administered as blinded study medication (ICS_{SD}) could be administered in separate inhaler devices (Sal + ICS_{SI}).
- ICS (FP) administered concurrently with salmeterol in a single device (ADVAIR).

In agreement with FDA, the outcomes of interest were:

- Asthma-related hospitalization
- Asthma-related intubation
- Asthma-related death
- All cause death

Results for asthma-related intubation and all cause death were consistent with the results obtained in the analysis and do not provide any additional insight beyond asthma-related death and asthma-related hospitalization. The results of these analyses can be found in Attachment 2.

In total, 263 studies including 117,845 patients are included in the database. These totals include both SNS and SMART. Treatment exposure information from sub-groups in SMART are provided as reference.

[Table 2](#) describes the data available for analysis by treatment category and includes the results of asthma-related deaths and asthma related hospitalizations from all studies in the database, thus providing an accounting of all outcomes and all patients for the treatments of interest.

Table 2 Patient-Years of Exposure and Asthma-Related Deaths and Hospitalizations in all GSK Studies (US and Non-US)

Treatment Category	Number of Studies	Number of Patients	Total Exposure Years	Asthma-Related Deaths per 10,000 Pt-Yrs	Patients with an Asthma-Related Hospitalization per 10,000 Pt-Yrs
Salmeterol-containing product	263	67219	23486	14	321
Non-LABA	231	48968	18433	4	246
Sal (without ICS)	80	11342	4352	25	239
Pla (without ICS)	62	9935	4104	2	175
ICS _{BK}	44	10135	4168	7	362
ICS _{SD}	96	14651	6387	0	72
Sal + ICS _{BK}	51	12881	5059	12	484
Sal + ICS _{SI}	27	3804	1486	7	155
ADVAIR	86	17891	6571	0	65
SMART Sub-Groups (numbers included in categories above)					
Sal (without ICS)	1	6513	2993	27	184
Pla (without ICS)	1	6463	2930	0	140
Pla + ICS _{BK}	1	6716	3156	10	355
Sal + ICS _{BK}	1	6663	3194	16	379

Note: Some studies contain more than one treatment comparison

Since ICS are defined as the gold standard treatment for all patients with persistent asthma, comparing the remaining treatment groups to ICS_{SD} allows for relative comparisons to the best treatment possible in the absence of salmeterol.

There was a 5-fold increase in the number of patients with an asthma-related hospitalization per 10,000 patient-years for ICS_{BK} compared with ICS_{SD} (362 and 72, respectively). This suggests that adherence to ICS_{BK} was less than with ICS_{SD}.

ADVAIR treatment resulted in the lowest rate of hospitalizations per 10,000 patient-years of exposure across all treatment groups and there were no deaths in patients receiving ADVAIR.

The results in [Table 2](#) provide an overall view of the GSK clinical trials database and provide insight into the frequencies of the outcomes of interest in each treatment category. However, direct comparisons of the treatment categories are limited as the rates of the outcomes are not adjusted for study differences (e.g., standard of care, doses of ICS, populations, and disease severity). The meta-analysis described in the next section was designed to account for these limitations.

3.2. Meta-Analysis of GSK-Sponsored Clinical Trials

The goal of the meta-analysis of GSK-sponsored clinical trials was to ascertain if there is an association with the outcomes of interest and treatment with salmeterol used in the absence (monotherapy) or presence of ICS. Each outcome was examined using two different meta-analytic techniques: 1) Risk Difference (RD) and 2) Peto odds ratio [[RM2008/00078/00](#)].

3.2.1. Organization and Approach

Studies selected for meta-analysis were drawn from the total safety database of 263 salmeterol-containing studies with 117,845 patients as outlined in Section 3.1.1. Analysis populations were constructed for each treatment category comparison of interest. For a study to be included in a specific analysis population, both treatment categories for comparison must have been present within the same study. This approach allows for control of important study differences such as different doses of ICS, changing standards of care, and different disease severity which could confound results.

3.2.1.1. Analysis measures and meta-analysis methods

The primary measure for the analysis of outcomes is the risk difference of rates between the treatment comparisons of interest. A supportive measure is the odds ratio of the rates from the treatment comparisons of interest. Methods of computing these measures and methods for meta-analysis of these measures are presented below.

Risk difference

The risk difference of rates describes the absolute difference in risk between the experimental group and the control group. A meta-analysis of the risk difference describes the absolute change in risk between the experimental group and the control group across individual studies. Meta-analysis of the risk difference combining results of individual studies incorporates a weight (based on variation) that is applied to the result of each study in calculating the overall meta-analysis result.

An advantage of a meta-analysis of the risk difference is that it can allow incorporation of studies with no event outcomes by using a continuity correction. For studies with no outcomes in either or both treatment groups, a continuity correction is applied in order to calculate the variance of the risk difference for these studies. This correction allows all studies in an analysis population to be included in the meta-analysis regardless of the presence or absence of event outcomes. However, the choice of the continuity correction may have an influence in situations where most studies either do not have an outcome or have one treatment group without an outcome. For this reason, a continuity correction of 0.5 was used for primary analyses of the risk difference and 0.1 was used in sensitivity analyses of the risk difference.

As the rates of outcomes were low, risk differences are multiplied by 10,000 times to describe the number of patients per 10,000 patients. A risk difference of less than 0 indicates a benefit to the experimental group (e.g., the salmeterol-containing groups) compared to the control group in a patient experiencing an outcome (e.g., RD=-20

indicates a benefit of 20 fewer patients per 10,000 patients experiencing an outcome) and a value greater than 0 indicates a detriment to the experimental group compared to the control group in a patient experiencing an outcome (e.g., RD=20 indicates a detriment of 20 more patients per 10,000 patients experiencing an outcome). A 95% confidence interval associated with a risk difference indicates a statistically significant difference at the 5% level if the confidence interval does not include 0.

Odds ratio

An odds ratio of rates describes the odds of experiencing an outcome for the experimental group relative to the odds for the control group. However, unlike the Risk Difference method which can include all available studies, the odds ratio only includes studies reporting an outcome of interest. A meta-analysis of the odds ratio describes the odds of experiencing an outcome for the experimental group relative to the odds for the control group across individual studies. Meta-analysis of the odds ratio combining results of individual studies incorporates a weight (based on variation) that is applied to the result of each study in calculating the overall meta-analysis result.

The Peto odds ratio is a statistical methodology which combines results of individual studies to produce an overall weighted odds ratio. Emphasis for this methodology is placed on the difference in the observed number of patients with an outcome and the expected number patients with an outcome. The expected number of patients with an outcome is a function of the overall rate in both the experimental and control groups. Due to the calculation of odds ratios, the Peto method is appropriate when trials have approximately equal numbers of patients in each group and outcomes are rare.

A disadvantage of the Peto odds ratio is that it does not allow for inclusion of studies with no outcomes. Thus, since outcomes were rare, particularly asthma-related deaths and intubations, a large number of studies did not have outcomes and so were not included in the construction of a Peto odds ratio. For example, in the meta-analysis of asthma-related deaths comparing salmeterol-containing products vs. non-LABA treatments, there were 35 asthma-related deaths, of which 30 asthma-related deaths came from two studies (SNS and SMART) and the five remaining asthma-related deaths came from five studies; therefore, only seven out of 215 studies contributed to the construction of the Peto odds ratio.

Odds ratios have bounds of zero to infinity. An odds ratio of less than 1 indicates a benefit to the experimental group (e.g., the salmeterol-containing groups) relative to the control group in a patient experiencing an outcome and can be expressed in terms of a percent benefit (e.g., OR=0.75 indicates a 25% benefit: $(1-0.75)*100$) and a value greater than 1 indicates a detriment to the experimental group relative to the control group in a patient experiencing an outcome and can be expressed in terms of a percent detriment (e.g., 1.75 indicates a 75% detriment: $(1.75-1)*100$). A 95% confidence interval associated with an odds ratio estimate indicates a statistically significant difference at the 5% level if the confidence interval does not include 1.

Summary of analysis measures and meta-analysis methods

Meta-analysis of risk differences is the focus of this document, as the meta-analytic methodology of this summary statistic incorporates all available studies and patients regardless of whether an outcome was reported in a particular study. The Peto odds ratio methodology is limited as it only includes studies reporting outcomes of interest and as outcomes were rare, particularly asthma-related deaths and intubations, a large number of studies did not have outcomes of interest and so were not included in the construction of a Peto odds ratio. Therefore, meta-analysis of odds ratios (Peto odds ratio) is a supportive measure. Results for the Peto odds ratio for the outcomes in analysis populations and sub-populations of interest can be found in Attachment 3.

In addition to the total population of all patients receiving salmeterol, outcomes in children and African Americans were examined.

3.2.1.2. Risk Difference Evaluation of Salmeterol Compared with Non-LABA

This analysis population was included for full transparency of all salmeterol comparison data since it includes the largest number of studies and patients. However, it represents the most heterogeneous comparison since it includes salmeterol in any form (i.e., SEREVENT or SEREVENT plus ICS or ADVAIR) compared with any non-LABA matched treatment study arm (i.e., ICS, leukotriene modifier, placebo, scheduled short-acting beta₂-agonist, etc.). This analysis population was designated as **Sal vs. non-LABA**.

3.2.1.3. Risk Difference Analysis Population Evaluating Salmeterol Used as Monotherapy

The safety profile of salmeterol in the absence of ICS was addressed in the meta-analysis by pooling data from studies which directly:

- Compared salmeterol (Sal) with placebo (Pla). In this comparison, neither treatment included concurrent ICS treatment. This analysis population was designated as **Sal vs. Pla**.

3.2.1.4. Risk Difference Analysis Populations Evaluating Salmeterol Use with ICS

The safety profile of salmeterol in the presence of ICS was addressed by analyzing data from studies which directly compared salmeterol used concurrently with ICS vs. ICS as separate treatment groups. There are three situations in a clinical trial during which a patient may receive ICS concurrently with salmeterol and the assurance of ICS use varies among them:

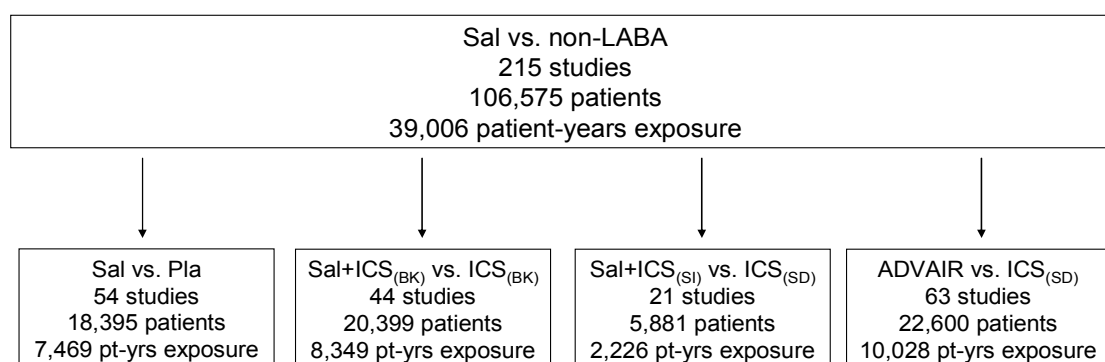
- Addition of salmeterol to background ICS (ICS_{BK}). In this clinical trial scenario, at the screening visit, patients report taking ICS prior to the study and are instructed to continue that ICS throughout the treatment period of the study. However, the ICS medication was not dispensed as part of the protocol nor was there systematic reinforcement or any measure of continued adherence to the medication. This analysis population was designated as **Sal + ICS_{BK} vs. ICS_{BK}**.

- Introduction of salmeterol and ICS as blinded study medications administered in separate inhaler devices (SI), administered concurrently where both medications are dispensed as study drug as part of the study protocol (SD). This analysis population was designated as **Sal + ICS_{SI} vs. ICS_{SD}**.
- Introduction of salmeterol and ICS as a blinded study medication in a single inhaler (ADVAIR). This analysis population was designated as **ADVAIR vs. ICS_{SD}**.

Only the ADVAIR vs. ICS_{SD} analysis population assures the concurrent use of ICS each time a patient was exposed to salmeterol. Therefore, this population was the primary population to inform on the safety profile of salmeterol in the presence of an ICS.

A schematic of the analysis populations and the number of studies and patients which contribute to each are shown in [Figure 15](#).

Figure 15 Diagram of Analysis Populations for Meta-Analysis



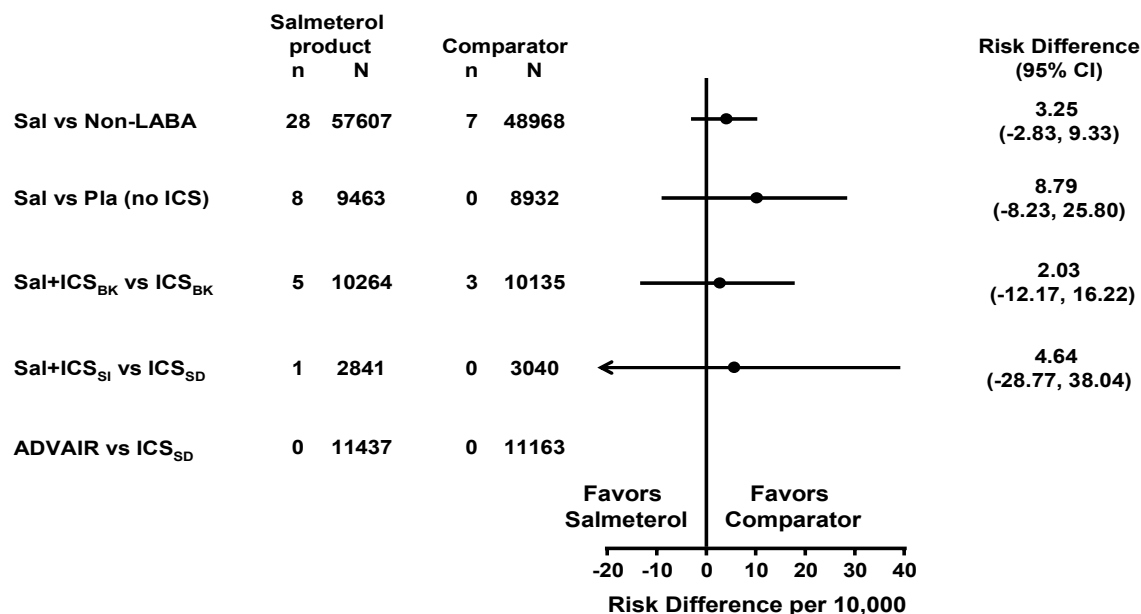
BK=background; SD=study drug; SI=separate inhalers

3.2.2. Results

3.2.2.1. Asthma-related Deaths

A total of 35 asthma-related deaths were reported in the analysis database. [Figure 16](#) displays the meta-analysis of the RD for asthma-related deaths for each of the analysis populations.

Figure 16 Meta-Analysis: Risk Difference for Asthma-Related Death (0.5 Continuity Correction)



There was no statistically significant increase in the number of asthma-related deaths for salmeterol compared with other comparators of interest. RDs decreased when patients used both salmeterol and ICS concurrently as study drug. There was only one asthma-related death in the comparison of Sal + ICS_{SI} vs. ICS_{SD} and no asthma-related deaths in the 11,437 patients who received ADVAIR.

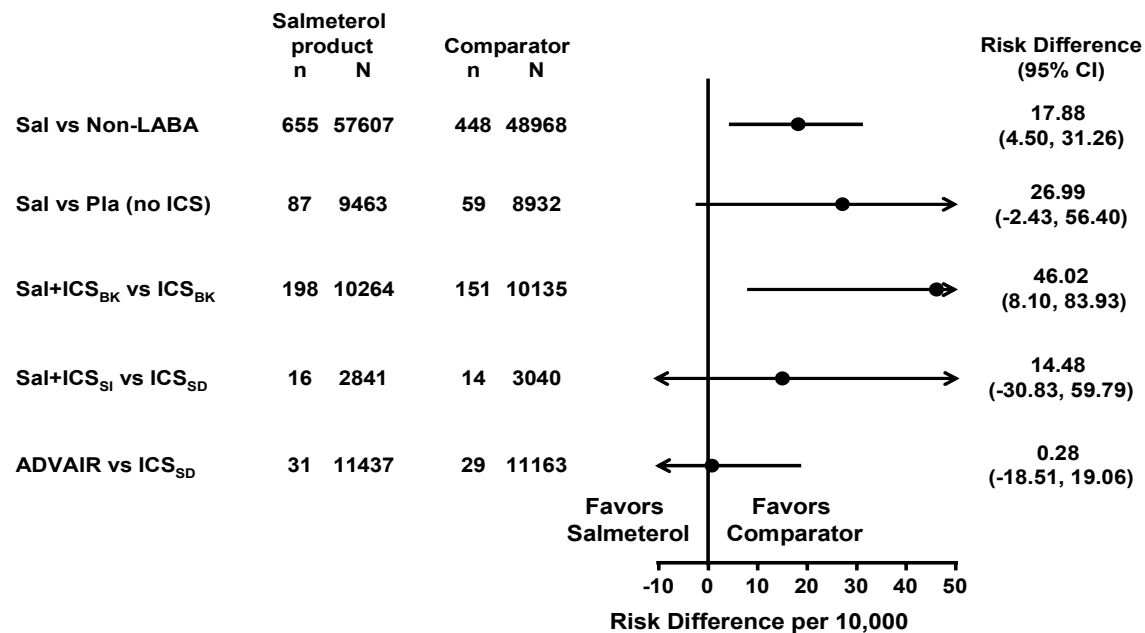
Of the 35 asthma-related deaths reported, 30 occurred in SMART and SNS together, accounting for 86% of the asthma related deaths in the GSK clinical database. Of the five asthma-related deaths not from SNS and SMART, three occurred in patients receiving salmeterol (two receiving salmeterol alone and one receiving salmeterol plus FP in separate inhalers) and two occurred in patients receiving other treatment (one receiving albuterol four times daily and one receiving placebo).

For studies where the concurrent use of salmeterol and ICS can be reasonably assured (e.g., ADVAIR and Sal + ICS_{SI}), there was no evidence of increased risk for asthma-related death. However, when salmeterol was used in the absence of an ICS or when use of an ICS was not controlled (e.g., Sal and Sal + ICS_{BK}), an increase in serious asthma-related events were observed.

3.2.2.2. Meta-Analysis Results for Asthma-Related Hospitalizations

A total of 1,103 of the 106,575 patients in the analysis database reported an asthma-related hospitalization. [Figure 17](#) displays the meta-analysis of the RD for patients with asthma-related hospitalization for each of the analysis populations.

Figure 17 Meta-Analysis: Risk Difference for Asthma-Related Hospitalization (0.5 Continuity Correction)



Overall, in [Figure 17](#), the RD for asthma-related hospitalization was statistically significantly increased for Sal compared to non-LABA and for Sal + ICS_{BK} compared to ICS_{BK}. The RD for asthma-related hospitalization was higher in patients who used salmeterol without an ICS and when ICS use was not controlled or dispensed by the protocol (i.e., salmeterol as blinded study drug added to background ICS). RD decreased when patients used both salmeterol and ICS as dispensed study drugs. No increased risk was observed when salmeterol was used concurrently with ICS in a fixed single inhaler (e.g., ADVAIR).

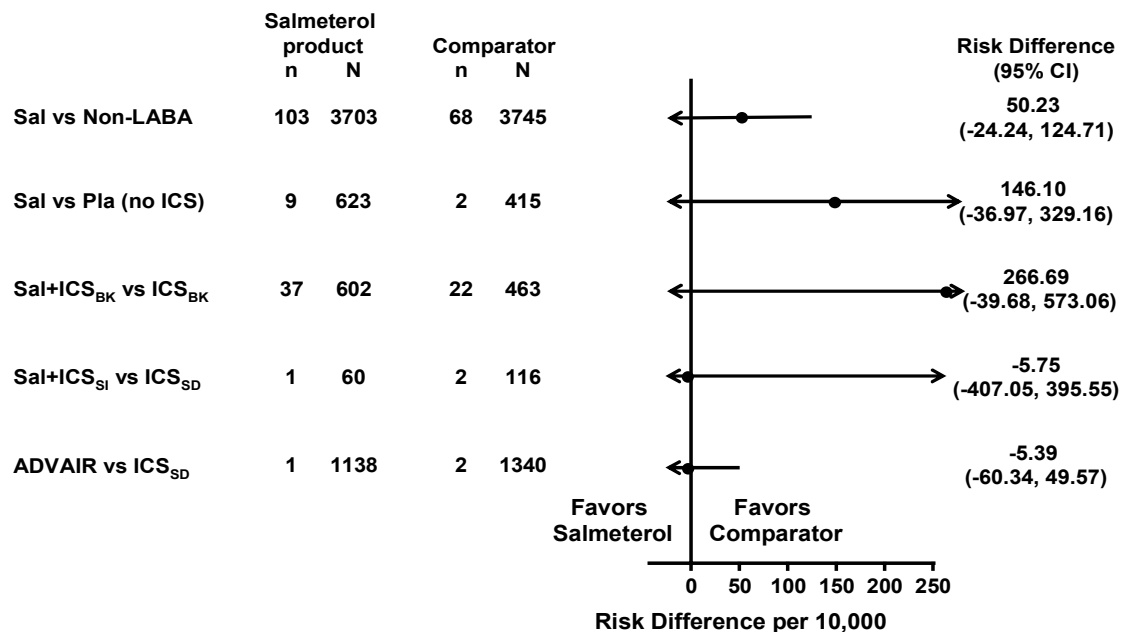
3.2.2.3. Outcomes in Children

Asthma is the most common chronic medical condition in children and is the number one cause of absence from school [[Asthma Facts and Figures](#), 2008]. However, studies in children are difficult to conduct due to multiple factors, including patient, parental and physician reluctance to participate in clinical trials, especially in children with symptomatic asthma who may receive placebo. In addition, the asthma phenotype in children is characterized by longer asymptomatic periods compared with adults, raising additional challenges when selecting study endpoints to show effectiveness during clinical trials [[Calhoun](#), 2003; [Chipps](#), 2006].

For this analysis, children in clinical trials were defined as less than 12 years of age. Across all the trials, only one pediatric asthma-related death was reported (patient was receiving albuterol four times daily). There was one intubation each for a patient receiving albuterol four times daily and in one receiving SEREVENT without concurrent

ICS. [Figure 18](#) displays the meta-analysis of the RD for pediatric patients with an asthma-related hospitalization for each of the analysis populations.

Figure 18 Meta-Analysis: Risk Difference for Asthma-Related Hospitalization (0.5 Continuity Correction): Pediatric Population



Overall, in [Figure 18](#), these data from studies in children are consistent with the total population and suggest patients taking salmeterol in the absence of ICS may be at increased risk of serious adverse outcomes. However, when salmeterol and ICS were used concurrently either as study drug (Sal + ICS_{SI}) or as ADVAIR, there appeared to be no increased risk of asthma-related events in children. Also similar to the data in the overall population, the risk was elevated with Sal + ICS_{BK} vs. ICS_{BK}, suggesting that poor adherence to concurrent ICS contributed to an increased number of patients with an asthma-related hospitalization.

3.2.2.4. Relationship with time periods and asthma-related hospitalizations

Salmeterol was first marketed as SEREVENT and launched in Europe in 1990 and later in the US in 1994. During the development of SEREVENT, concomitant use of ICS for patients with persistent asthma was less common since the role of inflammation in the pathophysiology of asthma was not widely appreciated. Over the last 10 to 15 years, based on a large body of clinical data, asthma treatment guidelines and educational programs have stressed the importance of treating all patients with persistent asthma with an ICS to control the underlying inflammatory process characteristic of patients with persistent asthma [[NAEPP](#), 2007]. Thus, current treatment guidelines and standards of care have evolved to recommend that LABA should be used as concurrent therapy with ICS. The evolution of the management of asthma with LABA and ICS in the US can be illustrated by examining currently available data. For example, SMART was initiated in 1996 and only 47% of the total study population reported concurrent use of ICS at

baseline. An observational study of trends in salmeterol-containing product dispensings among 287,572 asthma patients from a large US insurer, reported that during 2005-2007, 98% of patients received salmeterol with a concomitant ICS (e.g., 96.7% as ADVAIR and 1.1% as SEREVENT plus ICS in separate inhalers) [RM2008/00715/00]. In addition, US national tracking data confirm that “practices over the past decade are increasingly consistent with evidence-based guidelines” [Stafford, 2003].

If physician and patient awareness concerning the importance of ICS use in the management of asthma has increased, then adherence to ICS by patients may have improved over time. A possible temporal effect on outcomes with SEREVENT due to improved ICS adherence could be examined in the clinical trial database by examining outcomes from trials where SEREVENT was added to background ICS (ICS_{BK}). To test this concept, a *post-hoc* analysis was conducted to examine outcomes with SEREVENT added to ICS_{BK} in the study years prior to the year 2000 and study years 2000 and beyond. The year 2000 was selected since it falls after the 1997 NAEPP update and allowed time for implementation and acceptance of asthma educational awareness programs emphasizing the use of ICS in all patients with persistent asthma. The year 2000 was also selected since there was an upward inflection in overall ICS use in the US in that year (Figure 5). The only outcome with enough events to reasonably analyze by time period was asthma-related hospitalization.

Figure 19 and Figure 20 display the meta-analysis of the RD for adult and pediatric patients, respectively, who reported an asthma-related hospitalization while receiving ICS as background therapy. Studies were grouped by the date of study termination, however, since SMART is such a large study spanning both time periods, outcomes in SMART were grouped by the date of occurrence.

Figure 19 Meta-Analysis: Risk Difference for Asthma-Related Hospitalization (0.5 Continuity Correction): Adolescent and Adult Population: <2000 and ≥2000

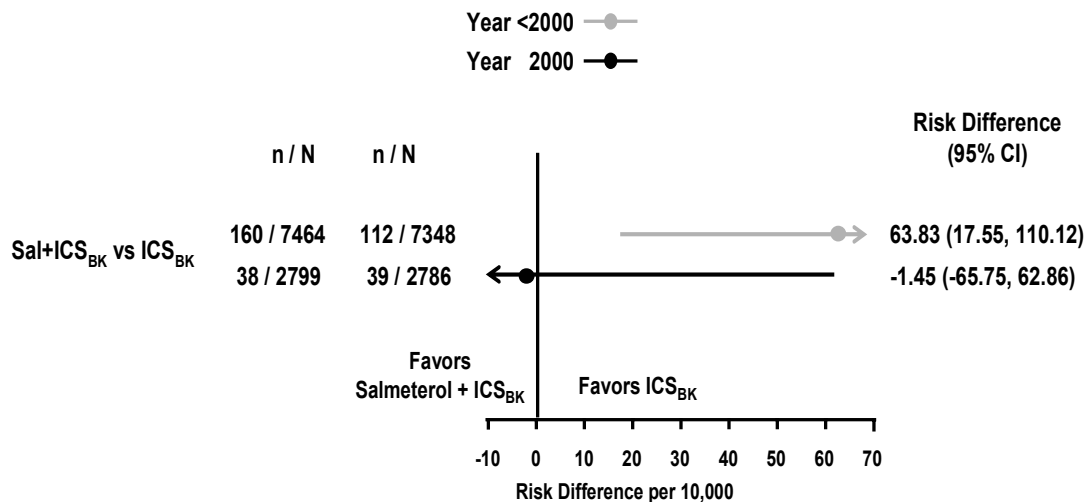
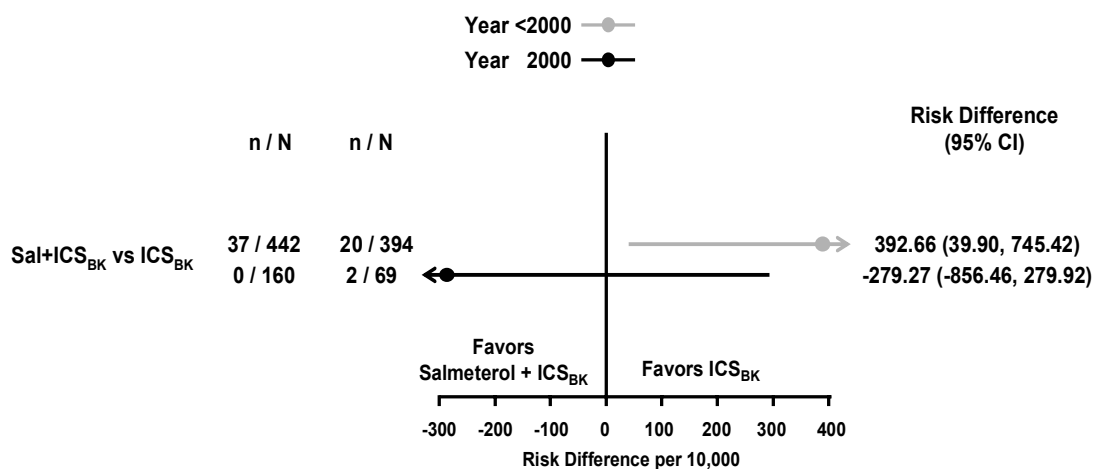


Figure 20 Meta-Analysis: Risk Difference for Asthma-Related Hospitalization (0.5 Continuity Correction): Pediatric Population: <2000 and ≥2000



When asthma-related hospitalizations were examined in discrete time periods, distinct differences were apparent for both adult and pediatric patients who added SEREVENT to pre-study or background ICS. The RDs for asthma-related hospitalizations suggested an elevated risk when SEREVENT was added to background ICS from studies prior to the

year 2000. The RD including the year 2000 and beyond, suggested no elevated risk with SEREVENT added to background ICS.

This examination of outcomes by early and late time periods reinforces the concept that the increased risk of serious asthma-related outcomes observed with salmeterol under conditions of use characteristic of its early years of clinical development and marketing appears to be mitigated by changes in medical practice that resulted in increased adherence to ICS and the appropriate use of long-acting beta₂-agonists with ICS.

3.2.2.5. Asthma-Related Intubations and All Cause Death Outcomes

Meta-analysis results for asthma-related intubations were similar to results for asthma-related death. These data can be found in Attachment 4.

In addition, meta-analysis results for all cause death do not provide any additional insight beyond asthma-related death and asthma-related hospitalization, reported above. These data can be found in Attachment 4.

3.2.2.6. Outcomes in African Americans

A systematic approach to examine serious asthma-related outcomes in African American patients was defined in the *a priori* analysis plan [RM2008/00078/00]. The results in African Americans can be found in Section 6.5 which discusses African Americans as a postulated at-risk population relative to salmeterol use.

3.3. Summary for Meta-Analyses of Randomized Controlled Trials

The results from the meta-analyses of over 200 studies and over 100,000 patients (including SMART and SNS) show that salmeterol used in the absence of an ICS may be associated with increased risk of serious asthma events (hospitalization, intubation and death). These meta-analyses also establish that the signal of potential elevated risk associated with salmeterol in the absence of ICS was mitigated with ICS use. For example patients did not appear to be at increased risk if their concurrent use of ICS and salmeterol was controlled in clinical trials (either as a fixed dose combination of salmeterol plus FP or when salmeterol and FP were used concurrently as blinded study drug in separate inhalers). Comparatively, if patients took salmeterol added to background pre-study ICS, they still appeared to be at some increased risk, likely due to the lack of adherence to background ICS. However, when asthma-related hospitalizations were examined by time period, there was no increased risk with salmeterol plus ICS likely due to increased use and adherence to ICS in the latter time period. Overall, results for children were consistent with results found in the larger meta-analysis for all patients.

Since the rates of serious asthma outcomes are low in our clinical programs, observational study designs allow for study of large populations to examine any potential association between salmeterol and these rare outcomes. These studies are described below.

4. RESULTS FROM OBSERVATIONAL STUDIES

4.1. Introduction

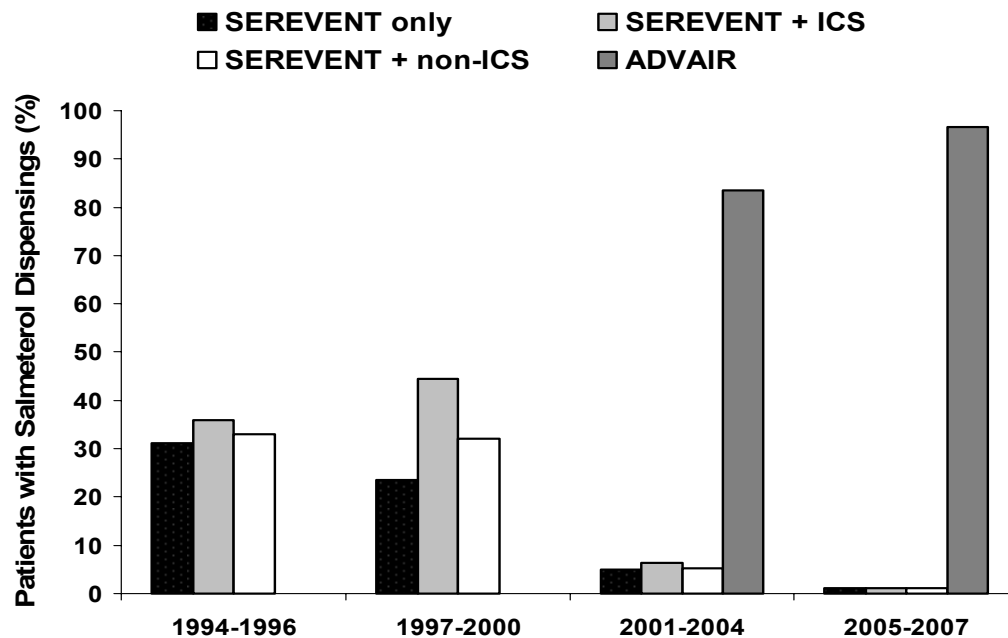
In addition to randomized clinical trials, observational studies provide important additional evidence regarding the benefits and risks of medications used widely in clinical practice. Large descriptive studies of patients dispensed salmeterol-containing products can be designed to demonstrate the frequency of concomitant ICS dispensing over time. Additional context can be provided by ecologic studies, which evaluate correlations between trends in medication use and serious asthma event rates at the group (national) level. Compared to randomized clinical trials, observational studies also offer greater statistical power and generalizability through use of large population-based patient databases. Therefore, observational study methods are well suited to determine whether exposure to medication is associated with rare events, such as asthma-related hospitalizations and mortality [[Strom, 2000](#)].

Results from observational studies showed no statistically significant increased risk associated with use of salmeterol-containing products and serious asthma-related adverse events. In addition, results for ADVAIR showed a statistically significant benefit, vs. ICS or ICS plus montelukast, for the outcomes of asthma-related hospitalizations or emergency department visits in both adult and pediatric populations.

4.2. Trends in Prescribing of Salmeterol-containing products, US

Evaluating the overall patterns in prescribing of salmeterol-containing products for asthma patients in the population over time is a critical part of assessing the benefit-to-risk profile of the medication. A recently completed study (WEUSRTP3275) [[RM2008/00715/00](#)] examined the prevalence of concomitant controller dispensing with salmeterol, either as SEREVENT plus a separate ICS or non-ICS controller within 30 days or as ADVAIR, from 1994 to 2007 among 287,572 adult asthma patients from a large employer-based healthcare claims database [[Figure 21](#)].

Figure 21 Proportion of Asthma Patients with Salmeterol-Containing Dispensings by Concomitant Controller Use, US, 1994—2007 [WEUSRTP3275]

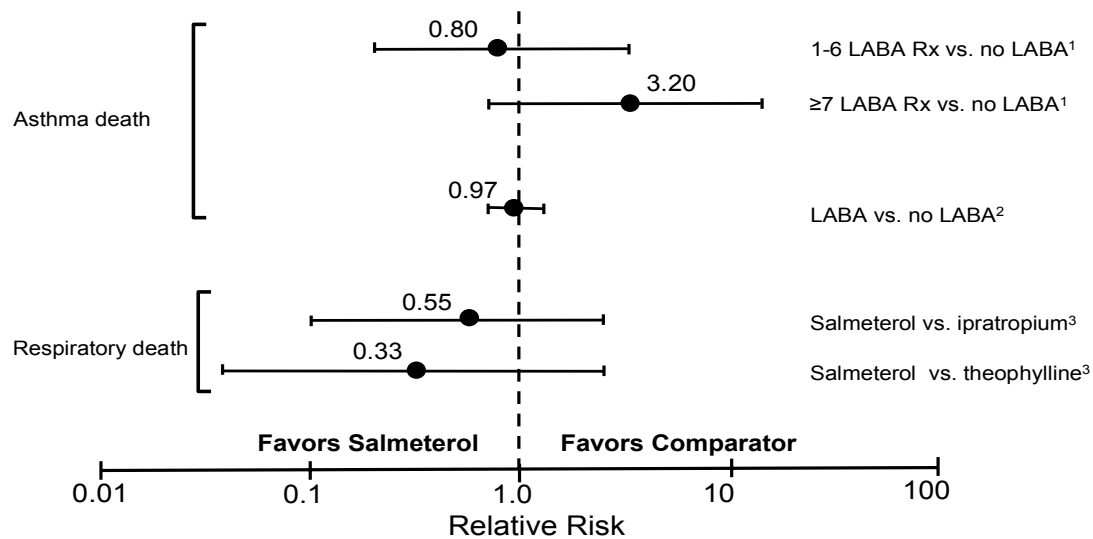


Overall, the proportion of patients dispensed SEREVENT without a concomitant ICS or other controller medication decreased from 31.2% during 1994 to 1996 to 1.2% during 2005 to 2007. By 2005 to 2007, 97% of patients received salmeterol as ADVAIR.

4.3. Observational Studies of Serious Asthma Events and SEREVENT Use

To further examine results reported from randomized clinical studies, observational studies designed to assess SEREVENT use and the risk of serious asthma-related outcomes were summarized. In a review of all published studies and unpublished GSK studies of observational design, a total of six studies of salmeterol and severe respiratory-related events were identified from the literature. Two were cohort studies [Lanes, 1998; Meier, 1997] and four were case-control studies [Williams, 1998; Lanes, 2002; Anderson, 2005; Wang, 2008]. All studies included data collected prior to 2002, before ADVAIR was widely available, and for five studies, salmeterol use was exclusively as SEREVENT. Figure 22 shows the results for the studies reporting on fatal outcomes.

Figure 22 Adjusted Relative Risk and 95% CIs of Asthma- or Respiratory-Related Death Associated with SEREVENT Use



¹Lanes et al. *Thorax* 2002;57:683-686 (n=903); 43 deaths

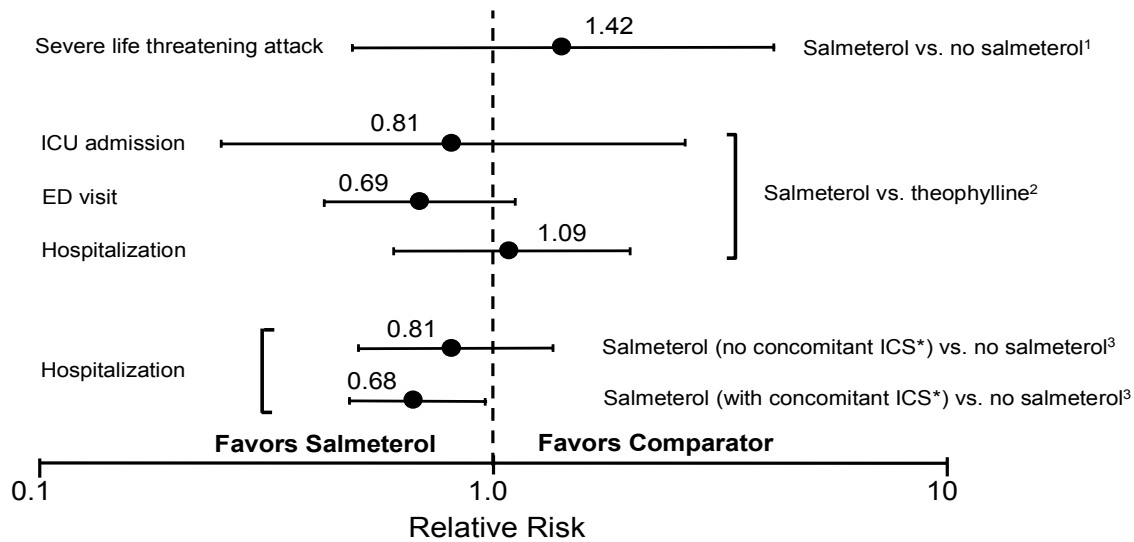
²Anderson et al. *BMJ* 2005;330:117-24 (n=1064); 532 deaths

³Meier. *Thorax* 1997;52:612-7 (n=16,919); 28 deaths

None of the studies of SEREVENT found a statistically significant increase in the risk of death or serious asthma-related outcomes. The largest case-control study of asthma-related death [Anderson, 2005] compared all asthma-related deaths from 1994 to 1998 according to death certificates from a UK population sample (n=532) to selected date-, age- and geographic area-matched controls with a hospital admission for acute asthma. Recent or past use of LABAs (>90% SEREVENT) was not associated with an increased risk of asthma mortality during the study period, and 95% of LABA use among asthmatics included a concomitant ICS prescription [Maringe, 2007].

Figure 23 shows the results from studies of serious asthma morbidity outcomes.

Figure 23 Adjusted Relative Risks and 95% CIs of Serious Asthma-Related Morbidity Associated with SEREVENT Use



¹Williams et al. *Thorax* 1998;53:7-13 (n= 233)

²Lanes et al. *Am J Respir Crit Care Med* 1998;158:857-61 (n=6533)

³Wang et al. *Curr Med Res Opin* 2008;24:859-67 (n=1940)

* Concomitant ICS defined as $\geq 50\%$ within 30 days

The largest case control study of asthma-related hospitalization was conducted in the US [Wang, 2008]. These results showed that when SEREVENT/salmeterol was dispensed with a concurrent ICS ($\geq 50\%$ of the time), salmeterol was associated with a statistically significantly lower risk of asthma hospitalization (relative to matched controls not using SEREVENT in the past year). When SEREVENT was dispensed without a concomitant ICS (i.e., $< 50\%$ of the time), salmeterol was not associated with a statistically significant decrease in risk of asthma hospitalization and no elevated risk was seen relative to matched controls. These results were based on data from over 100 managed care plans which identified 1,940 cases and matched controls selected from a cohort of more than 33,000 asthma patients from 2000 to 2001.

In summary, these large diverse observational studies conducted in the UK and US showed that SEREVENT was not associated with a statistically significant increase in the risk of asthma- or respiratory-related mortality or serious asthma morbidity after controlling for severity or preferential prescribing of SEREVENT to patients with more severe asthma.

4.4. Observational Studies of Serious Asthma-Related Events and ADVAIR Use

4.4.1. Introduction

Current asthma treatment guidelines highlight the importance of ICS to control the underlying inflammatory process of asthma [NHLBI, 1997; NAEPP, 2007]. Today, the

vast majority of salmeterol use in the US is ADVAIR (97% of total salmeterol use for asthma). Therefore, the relevant evaluation of contemporary use of salmeterol for the treatment of asthma is as ADVAIR. To this end, GSK conducted a systematic literature review to identify all published studies and GSK completed unpublished studies of ADVAIR vs. ICS or ADVAIR vs. ICS plus montelukast. Studies had to meet pre-defined methodological criteria [RM2008/00748/00].

The results of the meta-analysis indicated that the use of ADVAIR was associated with a statistically significantly lower risk of an asthma-related event (hospitalization and/or ED) relative to ICS monotherapy, as well as relative to ICS plus montelukast in real-world clinical practice in both adults and pediatric patients. This effect was observed across different regions of the US and across different healthcare systems (e.g., Managed care healthplans, Fee for Service Medicaid).

4.4.2. Results of Meta-Analysis of Observational Studies with Advair in Adults

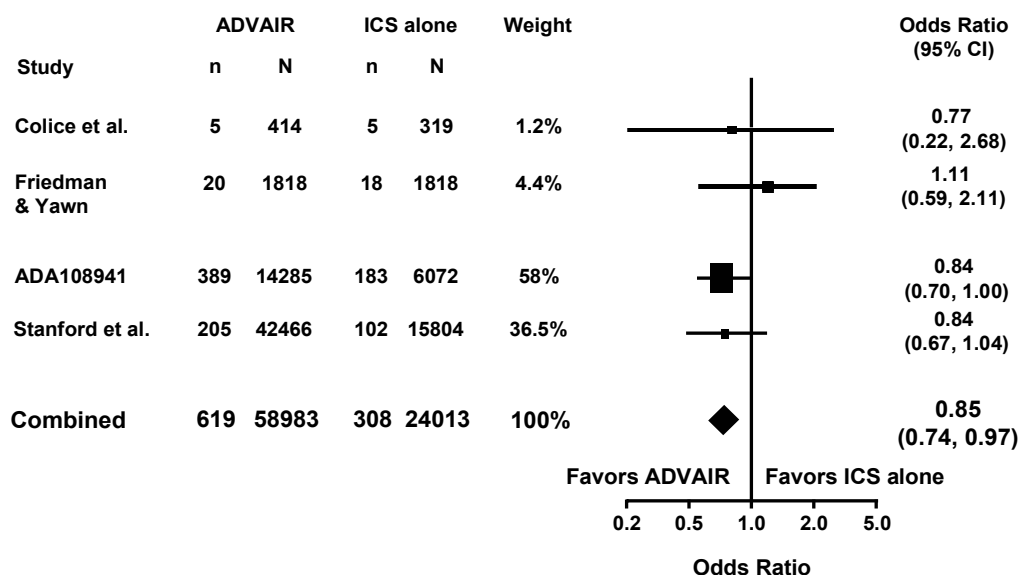
4.4.2.1. Identified studies

Four observational studies, with asthma-related hospitalizations and ED visits as separate endpoints, met the *a priori* criteria for inclusion into the meta-analysis. These studies were all cohort design and contributed a total of 82,996 patients, with 58,983 ADVAIR patients and 24,013 ICS monotherapy patients [RM2008/00748/00].

4.4.2.2. ADVAIR vs. ICS: Asthma-related hospitalizations

The overall odds ratio and corresponding 95% CI of the meta-analysis and each individual study outcome are visually displayed in Figure 24.

Figure 24 Meta-Analysis: Odds Ratio for Asthma-Related Hospitalization (Adults)

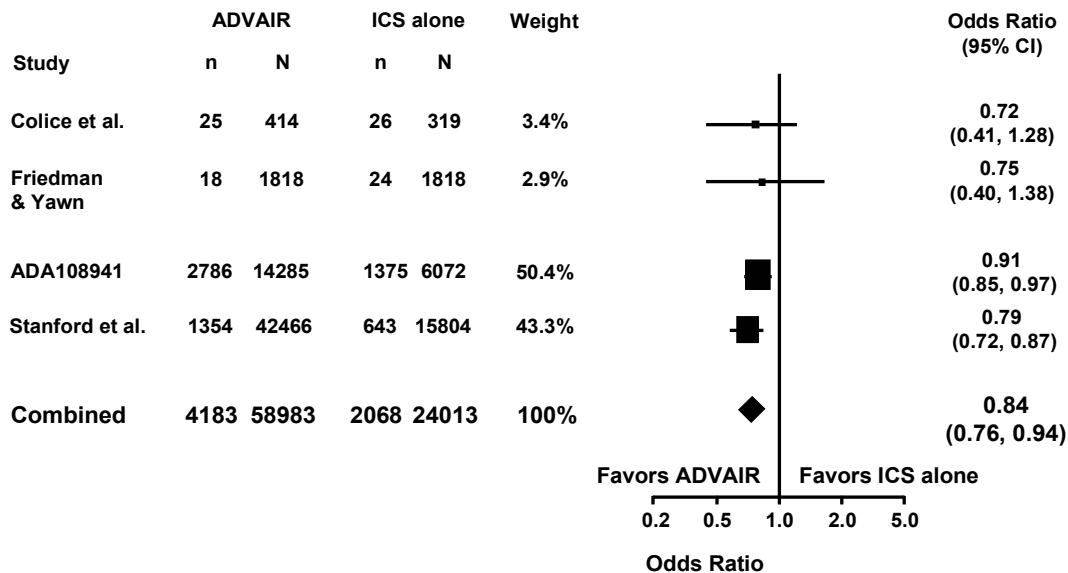


In this meta-analysis of 82,996 patients, ADVAIR was associated with a statistically significantly lower risk of having an asthma-related hospitalization (OR 0.85, 95% CI 0.74-0.97) compared to ICS monotherapy.

4.4.2.3. ADVAIR vs. ICS: Asthma-related emergency department visits

The overall odds ratio and corresponding 95% CI of the meta-analysis and each study individual outcome are displayed in [Figure 25](#)

Figure 25 Meta-Analysis: Odds Ratio for Asthma-Related Emergency Department Visits (Adults)



ADVAIR was associated with a statistically significantly lower risk of an asthma-related ED visit (OR 0.84, 95% CI 0.76-0.94) compared to ICS monotherapy.

4.4.3. Results of Meta-Analysis of Observational Studies with ADVAIR in Pediatrics

4.4.3.1. Identified Studies

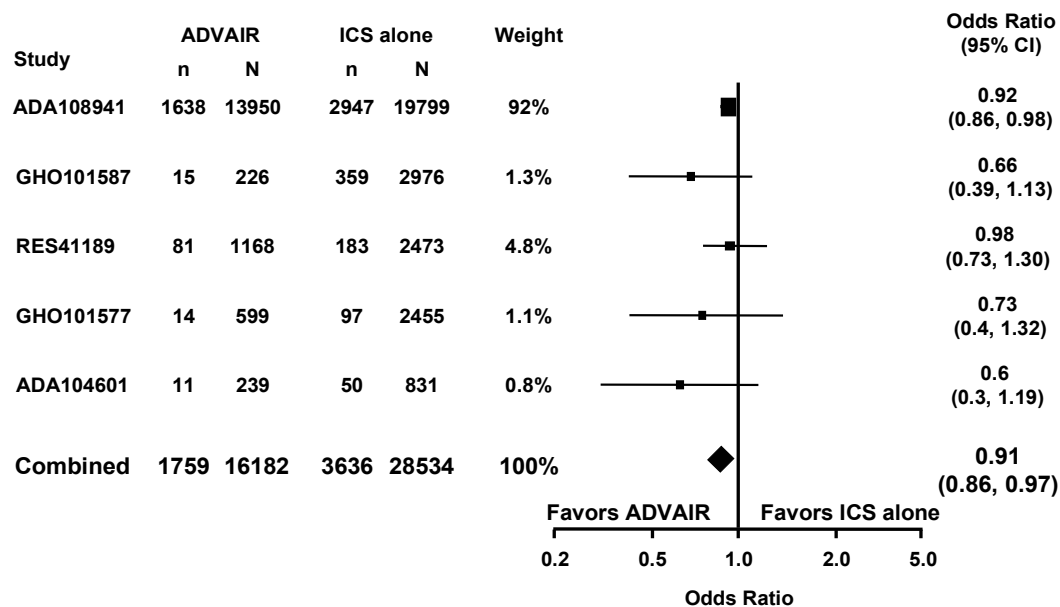
Five pediatric studies met the *a priori* criteria and were included in the meta-analysis for a total of 43,500 children with 16,368 using ADVAIR, 25,534 using ICS only and 1,598 using ICS plus montelukast. Due to the small number of hospitalizations observed in the studies (only one study reports an adjusted risk ratio), the combined endpoint of ED/hospitalization (a proxy for asthma exacerbation) is reported for: (1) ADVAIR vs. ICS and (2) ADVAIR vs. ICS plus montelukast. Pediatric patients were defined as 2 to 17 years of age [[RM2008/00748/00](#)].

4.4.3.2. ADVAIR vs. ICS: asthma-related hospitalizations

Due to the low event rate, only one study (ADA108941) reported a separate adjusted risk ratio, ADVAIR vs. FP, for an asthma hospitalization as an endpoint (HR=0.93; 95% CI=0.74, 1.16).

As indicated above, event rates for hospitalization were rare; therefore, five studies met the *a priori* criteria for inclusion into the meta-analysis and reported these outcomes as a combined endpoint of ED/hospitalization (Figure 26).

Figure 26 Relative Risk for Asthma-Related Combined ED/Hospitalizations: ADVAIR vs. ICS, Pediatric Studies



ADVAIR was associated with a statistically significantly lower risk of an asthma-related ED visit (OR 0.91, 95% CI 0.86-0.97).

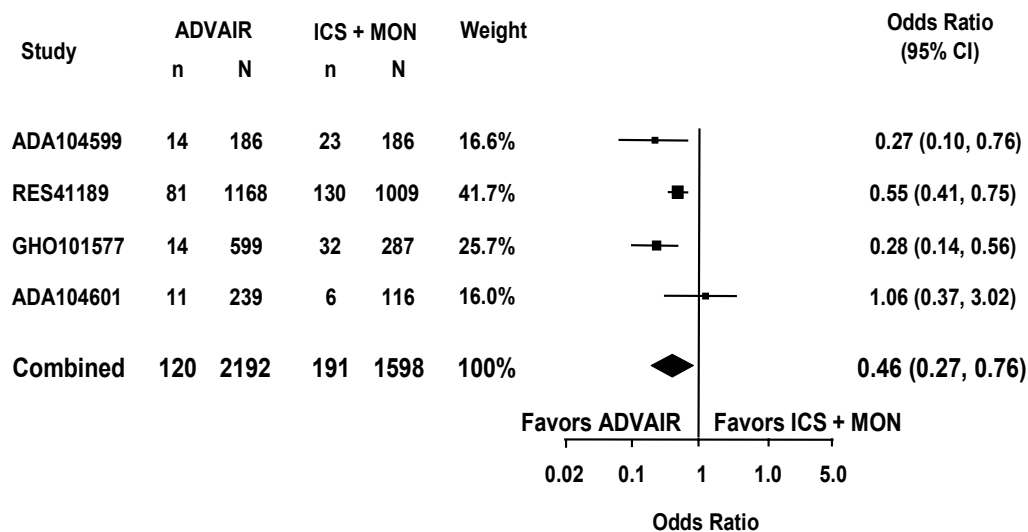
4.4.3.3. ADVAIR vs. ICS plus montelukast: asthma-related hospitalizations

When ICS alone does not sufficiently control asthma in children, the most recent asthma treatment guidelines [NAEPP, 2007] recommend the addition of salmeterol to ICS (administered as ADVAIR) as a therapeutic option to improve asthma control. The same treatment guidelines also recommend the addition of montelukast to ICS as an alternative option. ADVAIR DISKUS 100/50 BID is indicated in children 4 to 11 years of age who remain symptomatic on ICS. Therefore, results for the comparison of ADVAIR to an ICS plus montelukast regimen, which reflects an alternative therapy choice available in clinical practice, are presented below.

Four studies met the *a priori* criteria and compared the risk of combined asthma-related ED/hospitalization endpoint for ADVAIR vs. ICS plus montelukast, including a total of

3,790 patients with 2,192 ADVAIR users and 1,598 ICS plus montelukast users (Figure 27).

Figure 27 Relative Risk for Asthma-Related Combined ED/Hospitalizations: ADVAIR vs. ICS Plus Montelukast, Pediatric Studies



ADVAIR was associated with a statistically significantly lower risk of an asthma-related ED/hospitalization visit (OR 0.46, 95% CI 0.27-0.76) compared to ICS plus montelukast in pediatrics.

4.4.4. Benefits in Asthma Outcomes with ADVAIR: Summary of Observational Studies

4.4.4.1. Adults

The results of the meta-analysis encompassing over 80,000 patients and over 58,000 ADVAIR users, show that ADVAIR use was consistently associated with a statistically significantly lower risk of asthma-related events (hospitalization and ED) relative to ICS monotherapy in real-world clinical practice. This effect was observed in different regions, across different sub-populations (i.e., Managed Care, Fee for Service Medicaid) and in different clinical practices across the US. This meta-analysis of observational studies demonstrated a meaningful reduction in hospitalizations and ED visits that was obtained with ADVAIR use compared to an ICS in real-world settings.

4.4.4.2. Pediatrics

In a meta-analysis of all available studies which included 43,500 children (16,368 using ADVAIR, 28,534 using ICS and 1,598 using ICS plus montelukast) ADVAIR use was associated with a lower risk of asthma-related events (combined ED/hospitalization) relative to ICS in real-world clinical practice. In addition, when compared to an alternative treatment for children not controlled on ICS, ADVAIR use demonstrated a

statistically significantly lower risk of serious asthma-related events (combined ED/hospitalization) vs. ICS plus montelukast among children of similar asthma severity.

4.5. Ecologic Data Regarding Salmeterol-Containing Products and Serious Asthma Outcomes

An ecologic study design, where the correlations between trends in potential risk factors and serious asthma outcomes over time are assessed, is another important approach to consider as part of the benefit-to-risk profile review for salmeterol in asthma. Since the mid-1990s, trends in aggregated data suggest that while asthma-related morbidity rates have remained stable and mortality rates have declined in the US, the use of asthma medications, including salmeterol-containing products, has increased over this same period. If there was a strong association between use of salmeterol (SEREVENT or ADVAIR) and risk of severe asthma-related events, a parallel increase in those events would be expected as the annual number of salmeterol-containing pharmacy dispensings more than doubled from 2000 to 2006. The CDC reported asthma-related hospitalization rates (Figure 28) and asthma-related mortality rates (Figure 29) were plotted against the retail pharmacy dispensing totals for salmeterol-containing products (SEREVENT and ADVAIR) by year.

Figure 28 Age-Adjusted Asthma-Related Hospitalization Relative to Salmeterol-Containing Dispensings, US, 1994–2006

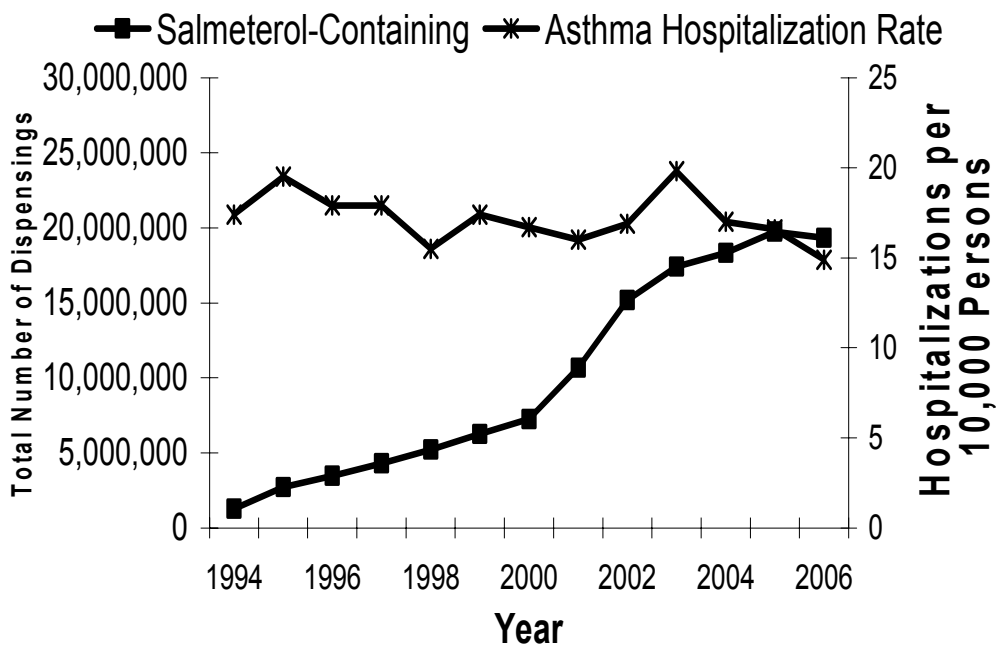
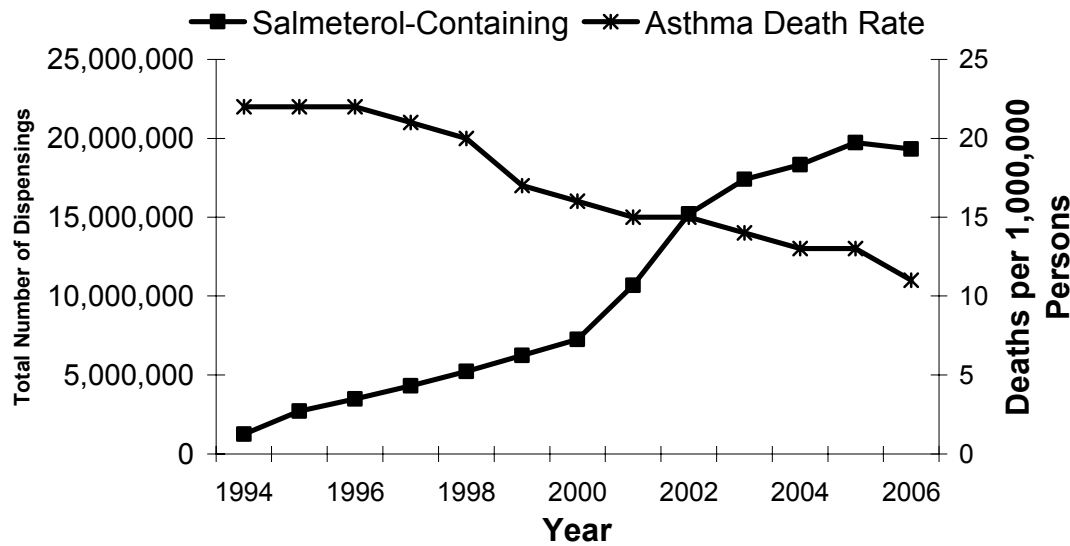


Figure 29 Age-Adjusted Asthma-Related Mortality Relative to Salmeterol-Containing Dispensings, US, 1994--2006



Over 13 years (1994 to 2006), dispensings of salmeterol-containing products have increased substantially while asthma-related hospitalization rates (Figure 28) were stable and asthma-related mortality rates (Figure 29) decreased [DiSantostefano, 2008].

4.6. Evidence from Observational Studies: Overall Summary

In summary, observational studies provide important information on the patterns of salmeterol use by the broad range of patients treated in clinical practice, both in aggregate and in terms of associated risk of serious events at the patient level. Since 2001, the vast majority of patients were dispensed salmeterol as ADVAIR.

In six studies in the US and UK, SEREVENT use was not associated with a statistically significant increased risk of asthma- or respiratory-related mortality nor serious asthma morbidity after adjusting for potential confounding by severity. In most studies there was lower risk of a serious asthma-related outcome in patients who received SEREVENT. Further, results from a meta-analysis of observational studies encompassing automated healthcare data from over 86,000 patients aged 18 and older across different regions and various health plans in the US suggests that ADVAIR use was associated with a statistically significantly lower risk of experiencing an asthma-related hospitalization or emergency room visit relative to ICS use. Similar beneficial trends in reductions in serious asthma events associated with ADVAIR vs. ICS were observed from six pediatric studies across various populations including over 45,000 children treated in real-world clinical practice. Finally, when examining trends in the US population data from 2001 to 2007 post-ADVAIR approval, salmeterol exposure more than doubled while the rate of asthma-related serious morbidity requiring hospital admission was relatively stable and asthma-related mortality declined.

Results from multiple, large observational studies did not confirm the signal of potential increased risk of severe asthma morbidity and mortality from early clinical trials with SEREVENT. On the contrary, the observational data suggest a beneficial role for salmeterol when used concurrently with ICS in decreasing the risk of severe asthma morbidity. With ADVAIR, a statistically significant reduction of an asthma-related hospitalization/ED visit was seen in adults and children compared with ICS and additionally in children compared with ICS plus montelukast,

5. ANALYSIS OF WORLDWIDE POST-MARKETING EXPERIENCE FROM SPONTANEOUS ADVERSE EVENT REPORTS

5.1. Disproportionality Analyses of Spontaneous Adverse Event Reports

Spontaneous adverse events are reported to FDA and/or to sponsors from health care professionals, patients, concerned acquaintances and from law firms. Historically, spontaneous adverse event reports have been evaluated using qualitative techniques such as individual case reviews and medical judgement. In March 2005, the FDA published a *Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment* [US HHS, 2005] which described the use of statistical or mathematical tools to provide additional information about the existence of an excess of adverse events reported for a product. One such method is Disproportionality Analysis (DPA), a quantitative signal detection tool that provides information on the reporting frequencies of adverse events relative to background reporting. In other words, DPA informs whether an adverse event of interest (i.e., fatal event) is spontaneously reported for a specific prescription product at a higher-than-expected rate (assuming that reporting of the same event of interest for all other prescription products for all diseases in a database represents the background [expected] rate).

In Section 3 of this document, outcomes for serious asthma-related adverse events (hospitalization and death) were evaluated in double-blind, randomized controlled trials with SEREVENT (both in presence and absence of concurrent ICS) and ADVAIR. The analysis showed that serious asthma-related adverse events in randomized controlled trials with SEREVENT occurred more frequently than comparator treatments, especially when SEREVENT was used in the absence of ICS or when SEREVENT was added to background ICS (defined as pre-study usual care for a study patient who is subsequently asked to continue pre-study mediations, but without supplying or monitoring adherence for any pre-study medications). No increased risk of serious asthma-related outcomes was observed for ADVAIR. The analysis of randomized controlled trials also found that a signal for potential elevated risk with SEREVENT appeared primarily during the early-marketing period when asthma was thought to be primarily a disease of bronchoconstriction and therefore, SEREVENT was often used in the absence of concurrent ICS, but not during the late-marketing period when SEREVENT was used almost exclusively with ICS. If these observations for SEREVENT were also occurring in the broad population of SEREVENT users in the community, then temporal signals associated with SEREVENT would likely be detectable from spontaneous adverse event reports.

The aim of this analysis was to assess the relative temporal reporting frequencies for death and hospitalization for SEREVENT (and ADVAIR) in adults and pediatric patients (0-16 years of age).

The data for SEREVENT were analyzed in two periods representing early and late marketing periods. The early period was defined as pre-1996 and the late period as 1996-2008. The events *fatal outcome* and *hospitalization* were evaluated for these two time periods. The cut-off date for this analysis is 1996, and not 2000 as reported for the randomized controlled trial data in Section 3. The 1996 date for the DPA analysis was maintained since it was used previously as the cut-off date for both the Pulmonary/Allergy Drugs Advisory Committee meeting in July 2005 and the Pediatric Advisory Committee meeting in November 2007. That date was previously selected because in 1995, labeling revisions and GSK associated communications for SEREVENT warned against the use of SEREVENT in significantly worsening or acutely deteriorating asthma. In light of this and the 1997 NHLBI's asthma guideline recommendations highlighting the appropriate use of LABA only with ICS, GSK believed that the more appropriate use of SEREVENT in this latter period would result in lower reporting frequencies of these serious outcomes.

5.1.1. Methods

DPA was conducted in the AERS spontaneous adverse event database described below using the empiric Bayes data mining algorithm, Multi-item Gamma Poisson Shrinker (MGPS) [DuMouchel, 1999; DuMouchel, 2001].

AERS, the US FDA's safety database, is a passive 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 all 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 March 2008, the public-release version of AERS contained approximately 3.5 million reports involving approximately 2,000 marketed drugs.

MGPS computes the empirical Bayes geometric mean (EBGM) and associated two-sided 90% confidence interval (EB05, EB95) for each drug-event pair in a database. EBGM represents the reporting frequency for a drug-event pair, relative to all other reports (all drugs and all events) in the database. An EBGM of 2 can be interpreted to mean that a drug-event pair has been reported 2 times as frequently as would be expected if reports involving the drug and reports of the event were independent. An EB05 of 2 indicates 95% confidence that the relative reporting ratio (EBGM) is at least 2. $EB05 \geq 2$ is generally recognized as a threshold for defining a safety signal. This threshold ensures with a high degree of confidence that, regardless of the number of reports, a particular drug-event combination is being reported at least twice as often as it would be if there were no association between the drug and the event [Szarfman, 2002].

“*Fatal outcome*” reports were defined as reports where 1) seriousness criterion was designated as death or 2) MedDRA Higher Level Term (HLT) for the case was coded as

death or sudden death. “Hospitalization” reports were defined as reports where the seriousness criterion was designated as *hospitalization*. If reports fit the criteria for both *hospitalization* and *fatal outcome*, they were classified in the “fatal outcome” category.

5.1.2. Limitations of Disproportionality Analyses

- DPA does not provide estimates of the *incidence* of adverse events, but can provide information about the *relative reporting* of events in the post-marketing setting.
- A high relative reporting frequency does not necessarily indicate a high incidence of the event or suggest a causal relationship between the drug and the event.
- Reporting rates may vary between populations and may be affected by many different factors, including publicity (e.g., media attention, Dear Doctor letters), length of time that a drug has been available in a market and association of an adverse event with another drug in the same or similar class. Hence, caution should be used in comparing EBGM or EB05 values, as they may reflect biases due to differential reporting.

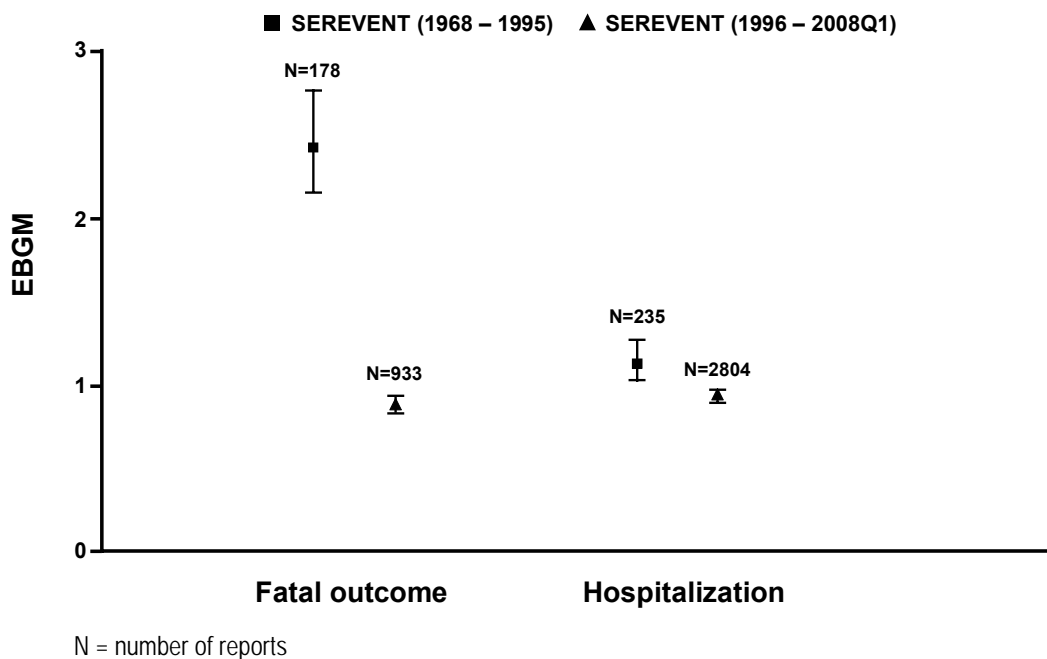
5.1.3. Results of DPA Analyses

The EBGM values for SEREVENT and ADVAIR and their lower and upper confidence bounds (EB05 and EB95) are shown for each event of interest in AERS.

5.1.3.1. Reporting patterns for SEREVENT in early and late marketing periods

Figure 30 displays EBGM values in AERS.

Figure 30 EBGM (EB05, EB95) Values for Events of Interest with SEREVENT in Early and Late Marketing Periods (pre-1996 and 1996-2008) in AERS

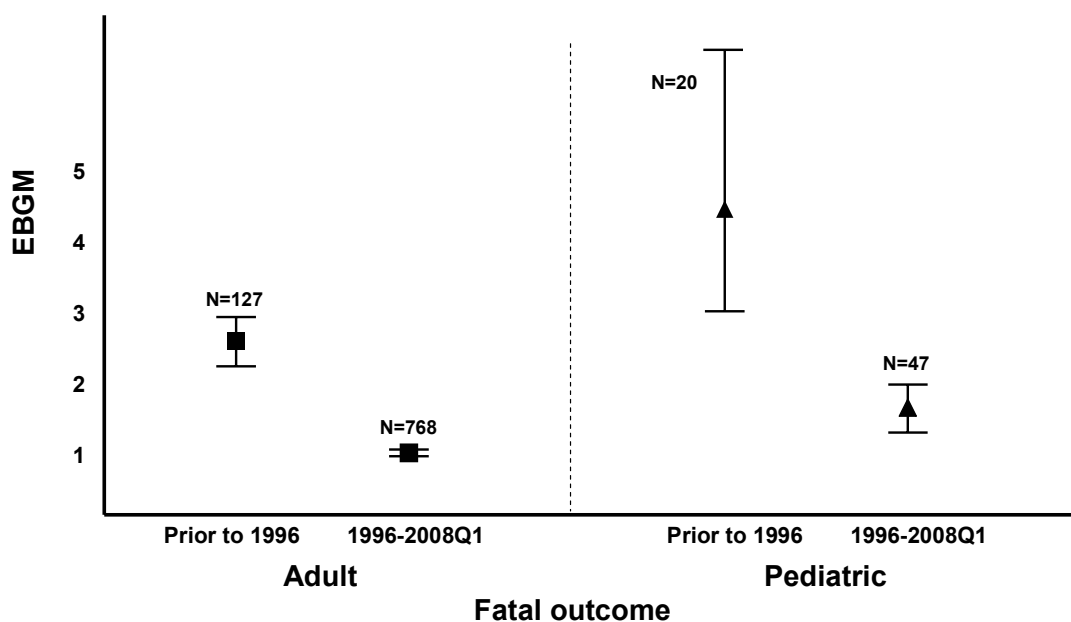


- The EB05 value for SEREVENT was 2.1 with respect to *fatal outcome* in the pre-1996 period, indicating a modestly elevated reporting frequency during this time period. However, the relative reporting frequency was not elevated (EB05 <1) in the 1996-2008 period. This finding is consistent with the reduction in asthma-related deaths seen in the data reported from observational studies and ecologic data (Section 4).
- The EBGM and EB05 values for SEREVENT were not elevated for *hospitalization* in either period.

5.1.3.2. Outcomes in children and adults

Since the DPA analysis of fatal outcomes indicated an EB05 >2 in the early marketing period (pre-1996), we further examined the relative reporting frequencies by early and late marketing periods for *fatal outcome* separately for adults and children (Figure 31).

Figure 31 EBGM (EB05, EB95) Values for SEREVENT and *Fatal Outcome* in Children and Adults in Early and Late SEREVENT Marketing Periods (pre-1996 and 1996-2008) in AERS

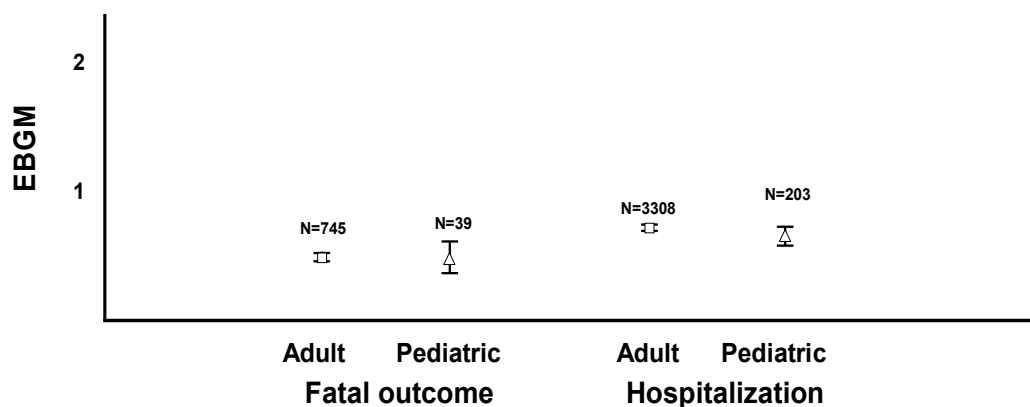


N = number of reports

Reduction in reporting of *fatal outcome* in the latter period was observed for both adults and children and may be related to broad communication following labeling changes for SEREVENT in 1995 and NHLBI's asthma guideline recommendations in 1997 that stressed the importance of ICS therapy.

Since ADVAIR was not available until after 1997, a temporal comparison of relative reporting rates for outcomes and ADVAIR cannot be conducted for these two time periods. DPA for *fatal outcome* and *hospitalization* with ADVAIR in adult and pediatrics since the time of first approval for ADVAIR are shown in Figure 32.

Figure 32 EBGM (EB05,EB95) Values for ADVAIR and *Fatal Outcomes* and *Hospitalizations* in Children and Adults in AERS



N = number of reports

The reporting frequencies for *fatal outcome* or *hospitalization* were not elevated for ADVAIR. In fact EBGM values were below one for both adults and children, suggesting that the rate for these events occurred below expected values.

5.1.3.3. Summary of disproportionality analyses

DPA was performed to evaluate relative reporting frequencies of *hospitalization* and *fatal outcome* with SEREVENT and ADVAIR.

- For SEREVENT, relative reporting frequencies for the outcomes of fatal event and hospitalization have declined from the early marketing period to the current marketing period. Reduction in these events may be related to broad communication following labeling changes for SEREVENT in 1995 and NHLBI's asthma guideline recommendations in 1997 that stressed the importance of ICS therapy.
- For ADVAIR, *hospitalization* and *fatal outcome* have been reported relatively infrequently and were reported at a rate below the expected rate.
- The DPA results for SEREVENT corroborate the signal from early randomized controlled trials that SEREVENT may be associated with an increase in serious asthma-related outcomes under conditions of use characteristic of the early marketing period but corroborate with later clinical trial results and observational data in detecting no signal in more recent years.
- The DPA results for ADVAIR confirm the results from randomized control trials (Section 2) that ADVAIR is not associated with any increase in *fatal outcome* or *hospitalization*. The DPA showed that these serious outcomes were reported as spontaneous adverse events at a rate lower than expected compared with other treatments. This supports the data from observational studies (Section 4) which found statistically significant reductions in hospitalization in cohort designed trials comparing ADVAIR to either ICS or ICS plus leukotriene modifier.

6. ALTERNATIVE EXPLANATIONS FOR OBSERVED SAFETY OUTCOMES WITH SALMETEROL

6.1. Introduction

In this document, results from randomized controlled trials have demonstrated that serious adverse events associated with salmeterol use occur primarily in patients not receiving ICS or in patients who may not be adherent to ICS. This was best illustrated in SMART in which nine asthma-related deaths occurred in salmeterol patients not on baseline ICS compared with none in the usual care (placebo) control group not on baseline ICS. Comparatively, there were four asthma-related deaths in patients receiving salmeterol and baseline ICS and three in the usual care (placebo) group receiving ICS.

ICS have been shown to reduce asthma mortality, and contemporary treatment of patients with persistent asthma mandates the use of ICS in all patients with persistent asthma. When the use of salmeterol was examined with concurrent ICS use, there was no evidence of increased risk of serious adverse events with salmeterol. In this document, GSK has postulated that behavioral factors, related to the misuse of asthma medications, is the most reasonable explanation for the outcomes seen in studies like SMART.

However, other alternative mechanisms have been postulated to explain the outcomes seen in studies like SMART. This section will describe other pharmacological mechanisms that have been postulated to affect clinical responses to beta₂-agonists.

6.2. Effect of Salmeterol on Desensitization and Down Regulation

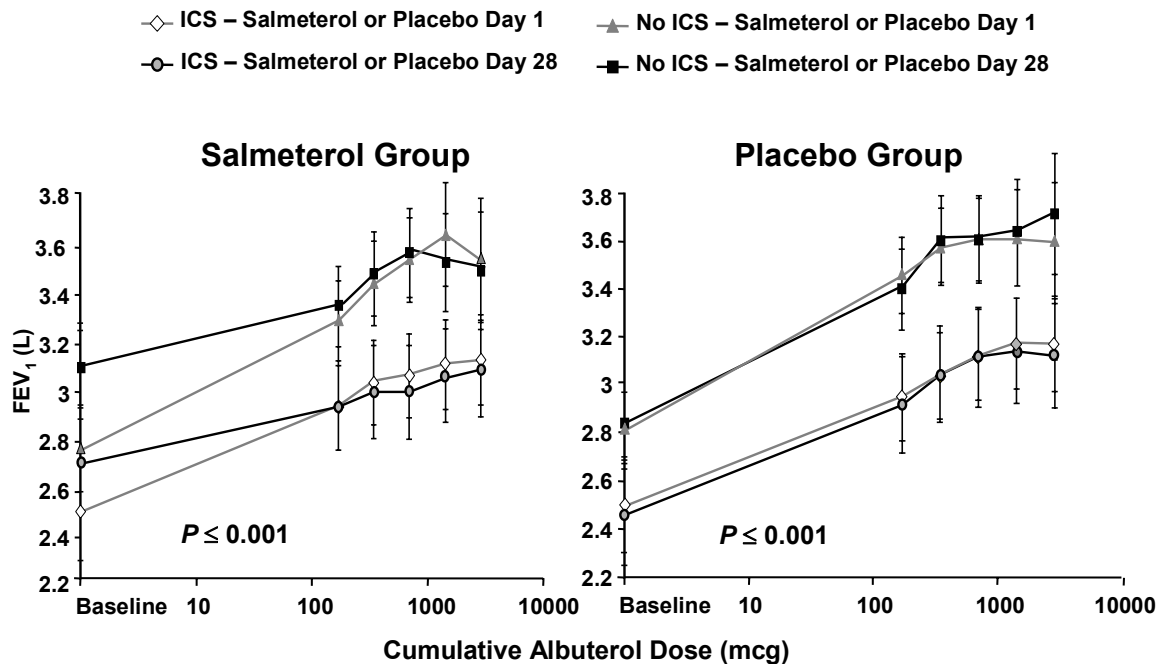
In general, the observation of tolerance to the bronchodilator properties of salmeterol has not been demonstrated in clinical trials. In year-long studies, the bronchodilator effect of salmeterol was preserved without diminution of effect [Britton, 1992]. Some loss of protection to allergen or exercise challenge with beta₂-agonists, including salmeterol, has been reported [Van Veen, 2003; Giannini, 2003]. But these effects are variable and generally minor and not observed in studies of the combination of salmeterol and an ICS [Paggiaro, 2006]. In addition, the development of tolerance was not associated with Arg16Gly genotypes [Lee, 2004].

The clinical situation where tolerance or down regulation could negatively affect asthma management is during the period of excessive beta₂-agonist stimulation during a severe asthma attack. In this clinical scenario, patients generally self-treat with frequent and high doses of short-acting beta₂-agonist in an attempt to “break” or relieve the symptoms of an asthma attack. If patients are unable to relieve their symptoms, they may seek medical assistance, often in the ED. Studies have examined the role of salmeterol in this clinical environment. In one study, patients presenting to the ED who failed to respond to continuously nebulized albuterol, were hospitalized and treated with salmeterol and demonstrated additional improvement in FEV₁ and stabilization of asthma [Peters, 2000]. In another study, patients who reported use of salmeterol prior to ED presentation were treated with continuous albuterol and these patients responded with a 50% improvement in lung function. Control patients in this study who had not received salmeterol prior to

ED presentation demonstrated a 49% improvement in lung function following continuous albuterol nebulization [Korosec, 1999].

In addition, a 28-day cross-over study of patients with stable asthma receiving salmeterol twice daily with and without ICS examined whether the cumulative dose-response to albuterol was altered compared with controls (Figure 33) [Nelson, 1999].

Figure 33 FEV₁ (mean \pm SE) Response to Cumulative Doubling Doses of Albuterol Before Day 1 and After Day 28



FEV₁ (mean \pm SE) response to cumulative doubling doses of albuterol before Day 1 and after Day 28

The results demonstrated no reduction in the cumulative albuterol dose-response after a single dose of salmeterol (Day 1) or after chronic dosing with salmeterol (Day 28). The positive response to albuterol was unaltered in salmeterol recipients (and controls) independent of ICS exposure.

Taken together, these clinical studies suggest that salmeterol remains an effective treatment during periods of acute worsening asthma and that salmeterol does not induce clinically relevant tolerance that reduces response to additional beta₂-agonists.

6.3. Effect of Salmeterol on Cardiac Response

Non-selective beta₂-agonists have been associated with increased heart rate and dysrhythmia, but salmeterol, the most highly selective beta₂-agonist available has not been associated with clinically significant untoward cardiac effects. SEREVENT and ADVAIR have been approved by regulatory agencies based on extensive development

programs in populations of adolescents and adults for the treatment of asthma and COPD as well as pediatric patients for the treatment of asthma. Within each of these clinical development programs, GSK has extensively collected ECGs and 24-hour ambulatory Holter monitoring. In clinical studies with SEREVENT or ADVAIR, changes in heart rate and blood pressure were infrequent and similar to comparator treatments. Clinically significant ECG abnormalities occurred infrequently with ADVAIR or SEREVENT and were similar to comparator treatments. In addition, there was no evidence that SEREVENT or ADVAIR increased the incidence of QTc prolongation at approved labeled doses [Chervinsky, 1999; Kavuru, 2000; Shapiro, 2000; Aubier, 1999].

Further, a large three-year study in over 6,000 patients with COPD, who would be at greater risk for co-existent cardiovascular disease because of their primary disease, found fewer cardiovascular events for patients receiving salmeterol or ADVAIR compared with placebo [Calverley, 2007]. In this same study, use of salmeterol was associated with a decrease in all cause mortality as well as COPD mortality.

Thus, large long-term studies of salmeterol in clinical practice have not shown evidence of clinically relevant untoward cardiovascular events.

6.4. Pharmacogenetic Studies with Salmeterol

Studies have suggested that *ADRB2* Arg16Gly polymorphisms may be important in modulating responses to beta₂-agonist therapy for asthma [Joos, 2001]. For example, in a report from retrospectively derived data from two different studies, Wechsler et al. suggested that patients with asthma who have the Arg/Arg genotype at codon 16 of the *ADRB2* may have an impaired therapeutic response to salmeterol in either the presence or absence of concurrent ICS [Wechsler, 2006]. Interpretation of these findings is limited since only 12 and 8 Arg/Arg patients in each of the studies, respectively, were available for analysis.

In contrast, larger retrospective studies reported by Bleecker et al. showed that the outcomes of pre-dose AM PEF, asthma symptoms, and rescue albuterol use were all improved and sustained over chronic treatment with LABAs independent of Arg16Gly genotypes [Bleecker, 2006; Bleecker, 2007].

GSK addressed the question of *ADRB2* Arg16Gly polymorphisms by conducting a prospective randomized, parallel group, double-blind, comparative 16-week trial (SFA100062) examining lung function and other measures of asthma control by genotype. The study enrolled approximately 540 adults and adolescents at least 12 years of age with persistent asthma who had either an Arg/Arg, Gly/Gly or Arg/Gly *ADRB2* genotype. There were two treatment arms: ADVAIR 100/50mcg BID or salmeterol 50mcg BID.

This study demonstrated that polymorphisms in *ADRB2* were not associated with a differential response to salmeterol. In addition, there was no effect of switching patients from short-acting beta₂-agonist use to an anticholinergic, effectively removing all exogenous beta₂-agonist influence. Similarly, following the withdrawal of either salmeterol or ADVAIR, there was no differential response based on genotype. For all

clinical outcomes, each genotype group remained above pre-treatment baselines during the 2-week washout period.

The question remains as to the functional significance of polymorphisms and fatal asthma. A separate study examined the association between polymorphisms in *ADRB2* and fatal or near-fatal asthma (defined as patients either intubated in a hospital emergency room or who had a $\text{PaCO}_2 > 45 \text{ mmHg}$). This study showed that there was no association of polymorphisms at the 16, 27 or 164 positions and fatal or near-fatal asthma [Weir, 1998]. Therefore, functional polymorphisms in *ADRB2* do not appear to be a major determinant of fatal or near-fatal asthma.

6.5. At Risk Population: African Americans

African Americans experience comparatively greater asthma morbidity and mortality than Caucasians and other ethnic groups [Heron, 2008; American Lung Association, 2007]. Studies have also shown that African Americans are dispensed less ICS than other ethnic groups, even when controlling for socioeconomic measures [Rand, 2000; Zoratti, 1998].

African Americans experienced relatively greater asthma morbidity and mortality compared with non-African Americans (e.g., Caucasians) in SMART [Nelson, 2006]. This led to the postulation that African Americans may represent a unique at risk population relative to non-Caucasians. To address this question, GSK conducted a year-long study in 475 African Americans comparing the exacerbation rates in patients receiving ADVAIR and ICS (SFA103153) [Bailey, 2008]. In brief, the study found that African Americans experienced a lower exacerbation rate on ADVAIR 100/50mcg BID (0.45/year) compared with FP 100 mcg BID (0.53/year; $p=0.169$).

In addition, the *a priori* analysis plan describes how the total dataset for African Americans was reviewed to examine the role (if any) of salmeterol in the occurrence of serious asthma-related events [RM2008/00078/00]. In brief, data were analyzed in three separate groups (referenced by the bolded phrase) below:

- African American data from **SMART**,
- African American data from all **Other US** studies (excluding SMART and the stand-alone study of African Americans [SFA103153]), and
- **SFA103153** data, the stand alone study in African Americas.

The three grouped populations above, designed to examine outcomes in African Americans, is an alternative approach to that taken with the total population. SMART was treated as a standalone population due to its size compared with the remaining randomized controlled trials. Furthermore, due to the limited numbers of African Americans remaining in the overall database from individual studies, this population was not added to the single large year-long trial (SFA103153) [Bailey, 2008] designed specifically to study African Americans since this study would likely overwhelm any contribution from African Americans in the overall database.

All but one asthma-related death in African Americans occurred in SMART and no asthma-related intubations occurred outside SMART. The other asthma-related death (in the Other US analysis population) occurred in a patient receiving salmeterol without concurrent ICS. The asthma-related deaths and intubations occurring in SMART are presented in [Table 3](#).

Table 3 Asthma-Related Intubation and Asthma-Related Death in African Americans in SMART

Analysis Population	Treatment		Intubation			Death		
	Sal N	Pla N	Sal n	Pla n	RD (95% CI)	Sal n	Pla n	RD (95% CI)
Sal vs. Pla	1,383	1,374	6	1	36.11 (-1.35, 73.56)	4	0	28.92 (0.62, 57.23)
Sal + ICS _{BK} vs. ICS _{BK}	983	945	11	2	90.74 (18.75, 162.73)	3	1	19.94 (-20.30, 60.17)

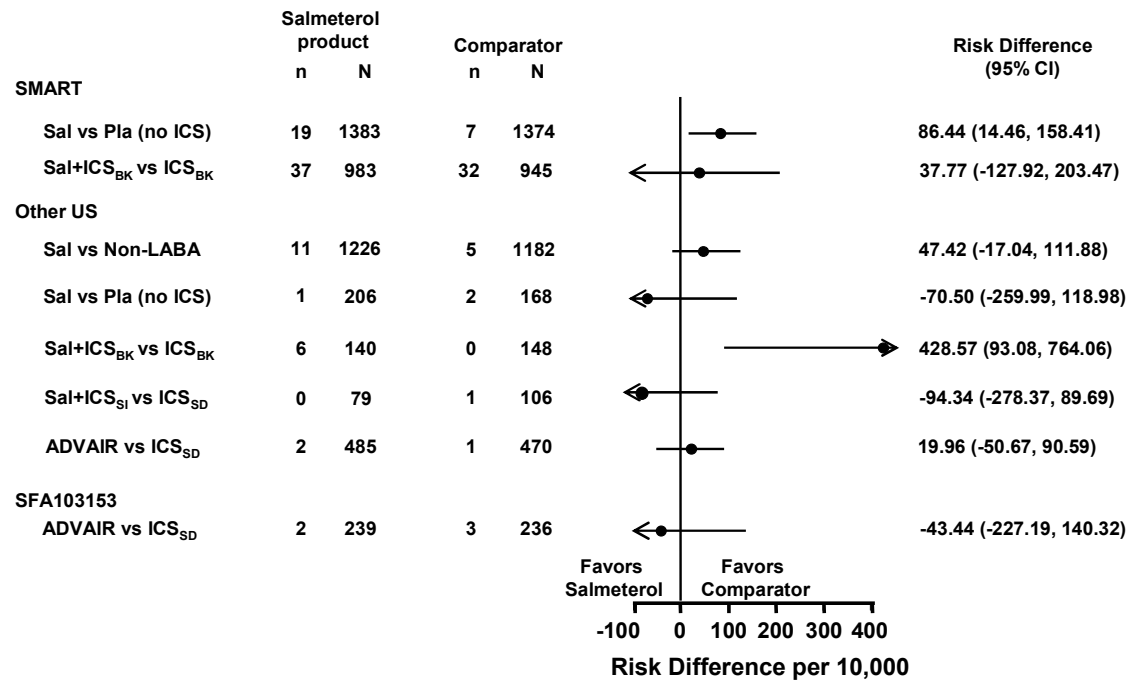
No intubations were reported in patients receiving Sal+ICS_{SD} or Advair.

The results for asthma-related intubation and death from SMART should be interpreted with caution, since very few events (n=29) occurred. Although the absolute number of events is low, it is noteworthy that the RD for intubation for SAL + ICS_{BK} vs. ICS_{BK} is greater than the RD for SAL + ICS_{BK} vs. Pla. The most probable explanation for why the RD is higher for Sal vs. ICS_{BK} compared with Sal vs. Pla in the absence of ICS may be related to the relative severity between these groups. Patients in SMART who received Sal + ICS_{BK} were likely to have more severe asthma compared with patients receiving Pla + ICS_{BK}. Subsequently, if adherence to ICS_{BK} was sub-optimal, both groups were essentially receiving salmeterol without ICS. Therefore, the Sal + ICS_{BK} patients may have been comparatively more severe and thus would be predicted to have more severe outcomes if patients were non-complaint to ICS_{BK}.

The RD results for asthma-related hospitalization for the three subgroups, 1) SMART, 2) Other US studies and 3) SFA103153, are shown in [Figure 34](#).

Compared to the analysis of the total population in [Section 3](#), the number of patients studied and the number of asthma-related hospitalizations was low. Nonetheless, the results in African Americans show the same trends seen in the total population (which includes African Americans). A total of 116 patients reported an asthma-related hospitalization of the 7,568 patients in the three databases.

Figure 34 Pooled Analysis of African American Subgroups: Risk Difference for Asthma-Related Hospitalization



In [Figure 34](#), the RD for asthma-related hospitalization was statistically significantly increased for Sal vs. Pla in the SMART dataset and for Sal + ICS_{BK} compared to ICS_{BK} in the Other US studies dataset. The RD for asthma-related hospitalization was not statistically significant for any other comparisons in the three datasets.

In the US today, nearly all salmeterol use is with concurrent ICS as ADVAIR. Thus, it is important to look closely at ADVAIR results. In the combined databases, four patients with a hospitalization were reported for ADVAIR compared with four in the FP control groups (results summed by adding data from other US studies and SFA103153).

Taken together, these data in African Americans suggest that salmeterol used in the absence of ICS, or with background ICS, may be associated with increased serious asthma-related outcomes. However, when salmeterol and ICS are known to be used concurrently, there is no signal of increased risk of serious asthma-related events in African Americans receiving salmeterol.

6.6. Other Mortality Studies with Salmeterol

Other than SMART, there are no other asthma studies specifically designed to evaluate mortality and salmeterol use. However, the recently reported TORCH study (Toward a Revolution in COPD Health) was designed to evaluate all cause and associated mortality results following three years of treatment regimens with salmeterol and ICS in patients with COPD [[Calverley, 2007](#)]. TORCH randomized more than 6,000 patients with

moderate to severe COPD to receive twice daily SEREVENT 50mcg, FP 500mcg, ADVAIR 50/500mcg, or placebo.

A summary of key mortality data is shown in [Table 4](#)

Table 4 Key Mortality Data from COPD Patients in TORCH

	PLACEBO		SEREVENT		FP		ADVAIR	
	N=1524		N=1521		N=1534		N=1533	
All deaths	231	(15.2%)	205	(13.5%)	246	(16.0%)	193	(12.6%)
Cardiovascular	71	(5%)	45	(3%)	61	(4%)	60	(4%)
Pulmonary	74	(5%)	80	(5%)	91	(6%)	61	(4%)
COPD related	91	(6%)	93	(6%)	106	(7%)	72	(5%)

TORCH found that the probability of all cause mortality was lowest (12.6%) with ADVAIR treatment compared with the other three treatments (13.5-16.0%). Notably, the percentage of patients who experienced a cardiovascular death was lower for both SEREVENT (3%) and ADVAIR (4%) compared with placebo (5%).

The benefit of salmeterol treatment (with or without ICS) in COPD was demonstrated in TORCH. The rate of moderate to severe COPD exacerbations was statistically significantly lower for ADVAIR recipients compared with SEREVENT, FLOVENT and placebo. The rate of moderate to severe COPD exacerbations was statistically significantly lower for salmeterol recipients compared with placebo.

While TORCH was conducted in patients with COPD, it is reasonable to assume that, if there was a pharmacologic mechanism by which salmeterol were causing serious adverse outcomes in patients with asthma, the same outcomes would also be seen in patients with COPD. Patients with COPD generally have significant co-existent metabolic and cardiovascular risk factors that could be adversely affected by beta₂-agonist use. However, the TORCH results showed that neither SEREVENT nor ADVAIR were associated with an increase in the probability of cardiovascular, pulmonary, COPD or all cause death. In addition, the benefits of salmeterol treatment in COPD were demonstrated by improved pulmonary function and reduction in exacerbation rate.

6.7. Summary of Alternative Explanations for Observed Safety Outcomes with Salmeterol

This section briefly reviewed alternative explanations which could explain an association of LABA use and the serious asthma-related outcomes reported primarily from SMART and SNS. However, there was no evidence of clinically relevant tolerance to beta₂-agonists with salmeterol, no evidence of an increase in clinically relevant cardiovascular events, no evidence of an association with specific *ADRB2* polymorphisms, and no evidence of an increased risk in African American patients. Long-term studies in patients with COPD (e.g., TORCH) show improved outcomes with salmeterol and do not support evidence of intrinsic pharmacologic toxicity. While the beta₂-adrenergic receptor and its function can be modulated by a host of biochemical and environmental factors, the

weight of evidence does not support a pharmacological mechanism linking salmeterol to severe asthma outcomes.

The most plausible explanation is related to the under-use of ICS. It is clear from the clinical data presented in Sections 3 and 4 that when salmeterol is used without an ICS or in a clinical situation where the ICS may be used sub-optimally; there may be an increased risk of asthma-related serious events. It is equally clear that when salmeterol is known to be used with ICS, there is no signal of increased risk of serious asthma-related outcomes. Therefore, the observed association between serious asthma-related events and salmeterol use is likely due to improper asthma management and not a function of any known detrimental pharmacological mechanism of LABA.

7. OVERALL BENEFIT TO RISK PROFILE

7.1. Overall Benefits of LABA and Position in Guidelines

The combination of salmeterol with an ICS provides unsurpassed asthma control to patients by improving lung function, preventing daytime and nighttime symptoms and decreasing the use of rescue medications. A review of over 20 years of clinical experience has demonstrated that there is no increased risk of serious asthma-related events when salmeterol is used appropriately with an ICS. The effectiveness of LABA used concurrently with ICS is accepted in all evidenced-based national and international guidelines, and as such, the combination is recommended as a preferred step in the therapeutic management of both adult and pediatric patients requiring additional treatment beyond low-dose ICS alone.

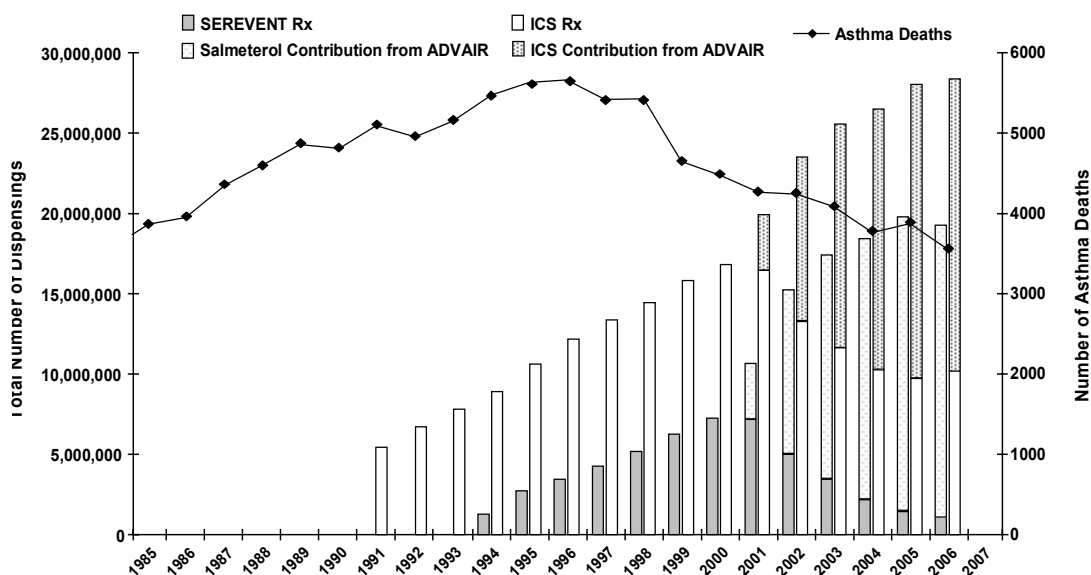
When LABA products were first introduced in the early 1990s, the standard of asthma care at the time did not fully recognize the importance of inflammation as the primary mechanism for worsening asthma and its role in contributing to airway smooth muscle dysfunction. Therefore, LABA development plans and asthma treatment guidelines did not stress that LABA should only be used with ICS. However, the current understanding of the pathophysiology of asthma and best therapeutic practices for asthma management recognize that all patients with persistent asthma should be treated with an anti-inflammatory agent, preferably an ICS. In fact, current guidelines highlight that patients receiving LABA should be educated regarding correct use of LABA and that patients must be instructed not to stop anti-inflammatory therapy while taking LABA even though their symptoms may significantly improve. This last point is critical, because inflammation may be present in the absence of symptoms. While asthma can be a debilitating outpatient disease, impacting day-to-day life through troublesome daytime and nighttime symptoms, asthma is also a serious disease that can be fatal. However, experts agree that most asthma deaths can be prevented through consistent adherence to an asthma management plan which includes ICS as the cornerstone of treatment [NAEPP, 2007]. In fact, experts investigating deaths from asthma cite ICS under-treatment and poor adherence to asthma medications as primary causes related to most asthma deaths [Wilcox, 2008; Bergstrom, 2008]

7.1.1. Characterization of Salmeterol Safety Based on Contemporary Use

It is also important to consider the impact of a therapy as it relates to its current use in the community. The recognition that all patients with persistent asthma should regularly use an ICS has gained greater acceptance over the past decade [NAEPP, 2007; Stafford, 2003]. For example, SMART was initiated in 1996, yet less than half the patients receiving salmeterol in the study were also receiving an ICS at baseline. In 2008, greater than 99% of all patients in the US receiving salmeterol for asthma were also receiving concurrent ICS. In fact, over 98% of salmeterol use in asthma is in the form of the combination product, ADVAIR [Surveillance Data Incorporated, 2008].

Also, the number of asthma deaths have decreased by 34% between 1998 and 2006, while, at the same time, dispensing of salmeterol-containing products (primarily ADVAIR since 2002) has increased from approximately 5.2 million to 19.2 million dispensings (Figure 35).

Figure 35 Number of Asthma Deaths Relative to ICS- and Salmeterol-Containing Dispensings, US, 1991-2006



In light of the decade-long decline in the asthma death rate, which is correlated with increasing sales of ADVAIR and decreasing sales of SEREVENT for asthma and the comprehensive review of salmeterol-containing products from clinical trials databases and real-world settings, the earlier safety signal has been mitigated.

In summary, in the comprehensive safety review, including the meta-analyses of clinical trial results and an extensive assessment of observation data from clinical practice, no signal of elevated risk appears under conditions of use consistent with contemporary treatment guidelines, i.e., with concurrent use of ICS. Thus, the increased risk of serious asthma-related outcomes observed with salmeterol under outmoded conditions of use has

been mitigated now that the standard of care for all patients with asthma mandates that salmeterol only be used with ICS.

7.2. Benefit-to-Risk Profile of Salmeterol in the Treatment of Asthma in Adults and Children

The benefit-to-risk profile for salmeterol-containing products is favorable in adults and children when used according to contemporary treatment guidelines and standards of care mandating concurrent ICS therapy.

The impact of asthma on patients' daily lives is substantial. Asthma limits patients' activities including sports and recreation, disturbs sleep, and cause patients to miss work and school. When asthma symptoms increase, patients feel panic, and are afraid of having to go to the emergency room or hospital because of their asthma. Poorly controlled asthma leads to exacerbations, which can cause hospitalization and emergency department visits. The combination of salmeterol with an ICS is unsurpassed in improving overall control of asthma. Asthma control was demonstrated in clinical studies by an improvement in lung function, prevention of daytime and nighttime symptoms, and reduction in the need for rescue medication. Overall, in the adolescent and adult studies specifically designed to examine efficacy, concurrent use of salmeterol and ICS (as SEREVENT plus ICS or ADVAIR) resulted in greater asthma control and quality of life compared with equipotent or higher doses of ICS and compared with ICS in combination with other controller therapies (e.g., montelukast). Analyses of clinical data evaluating the event of asthma exacerbations demonstrated that salmeterol plus ICS vs. ICS statistically significantly reduced the rate of asthma exacerbations requiring oral corticosteroids. In addition, observational studies of ADVAIR showed statistically significant reductions of asthma-related ED visits and hospitalizations.

In the clinical situation when ICS alone do not sufficiently control asthma in children, evidence-based treatment guidelines recommend either increasing the ICS dose or adding another controller therapy, including LABA or leukotriene modifier. Results from randomized clinical trials demonstrated greater improvements in clinical outcomes for children receiving salmeterol plus ICS relative to higher dose ICS. Additionally, studies of observational studies of ADVAIR use in children showed statistically significant reductions in the combined endpoint of ED visits/hospitalizations when compared with ICS and when compared with ICS plus leukotriene modifier.

While the efficacy of salmeterol used appropriately with an ICS is substantial, concerns have been raised that use of salmeterol may be associated with serious asthma outcomes, specifically asthma-related deaths and hospitalizations. This signal was seen primarily in two studies of SEREVENT: one study in the early 1990s conducted in the UK (SNS) and one study conducted primarily in the late 1990s in the US (SMART) showed a slight increase in asthma-related deaths.

To further evaluate the potential association between salmeterol and serious asthma-related outcomes, GSK evaluated and analyzed the following large databases which span over 20 years of clinical experience:

- The meta-analysis of the randomized clinical trials database (including 215 studies and 106,757) found increases in serious asthma-related outcomes when salmeterol was used without an ICS or when patient use of ICS with salmeterol was not assured. In contrast, there was no evidence of increased risk for asthma-related death, asthma-related hospitalization, asthma-related intubation and all cause death when salmeterol and ICS use was used appropriately.
- The meta-analyses of four observational studies in adults (n=82,996) demonstrated a significant reduction in hospitalizations and ED visits with ADVAIR use compared to an ICS in clinical practice. The meta-analyses of five observational studies in children (n=43,500) demonstrated a significant reduction in combined hospitalizations/ED visits with ADVAIR use compared to an ICS and when compared with ICS + montelukast in clinical practice.
- An ecologic analysis found that over 13 years from 1994 to 2006, dispensing of salmeterol-containing products increased substantially while CDC reported asthma-related hospitalization rates were stable and asthma-related mortality rates decreased.
- An analysis of the FDA AERS database showed that ADVAIR was not associated with any increase in *fatal outcome* or *hospitalization*. The analysis for SEREVENT found that prior to 1997; SEREVENT corroborated the signal from early randomized controlled trials that SEREVENT may be associated with an increase in serious asthma-related outcomes under conditions of use characteristic of the early marketing period. However the analysis also corroborated with later clinical trial results and observational data in detecting no signal in more recent years.

When viewed in its entirety, the combination of salmeterol with an ICS provides unsurpassed asthma control to patients by improving lung function, preventing daytime and nighttime symptoms and decreasing the use of rescue medications. A review of over 20 years of clinical experience has demonstrated that there is no increased risk of serious asthma-related events when salmeterol is used appropriately with an ICS.

For ADVAIR, there was no evidence of increased risk for asthma-related death, asthma-related hospitalization, asthma-related intubation and all cause death. Therefore no regulatory action is necessary for this product.

However, when salmeterol is used in the absence of an ICS or when an ICS is not taken appropriately, an increase in serious asthma-related events have been observed.

Therefore, GSK has submitted a labeling supplement to reinforce the importance of maintaining concurrent ICS therapy while being treated with SEREVENT DISKUS. GSK believes the continued availability of SEREVENT DISKUS for the treatment of asthma ensures access to this effective medicine in patients where the fixed-dose combination may be unavailable, for patients who require an inhaled corticosteroid other than fluticasone propionate, or for the prescriber who needs the additional flexibility of ICS doses beyond those available in the fixed dose combination product.

In conclusion, appropriate concurrent use of salmeterol with ICS, whether as ADVAIR or SEREVENT plus ICS, has significantly advanced the care and well-being of patients with asthma and remains a preferred treatment option based on evidence-based asthma

treatment guidelines. It is critical that these products continue to be available to maintain the high standard of care that is currently available to patients with asthma.

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ATTACHMENT 1 METHODS FOR CLINICAL TRIALS EFFICACY ANALYSIS

For the efficacy analysis of GSK randomized controlled trials, all double-blind, randomized, parallel group, repeat-dose studies of salmeterol (including salmeterol-containing treatment arms, e.g., ADVAIR) meeting pre-specified criteria were selected. Studies specifically designed and powered to establish the efficacy of salmeterol when used appropriately with concurrent ICS, and for which efficacy data were available in a consistent format for comparison across studies, were selected. Since each of the studies selected was individually powered to evaluate efficacy, a meta-analysis was not performed; rather, the relevant efficacy parameters were examined individually for each study.

Studies where salmeterol as study drug was administered in the absence of ICS were excluded since salmeterol was not used appropriately according to current guidelines and medical practice. Additionally, studies where salmeterol as study drug was added to background ICS were excluded from the efficacy analysis since there was no systematic reinforcement or any measure of continued adherence to the medication during the study.

Studies containing a treatment arm of salmeterol plus ICS, administered either as combination therapy or via separate inhalers, compared with a treatment arm of ICS, either alone or administered with additional non-ICS therapy, were selected for additional evaluation for potential inclusion in the efficacy analysis.

[Table 1](#) shows the pre-defined criteria initially applied in order to determine which individual studies would be included in the efficacy analysis.

Table 1 Criteria for Study Inclusion in Efficacy Analysis

Inclusion Criteria	Exclusion Criteria
Study drugs include salmeterol + ICS (combination or separate inhalers) compared with ICS	Study drug salmeterol monotherapy or salmeterol added to background ICS
Double-blind, parallel group	Crossover studies
Repeat dose	Patient population with controlled asthma at randomization
Study powered for efficacy	Study terminated prior to reaching target sample size
	Studies of unapproved dosing regimens (e.g. once daily)
	Exercise-induced bronchospasm (EIB) studies
	Studies with variable dosing ¹
	Studies with randomization to lower dose of ICS (i.e., step down studies)

1. Exception: SAM40027 (GOAL) included variable dosing, with titration after the first 12 weeks of double-blind study drug. Only the data from the first 12 weeks of this study are included in the analysis.

Efficacy data were extracted from the statistical tables within the GSK Clinical Study Report from each of these studies; if statistical tables were not available, the GSK Clinical Trial Register (CTR) Summary [[Clinical Trial Register](#)[Clinical Trial Register](#)[Clinical Trial Register](#)] or the publication was used as the data source. The following criteria were then applied for inclusion of specific data in the analysis, to allow a comparison of similar efficacy data across studies.

- Intent-to-Treat (ITT) population data available
- One or more of the following efficacy parameter(s) available:
 - AM pre-dose forced expiratory volume in 1 second (FEV₁) (L)
 - AM PEF (L/min) over entire study period
 - Days with no asthma symptoms (symptom-free days, %)
 - Days with no use of albuterol for asthma symptoms (rescue-free days, %)
 - Asthma Quality of Life Questionnaire
- Mean change from baseline data available

Efficacy data for this analysis were grouped according to treatment comparisons, and then by patient age. These groupings are as follows.

- Treatment comparison:
 - salmeterol plus ICS vs. same dose ICS
 - salmeterol plus ICS vs. higher dose ICS
 - salmeterol plus ICS vs. ICS plus additional non-ICS therapy (e.g., montelukast)
- Patient age ≥ 12 years or < 12 years

Classification of the comparator ICS as the “same” or “higher” total daily dose was performed using a direct comparison of the total daily dose for the same ICS (e.g., ADVAIR compared with FP alone), or using GINA guidelines for classification of equipotent ICS doses for different ICS (e.g., ADVAIR [which contains FP] compared with budesonide) [[GINAGINA](#), 2007].

Within each treatment comparison, the difference in mean change from baseline values for each efficacy parameter was computed as the mean change from baseline for the salmeterol plus ICS treatment group minus the mean change from baseline for the ICS treatment group.

Because some studies had more than one relevant treatment comparison for this analysis, e.g., treatment groups of ICS at the same dose and ICS at a higher dose within the same study, the same study may contribute data more than once within the treatment comparison groupings listed above.

[Table 2](#) lists the studies included in the efficacy analysis.

Table 2 Studies Included in the Efficacy Analysis

Study	Age Range (years)	Duration of Double-Blind Therapy (Days)	Treatment Regimen (mcg)	N
Adolescent/Adult Studies				
FLTA4021	12-77	84	SAL 50 BID + FP 100 BID	118
			FP 250 BID	114
			TAA 600 BID	118
FLTA4022	12-79	84	SAL 50 BID + FP 100 BID	113
			FP 250 BID	109
			TAA 600 BID	108
SAM30010	16-74	14	ADVAIR 250/50 BID	24
			FP 250 BID	23
SAM30013	12-86	84	ADVAIR 100/50 BID	121
			FP 250 BID	116
SAM40027 (Stratum 1)	12-83	364	ADVAIR 100/50 BID	548
			FP 100 BID	550
SAM40027 (Stratum 2)	12-83	364	ADVAIR 100/50 BID	585
			FP 100 BID	578
SAM40027 (Stratum 3)	12-83	364	ADVAIR 250/50 BID	576
			FP 250 BID	579
SAM40034	18-60	84	ADVAIR 100/50 BID	75
			FP 250 BID	79
SAM40090	12-70	84	ADVAIR 100/50 BID	242
			FP 250 BID	241
SAS30001	12-77	84	ADVAIR 100/50 BID	95
			FP 100 BID	97
SAS30003	12-81	84	ADVAIR 100/50 BID	92
			FP 100/50 BID	89
SAS30004	12-82	84	ADVAIR 250/50 BID	94
			FP 250 BID	91
SAS30015	12-79	84	ADVAIR 100/50 BID	78
			BDP 200 BID	78
SAS30017	12-73	84	ADVAIR 100/50 BID	88
			FP 100 BID	89
SAS30036	15-80	56	ADVAIR 250/50 BID	194
			FP 250 BID + theophylline 200 BID	189
SAS30039	12-80	84	ADVAIR 250/50 BID	180
			FP 250 BID	182
SAS40009	18-70	84	ADVAIR 250/50 BID	180
			FP 500 BID	187
SAS40015	15-79	84	ADVAIR 100/50 BID	404
			FP 100 BID + montelukast 10mg QD	401
SAS40018	15-83	84	ADVAIR 100/50 BID	222
			FP 100 BID + montelukast 10mg QD	225

Study	Age Range (years)	Duration of Double-Blind Therapy (Days)	Treatment Regimen (mcg)	N
SAS40068	12-77	168	ADVAIR 100/50 BID	262
			FP 100 BID	270
SFCA3002	12-70	84	ADVAIR 100/50 BID	92
			FP 100 BID	90
SERL04	12-80	168	ADVAIR 250/50 BID	180
			Budesonide 800 BID	173
SFCA3003	12-69	84	ADVAIR 250/50 BID	84
			FP 250 BID	84
SFCB3019	12-79	196	ADVAIR 500/50 BID	167
			FP 500 BID + SAL 50 BID	171
			FP 500 BID	165
SFCB3022	12-79	84	ADVAIR 100/50 BID DPI	167
			ADVAIR 100/50 BID MDI	165
			FP 100 BID	165
SFCB3023	12-82	84	ADVAIR 500/50 BID DPI	161
			ADVAIR 500/50 BID MDI	176
			FP 500 BID	172
SLGA5017	18-77	168	SAL 50 BID + BDP 168 BID	239
			BDP 336 BID	244
SLGA5018	18-82	168	SAL 50 BID + BDP 168 BID	260
			BDP 336 BID	254
SLGA5021	12-77	168	SAL 50 BID + FP 100 BID	246
			FP 250 BID	243
SLGA5022	12-74	168	SAL 50 BID + FP 100 BID	221
			FP 250 BID	216
SLGB4010	16-75	168	SAL 50 BID + FP 250 BID	171
			FP 250 BID	160
			FP 500 BID	165
Pediatric Studies				
SAM102318	4-16	56	ADVAIR 100/50 BID	137
			FP 200 BID	144
SAM104926	4-11	84	ADVAIR 100/50 BID	150
			FP 200 BID	153
SAM40012	4-11	168	ADVAIR 100/50 BID	181
			FP 200 BID	186
SLGB4014	6-16	378	SAL 50 BID + BDP 200 BID	60
			BDP 400 BID	60

BDP=beclomethasone dipropionate; DPI= dry powder inhaler (Diskus); FP=fluticasone propionate; MDI=metered-dose inhaler; SAL= salmeterol; TAA= Triamcinolone acetonide

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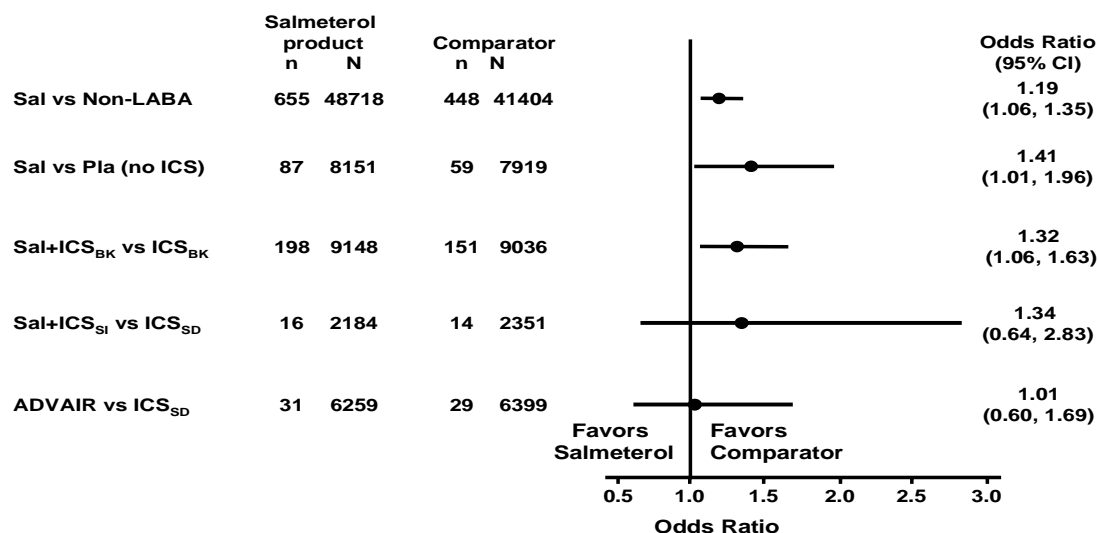
ATTACHMENT 2**PATIENT-YEARS OF EXPOSURE AND
OUTCOMES FOR ASTHMA-RELATED
INTUBATIONS AND ALL CAUSE DEATHS**

Treatment Category	Number of Studies	Number of Subjects	Total Exposure Years	All-cause Deaths per 10,000 Pt-Yrs	Subjects with an Asthma-Related Intubation per 10,000 Pt-Yrs
Salmeterol-containing product	263	67219	23486	51	22
Non-LABA	231	48968	18433	35	15
Sal (without ICS)	80	11342	4352	64	37
Pla (without ICS)	62	9935	4104	54	29
ICS _{BK}	44	10135	4168	29	31
ICS _{SD}	96	14651	6387	9	0
Sal + ICS _{BK}	51	12881	5059	47	43
Sal + ICS _{SI}	27	3804	1486	20	13
ADVAIR	86	17891	6571	5	0
SMART Sub-Groups (included in numbers above)					
Sal (without ICS)	1	6513	2993	80	43
Pla (without ICS)	1	6463	2930	68	27
Pla + ICS _{BK}	1	6716	3156	38	38
Sal + ICS _{BK}	1	6663	3194	56	56

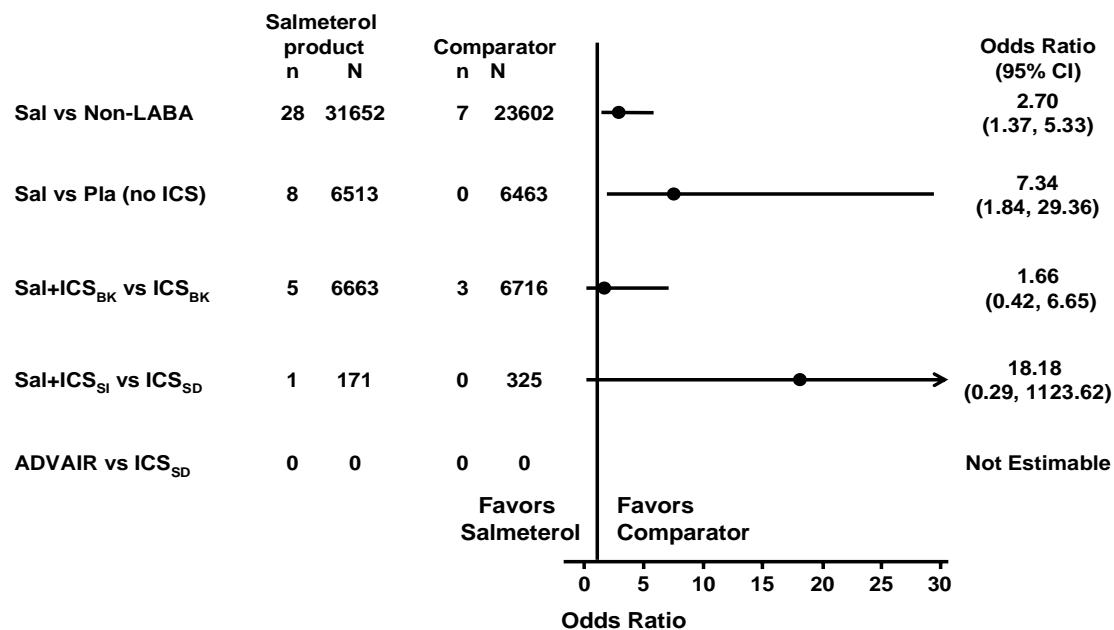
Note: Some studies contain more than one treatment comparison.

ATTACHMENT 3 PETO ODDS RATIO OF OUTCOMES AND SUB-POPULATIONS OF INTEREST

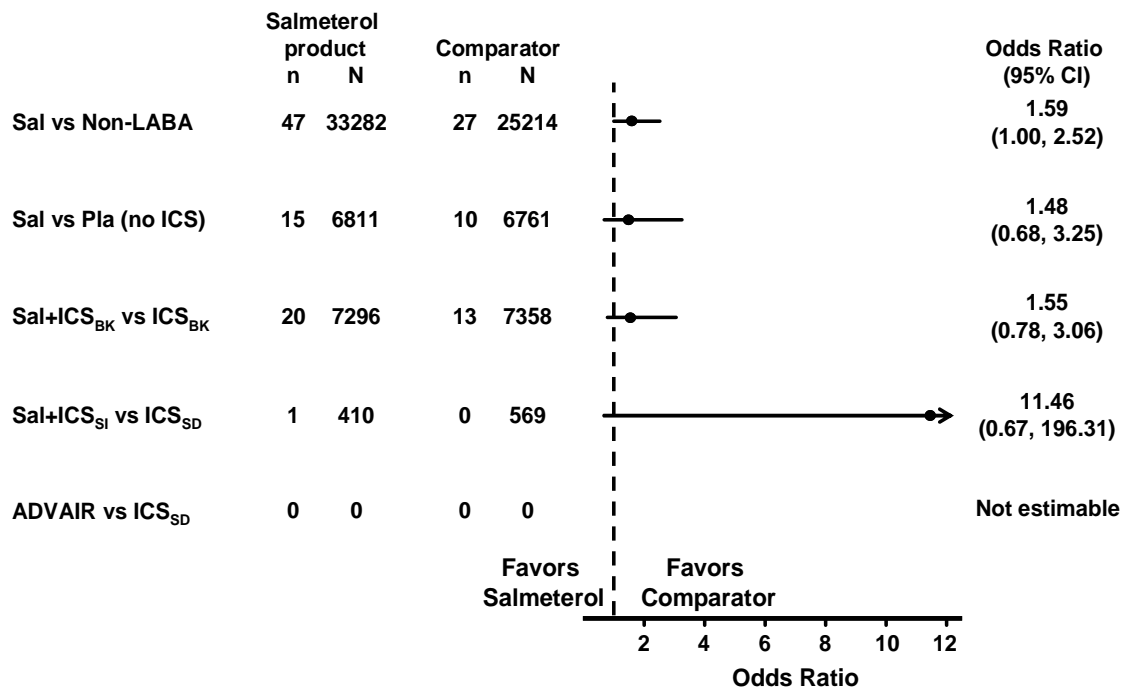
Meta-Analysis: Odds Ratio for Asthma-Related Hospitalization (0.5 Continuity Correction)



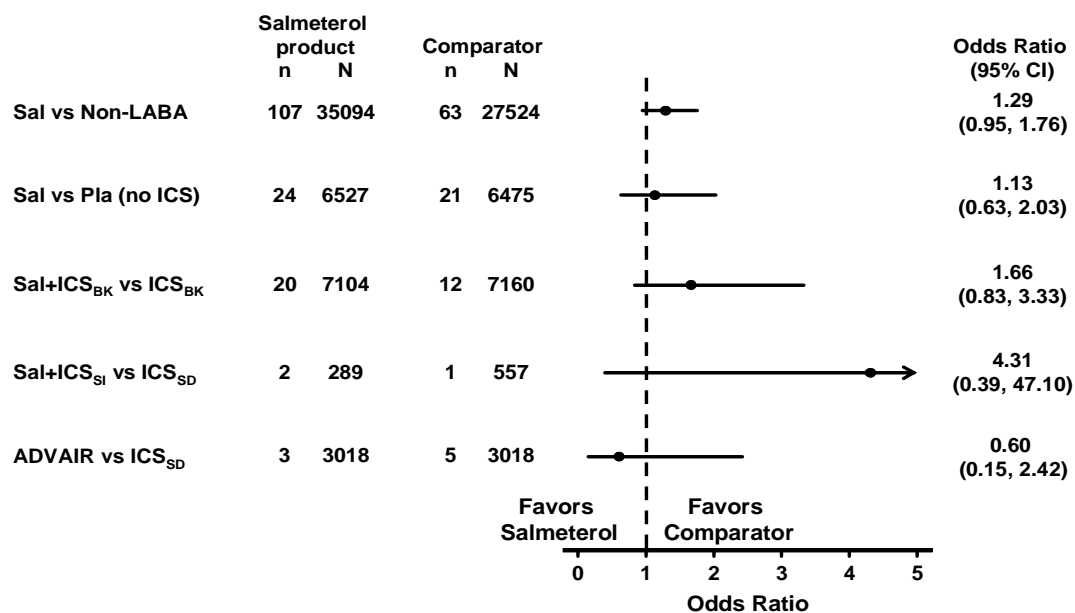
Meta-Analysis: Odds Ratio for Asthma-Related Death (0.5 Continuity Correction)



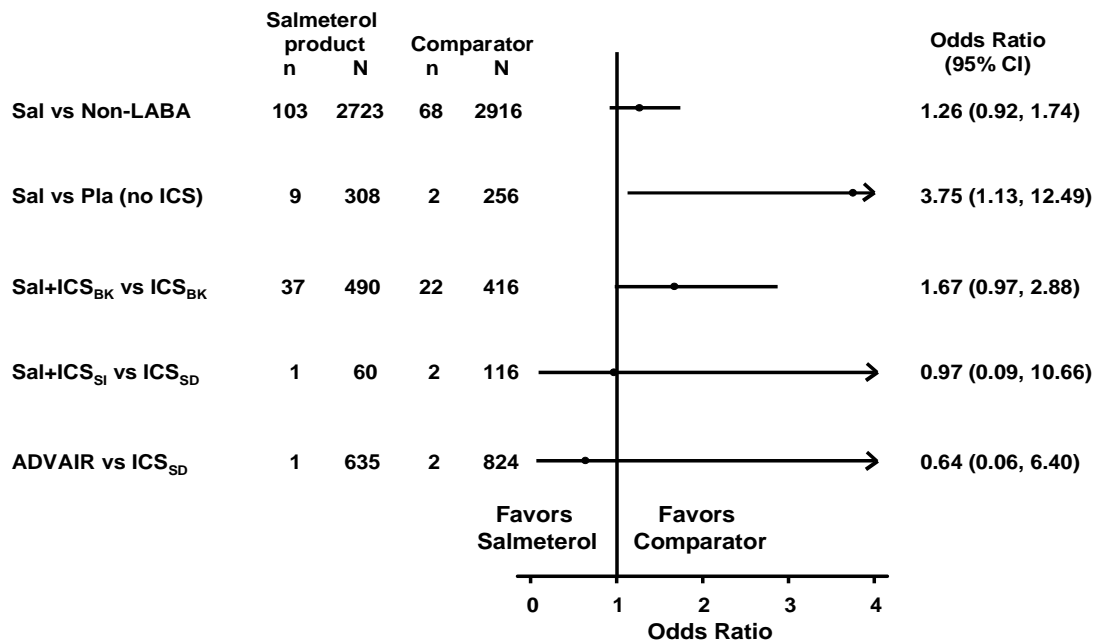
Meta-Analysis: Odds Ratio for Asthma-Related Intubation (0.5 Continuity Correction)



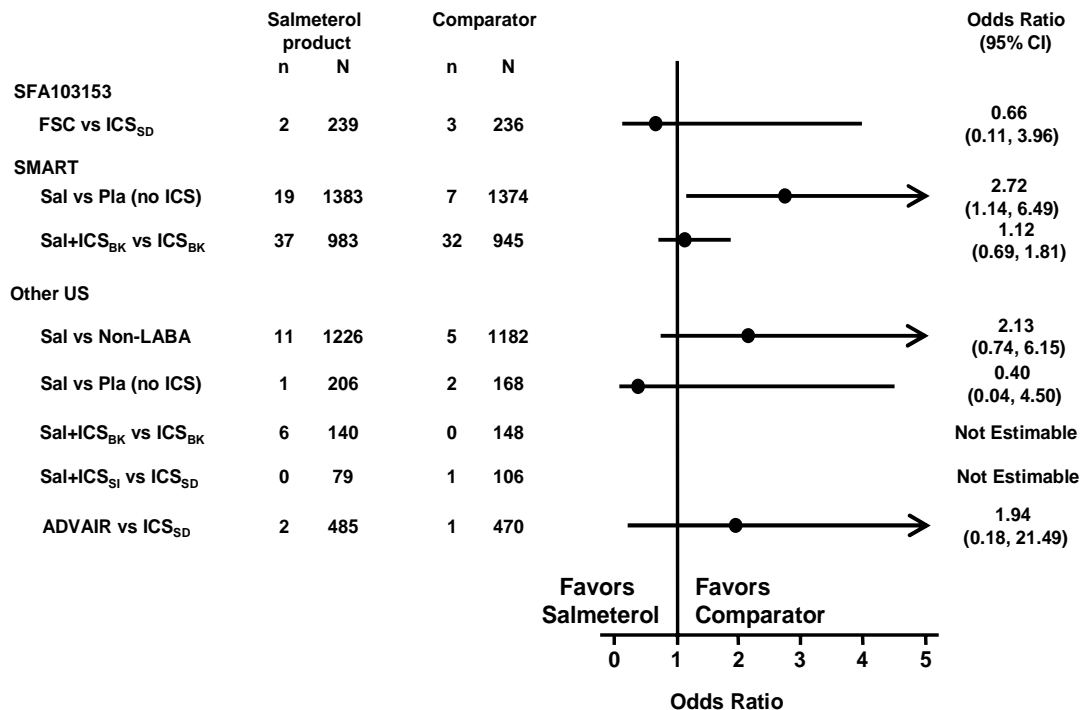
Meta-Analysis: Odds Ratio for All Cause Death (0.5 Continuity Correction)



Meta-Analysis: Odds Ratio for Asthma-Related Hospitalization (0.5 Continuity Correction): Pediatric Population

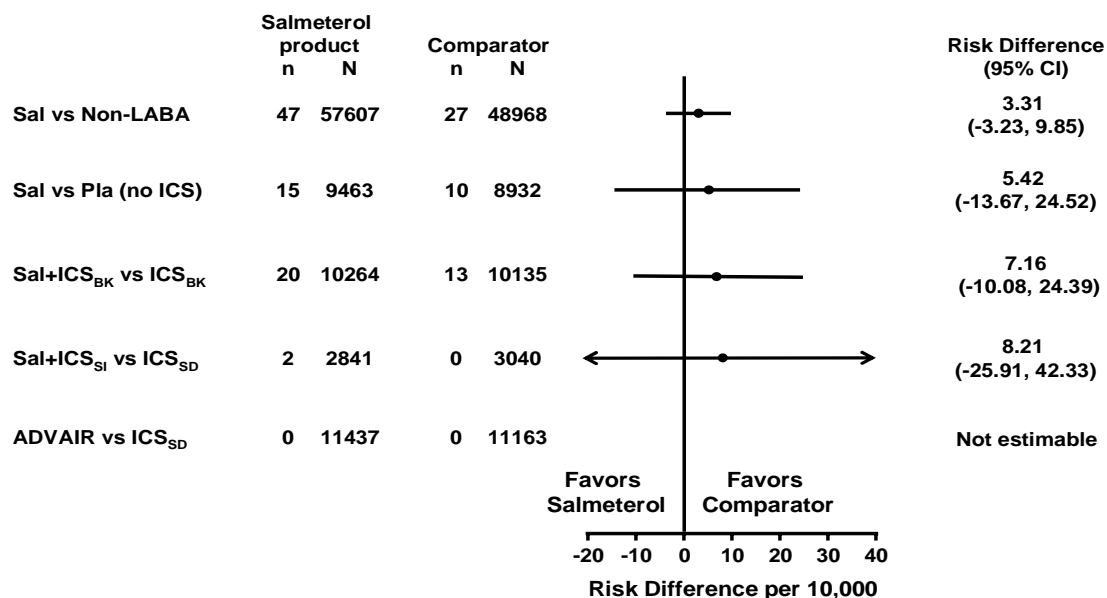


Pooled Analysis of African American Subgroups: Odds Ratio for Asthma-Related Hospitalization

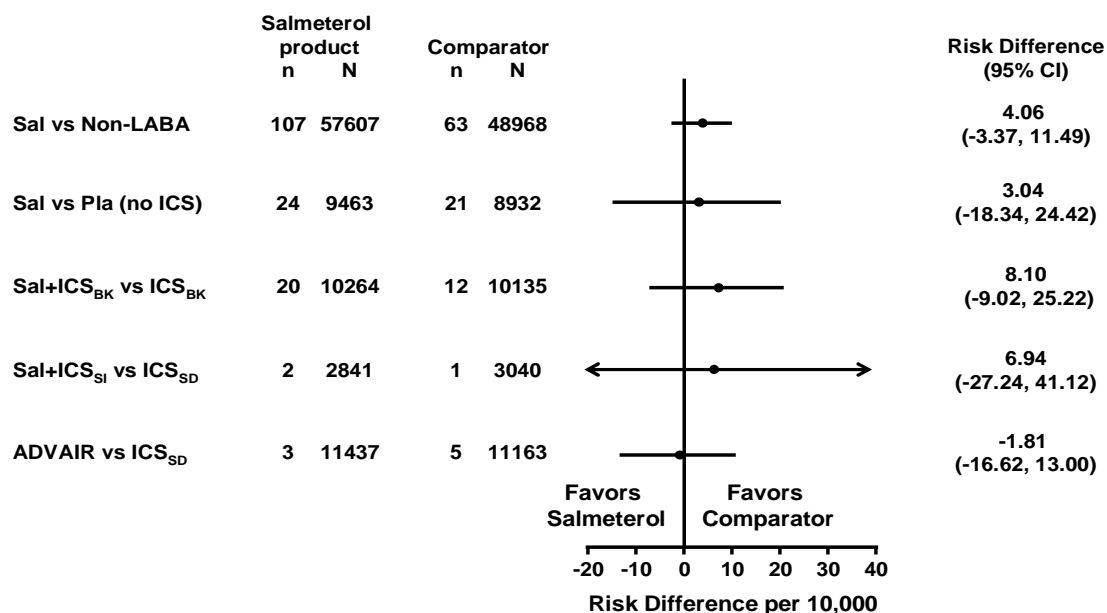


ATTACHMENT 4 ADDITIONAL RISK DIFFERENCE ANALYSIS

Meta-Analysis: Risk Difference for Asthma-Related Intubation (0.5 Continuity Correction)



Meta-Analysis: Risk Difference for All Cause Death (0.5 Continuity Correction)



SEREVENT® DISKUS®

(salmeterol xinafoate inhalation powder)

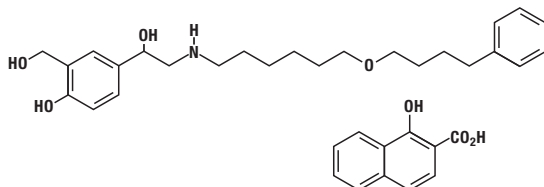
For Oral Inhalation Only

WARNING

Long-acting beta₂-adrenergic agonists, such as salmeterol, the active ingredient in SEREVENT DISKUS, may increase the risk of asthma-related death. Therefore, when treating patients with asthma, SEREVENT DISKUS should only be used as additional therapy for patients not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies, including SEREVENT DISKUS. Data from a large placebo-controlled US study that compared the safety of salmeterol (SEREVENT® Inhalation Aerosol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176 patients treated for 28 weeks on salmeterol versus 3 deaths out of 13,179 patients on placebo) (see WARNINGS and CLINICAL TRIALS: Asthma: *Salmeterol Multi-center Asthma Research Trial*).

DESCRIPTION

SEREVENT DISKUS (salmeterol xinafoate inhalation powder) contains salmeterol xinafoate as the racemic form of the 1-hydroxy-2-naphthoic acid salt of salmeterol. The active component of the formulation is salmeterol base, a highly selective beta₂-adrenergic bronchodilator. The chemical name of salmeterol xinafoate is 4-hydroxy-α¹-[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol, 1-hydroxy-2-naphthalenecarboxylate. Salmeterol xinafoate has the following chemical structure:



Salmeterol xinafoate is a white powder with a molecular weight of 603.8, and the empirical formula is C₂₅H₃₇NO₄•C₁₁H₇O₃. It is freely soluble in methanol; slightly soluble in ethanol, chloroform, and isopropanol; and sparingly soluble in water.

SEREVENT DISKUS is a specially designed plastic inhalation delivery system containing a double-foil blister strip of a powder formulation of salmeterol xinafoate intended for oral inhalation only. The DISKUS®, which is the delivery component, is an integral part of the drug product. Each blister on the double-foil strip within the unit contains 50 mcg of salmeterol administered as the salmeterol xinafoate salt in 12.5 mg of formulation containing lactose (which contains milk proteins). After a blister containing medication is opened by activating the DISKUS, the medication is dispersed into the airstream created by the patient inhaling through the mouthpiece.

Under standardized in vitro test conditions, SEREVENT DISKUS delivers 47 mcg when tested at a flow rate of 60 L/min for 2 seconds. In adult patients with obstructive lung disease and severely compromised lung function (mean forced expiratory volume in 1 second [FEV₁] 20% to 30% of predicted), mean peak inspiratory flow (PIF) through a DISKUS was 82.4 L/min (range, 46.1 to 115.3 L/min).

The actual amount of drug delivered to the lung will depend on patient factors, such as inspiratory flow profile.

CLINICAL PHARMACOLOGY

Mechanism of Action: Salmeterol is a long-acting beta₂-adrenergic agonist. In vitro studies and in vivo pharmacologic studies demonstrate that salmeterol is selective for beta₂-adrenoceptors compared with isoproterenol, which has approximately equal agonist activity on beta₁- and beta₂-adrenoceptors. In vitro studies show salmeterol to be at least 50 times more selective for beta₂-adrenoceptors than albuterol. Although beta₂-adrenoceptors are the predominant adrenergic receptors in bronchial smooth muscle and beta₁-adrenoceptors are the predominant receptors in the heart, there are also beta₂-adrenoceptors in the human heart comprising 10% to 50% of the total beta-adrenoceptors. The precise function of these receptors has not been established, but they raise the possibility that even highly selective beta₂-agonists may have cardiac effects.

The pharmacologic effects of beta₂-adrenoceptor agonist drugs, including salmeterol, are at least in part attributable to stimulation of intracellular adenylyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

In vitro tests show that salmeterol is a potent and long-lasting inhibitor of the release of mast cell mediators, such as histamine, leukotrienes, and prostaglandin D₂, from human lung. Salmeterol inhibits histamine-induced plasma protein extravasation and inhibits platelet-activating factor-induced eosinophil accumulation in the lungs of guinea pigs when administered by the inhaled route. In humans, single doses of salmeterol administered via inhalation aerosol attenuate allergen-induced bronchial hyper-responsiveness.

Pharmacokinetics: Salmeterol xinafoate, an ionic salt, dissociates in solution so that the salmeterol and 1-hydroxy-2-naphthoic acid (xinafoate) moieties are absorbed, distributed, metabolized, and eliminated independently. Salmeterol acts locally in the lung; therefore, plasma levels do not predict therapeutic effect.

Absorption: Because of the small therapeutic dose, systemic levels of salmeterol are low or undetectable after inhalation of recommended doses (50 mcg of salmeterol inhalation powder twice daily). Following chronic administration of an inhaled dose of 50 mcg of salmeterol inhalation powder twice daily, salmeterol was detected in plasma within 5 to 45 minutes in 7 patients with asthma; plasma concentrations were very low, with mean peak concentrations of 167 pg/mL at 20 minutes and no accumulation with repeated doses.

Distribution: The percentage of salmeterol bound to human plasma proteins averages 96% in vitro over the concentration range of 8 to 7,722 ng of salmeterol base per milliliter, much higher concentrations than those achieved following therapeutic doses of salmeterol.

Metabolism: Salmeterol base is extensively metabolized by hydroxylation, with subsequent elimination predominantly in the feces. No significant amount of unchanged salmeterol base has been detected in either urine or feces.

An in vitro study using human liver microsomes showed that salmeterol is extensively metabolized to α-hydroxysalmeterol (aliphatic oxidation) by cytochrome P450 3A4 (CYP3A4). Ketoconazole, a strong inhibitor of CYP3A4, essentially completely inhibited the formation of α-hydroxysalmeterol in vitro.

Elimination: In 2 healthy subjects who received 1 mg of radiolabeled salmeterol (as salmeterol xinafoate) orally, approximately 25% and 60% of the radiolabeled salmeterol was eliminated in urine and feces, respectively, over a period of 7 days. The terminal elimination half-life was about 5.5 hours (1 volunteer only).

The xinafoate moiety has no apparent pharmacologic activity. The xinafoate moiety is highly protein bound (>99%) and has a long elimination half-life of 11 days.

Special Populations: The pharmacokinetics of salmeterol base has not been studied in elderly patients nor in patients with hepatic or renal impairment. Since salmeterol is predominantly cleared by hepatic metabolism, liver function impairment may lead to accumulation of salmeterol in plasma. Therefore, patients with hepatic disease should be closely monitored.

Drug Interactions: Salmeterol is a substrate of CYP3A4.

Inhibitors of Cytochrome P450 3A4: Ketoconazole: In a placebo-controlled, crossover drug interaction study in 20 healthy male and female subjects, coadministration of salmeterol (50 mcg twice daily) and the strong CYP3A4 inhibitor ketoconazole (400 mg once daily) for 7 days resulted in a significant increase in plasma salmeterol exposure as determined by a 16-fold increase in AUC (ratio with and without ketoconazole 15.76; 90% CI: 10.66, 23.31) mainly due to increased bioavailability of the swallowed portion of the dose. Peak plasma salmeterol concentrations were increased by 1.4-fold (90% CI: 1.23, 1.68). Three (3) out of 20 subjects were withdrawn from salmeterol and ketoconazole coadministration due to beta-agonist-mediated systemic effects (2 with QTc prolongation and 1 with palpitations and sinus tachycardia). Coadministration of salmeterol and ketoconazole did not result in a clinically significant effect on mean heart rate, mean blood potassium, or mean blood glucose. Although there was no statistical effect on the mean QTc, coadministration of salmeterol and ketoconazole was associated with more frequent increases in QTc duration compared with salmeterol and placebo administration. Due to the potential increased risk of cardiovascular adverse events, the concomitant use of salmeterol with strong CYP3A4 inhibitors, (e.g., ketoconazole, ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nefinavir, saquinavir, telithromycin) is not recommended.

Erythromycin: In a repeat-dose study in 13 healthy subjects, concomitant administration of erythromycin (a moderate CYP3A4 inhibitor) and salmeterol inhalation aerosol resulted in a 40% increase in salmeterol C_{max} at steady state (ratio with

and without erythromycin 1.4; 90% CI: 0.96, 2.03; p = 0.12), a 3.6-beat/min increase in heart rate (95% CI: 0.19, 7.03; p<0.04), a 5.8-msec increase in QTc interval (95% CI: -6.14, 17.77; p = 0.34), and no change in plasma potassium.

Pharmacodynamics: Inhaled salmeterol, like other beta-adrenergic agonist drugs, can in some patients produce dose-related cardiovascular effects and effects on blood glucose and/or serum potassium (see PRECAUTIONS: General). The cardiovascular effects (heart rate, blood pressure) associated with salmeterol inhalation aerosol occur with similar frequency, and are of similar type and severity, as those noted following albuterol administration.

The effects of rising doses of salmeterol and standard inhaled doses of albuterol were studied in volunteers and in patients with asthma. Salmeterol doses up to 84 mcg administered as inhalation aerosol resulted in heart rate increases of 3 to 16 beats/min, about the same as albuterol dosed at 180 mcg by inhalation aerosol (4 to 10 beats/min). Adolescent and adult patients receiving 50-mcg doses of salmeterol inhalation powder (N = 60) underwent continuous electrocardiographic monitoring during two 12-hour periods after the first dose and after 1 month of therapy, and no clinically significant dysrhythmias were noted. Also, pediatric patients receiving 50-mcg doses of salmeterol inhalation powder (N = 67) underwent continuous electrocardiographic monitoring during two 12-hour periods after the first dose and after 3 months of therapy, and no clinically significant dysrhythmias were noted.

In 24-week clinical studies in patients with chronic obstructive pulmonary disease (COPD), the incidence of clinically significant abnormalities on the predose electrocardiograms (ECGs) at Weeks 12 and 24 in patients who received salmeterol 50 mcg was not different compared with placebo.

No effect of treatment with salmeterol 50 mcg was observed on pulse rate and systolic and diastolic blood pressure in a subset of patients with COPD who underwent 12-hour serial vital sign measurements after the first dose (N = 91) and after 12 weeks of therapy (N = 74). Median changes from baseline in pulse rate and systolic and diastolic blood pressure were similar for patients receiving either salmeterol or placebo (see ADVERSE REACTIONS).

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

CLINICAL TRIALS

Asthma: During the initial treatment day in several multiple-dose clinical trials with SEREVENT DISKUS in patients with asthma, the median time to onset of clinically significant bronchodilatation (≥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 ≥15% improvement in FEV₁. Maximum improvement in FEV₁ generally occurred within 180 minutes, and clinically significant improvement continued for 12 hours in most patients.

In 2 randomized, double-blind studies, SEREVENT DISKUS was compared with albuterol inhalation aerosol and placebo in adolescent and adult patients with mild-to-moderate asthma (protocol defined as 50% to 80% predicted FEV₁, actual mean of 67.7% at baseline), including patients who did and who did not receive concurrent inhaled corticosteroids. The efficacy of SEREVENT DISKUS was demonstrated over the 12-week period with no change in effectiveness over this time period (see Figure 1). There were no gender- or age-related differences in safety or efficacy. No development of tachyphylaxis to the bronchodilator effect was noted in these studies. FEV₁ measurements (mean change from baseline) from these two 12-week studies are shown in Figure 1 for both the first and last treatment days.

Figure 1. Serial 12-Hour FEV₁ From Two 12-Week Clinical Trials in Patients With Asthma

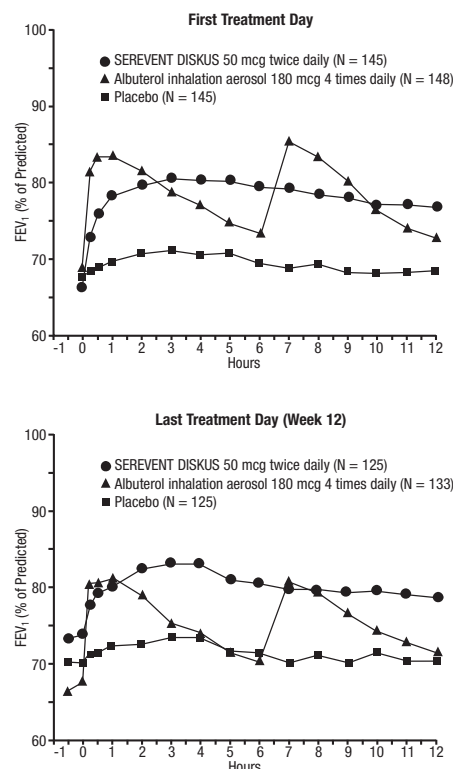


Table 1 shows the treatment effects seen during daily treatment with SEREVENT DISKUS for 12 weeks in adolescent and adult patients with mild-to-moderate asthma.

Table 1. Daily Efficacy Measurements in Two 12-Week Clinical Trials (Combined Data)

Parameter	Time	Placebo	SEREVENT DISKUS	Albuterol Inhalation Aerosol
No. of randomized subjects		152	149	148
Mean AM peak expiratory flow (L/min)	baseline	394	395	394
	12 weeks	396	427*	394
Mean % days with no asthma symptoms	baseline	14	13	12
	12 weeks	20	33	21
Mean % nights with no awakenings	baseline	70	63	68
	12 weeks	73	85*	71
Rescue medications (mean no. of inhalations per day)	baseline	4.2	4.3	4.3
	12 weeks	3.3	1.6†	2.2
Asthma exacerbations		14%	15%	16%

*Statistically superior to placebo and albuterol (p<0.001).

†Statistically superior to placebo (p<0.001).

Maintenance of efficacy for periods up to 1 year has been documented.

SEREVENT® DISKUS® (salmeterol xinafoate inhalation powder)

SEREVENT DISKUS and SEREVEN[®] (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. SEREVEN DISKUS 50 mcg and SEREVEN 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 SEREVEN DISKUS and SEREVEN Inhalation Aerosol for the prevention of exercise-induced bronchospasm (EIB). Therefore, while SEREVEN DISKUS was comparable to SEREVEN 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 SEREVEN 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 SEREVEN 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 SEREVEN 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 SEREVEN 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 SEREVEN 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 SEREVEN 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 SEREVEN 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 SEREVEN 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)		SEREVEN DISKUS (N = 52)	
		n	% Total	n	% Total
0.5-Hour postdose exercise challenge	% Fall in FEV ₁				
	<10%	15	29	31	60
	≥10%, <20%	3	6	11	21
	≥20%	34	65	10	19
Mean maximal % fall in FEV ₁ (SE)		-25% (1.8)		-11% (1.9)	
8.5-Hour postdose exercise challenge	% Fall in FEV ₁				
	<10%	12	23	26	50
	≥10%, <20%	7	13	12	23
	≥20%	33	63	14	27
Mean maximal % fall in FEV ₁ (SE)		-27% (1.5)		-16% (2.0)	

In 2 randomized studies in children 4 to 11 years old with asthma and EIB (N = 50), a single 50-mcg dose of SEREVEN 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 (SEREVEN Inhalation Aerosol) 42 mcg twice daily over 28 weeks compared to placebo when added to usual asthma therapy.

A planned interim analysis was conducted when approximately half of the intended number of patients had been enrolled (N = 26,355), which led to premature termination of the study. The results of the interim analysis showed that patients receiving salmeterol were at increased risk for fatal asthma events (see Table 3 and Figure 2). In the total population, a higher rate of asthma-related death occurred in patients treated with salmeterol than those treated with placebo (0.10% vs. 0.02%; relative risk 4.37 [95% CI 1.25, 15.34]).

Post-hoc subpopulation analyses were performed. In Caucasians, asthma-related death occurred at a higher rate in patients treated with salmeterol than in patients treated with placebo (0.07% vs. 0.01%; relative risk 5.82 [95% CI 0.70, 48.37]). In African Americans also, asthma-related death occurred at a higher rate in patients treated with salmeterol than those treated with placebo (0.31% vs. 0.04%; relative risk 7.26 [95% CI 0.89, 58.94]). Although the relative risks of asthma-related death were similar in Caucasians and African Americans, the estimate of excess deaths in patients treated with salmeterol was greater in African Americans because there was a higher overall rate of asthma-related death in African American patients (see Table 3).

The data from the SMART study are not adequate to determine whether concurrent use of inhaled corticosteroids or other asthma-controller therapy modifies the risk of asthma-related death.

Table 3. Asthma-Related Deaths in the 28-Week Salmeterol Multi-center Asthma Research Trial (SMART)

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

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

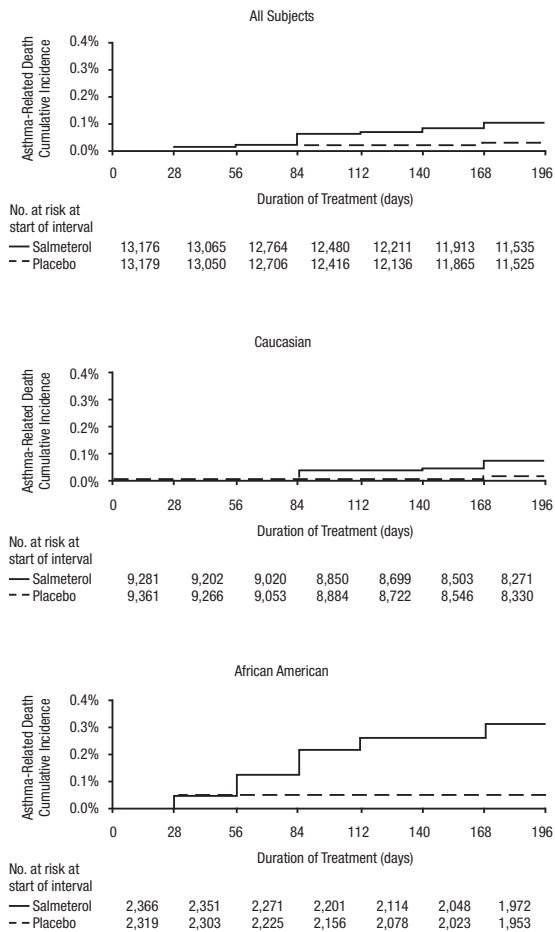
†Relative risk is the ratio of the rate of asthma-related death in the salmeterol group and the rate in the placebo group. The relative risk indicates how many more times likely an asthma-related death occurred in the salmeterol group than in the placebo group in a 28-week treatment period.

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

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

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

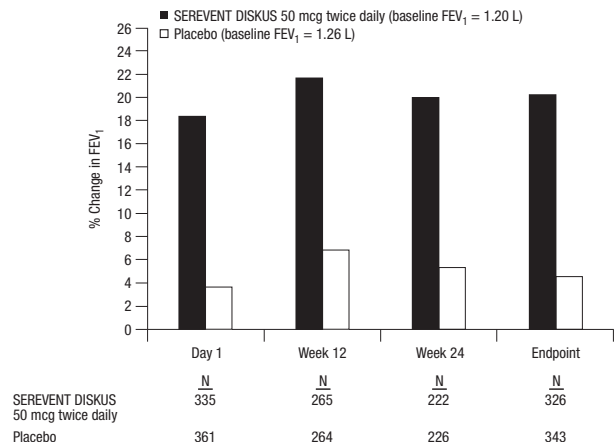
Figure 2. Cumulative Incidence of Asthma-Related Deaths in the 28-Week Salmeterol Multi-center Asthma Research Trial (SMART), by Duration of Treatment



Chronic Obstructive Pulmonary Disease: In 2 clinical trials evaluating twice-daily treatment with SEREVEN 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 SEREVEN DISKUS did not result in significant improvements in secondary endpoints assessing COPD symptoms in either clinical trial. Both trials were randomized, double-blind, parallel-group studies of 24 weeks' duration and were identical in design, patient entrance criteria, and overall conduct.

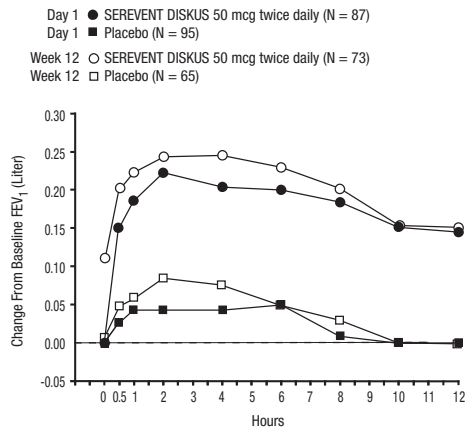
Figure 3 displays the integrated 2-hour postdose FEV₁ results from the 2 clinical trials. The percent change in FEV₁ refers to the change from baseline, defined as the predose value on Treatment Day 1. To account for patient withdrawals during the study, Endpoint (last evaluable FEV₁) data are provided. Patients receiving SEREVEN DISKUS 50 mcg had significantly greater improvements in 2-hour postdose FEV₁ at Endpoint (216 mL, 20%) compared to placebo (43 mL, 5%). Improvement was apparent on the first day of treatment and maintained throughout the 24 weeks of treatment.

Figure 3. Mean Percent Change From Baseline in Postdose FEV₁, Integrated Data From 2 Trials of Patients With Chronic Bronchitis and Airflow Limitation



Onset of Action and Duration of Effect: The onset of action and duration of effect of SEREVEN DISKUS were evaluated in a subset of patients (n = 87) from 1 of the 2 clinical trials discussed above. Following the first 50-mcg dose, significant improvement in pulmonary function (mean FEV₁ increase of 12% or more and at least 200 mL) occurred at 2 hours. The mean time to peak bronchodilator effect was 4.75 hours. As seen in Figure 4, evidence of bronchodilation was seen throughout the 12-hour period. Figure 4 also demonstrates that the bronchodilating effect after 12 weeks of treatment was similar to that observed after the first dose. The mean time to peak bronchodilator effect after 12 weeks of treatment was 3.27 hours.

Figure 4. Serial 12-Hour FEV₁ on the First Day and at Week 12 of Treatment



INDICATIONS AND USAGE

Asthma: SEREVENT DISKUS is indicated for long-term, twice-daily (morning and evening) administration in the maintenance treatment of asthma and in the prevention of bronchospasm in patients 4 years of age and older with reversible obstructive airway disease, including patients with symptoms of nocturnal asthma.

Long-acting beta₂-adrenergic agonists, such as salmeterol, the active ingredient in SEREVENT DISKUS, may increase the risk of asthma-related death (see WARNINGS). Therefore, when treating patients with asthma, SEREVENT DISKUS should only be used as additional therapy for patients not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies, including SEREVENT DISKUS. It is not indicated for patients whose asthma can be managed by occasional use of inhaled, short-acting beta₂-agonists or for patients whose asthma can be successfully managed by inhaled corticosteroids or other controller medications along with occasional use of inhaled, short-acting beta₂-agonists.

SEREVENT DISKUS is also indicated for prevention of exercise-induced bronchospasm in patients 4 years of age and older.

Chronic Obstructive Pulmonary Disease: SEREVENT DISKUS is indicated for the long-term, twice-daily (morning and evening) administration in the maintenance treatment of bronchospasm associated with COPD (including emphysema and chronic bronchitis).

CONTRAINDICATIONS

SEREVENT DISKUS is contraindicated in patients with a history of hypersensitivity to salmeterol or any other component of the drug product (see DESCRIPTION and ADVERSE REACTIONS: Observed During Clinical Practice: *Non-Site Specific*).

WARNINGS

Long-acting beta₂-adrenergic agonists, such as salmeterol, the active ingredient in SEREVENT DISKUS, may increase the risk of asthma-related death. Therefore, when treating patients with asthma, SEREVENT DISKUS should only be used as additional therapy for patients not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies, including SEREVENT DISKUS.

- A large 28-week, placebo-controlled US study comparing the safety of salmeterol (SEREVENT Inhalation Aerosol) with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in patients receiving salmeterol (see CLINICAL TRIALS: Asthma: *Salmeterol Multi-center Asthma Research Trial*). Given the similar basic mechanisms of action of beta₂-agonists, it is possible that the findings seen in the SMART study represent a class effect.
- A 16-week clinical study performed in the United Kingdom, the Salmeterol Nationwide Surveillance (SNS) study, showed results similar to the SMART study. In the SNS study, the rate of asthma-related death was numerically, though not statistically significantly, greater in patients with asthma treated with salmeterol (42 mcg twice daily) than those treated with albuterol (180 mcg 4 times daily) added to usual asthma therapy.

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

It is important to watch for signs of worsening asthma, such as increasing use of inhaled, short-acting beta₂-agonists or a significant decrease in PEF or lung function. Such findings require immediate evaluation. Patients should be advised to seek immediate medical attention should their condition deteriorate.

SEREVENT DISKUS should not be used to treat acute symptoms. It is crucial to inform patients of this and prescribe an inhaled, short-acting beta₂-agonist for this purpose and to warn them that increasing inhaled beta₂-agonist use is a signal of deteriorating asthma that requires prompt consultation with a physician.

SEREVENT DISKUS should not be initiated in patients with significantly worsening or acutely deteriorating asthma, which may be a life-threatening condition. Serious acute respiratory events, including fatalities, have been reported both in the United States and worldwide when SEREVENT has been initiated in this situation. Although it is not possible from these reports to determine whether SEREVENT contributed to these adverse events or simply failed to relieve the deteriorating asthma, the use of SEREVENT DISKUS in this setting is inappropriate.

SEREVENT DISKUS is not a substitute for inhaled or oral corticosteroids. Corticosteroids should not be stopped or reduced when SEREVENT DISKUS is initiated.

See PRECAUTIONS: Information for Patients and the Medication Guide accompanying the product.

The following additional WARNINGS about SEREVENT DISKUS should be noted.

1. SEREVENT DISKUS should not be used as a treatment for acutely deteriorating asthma. SEREVENT DISKUS is intended for the maintenance treatment of asthma (see INDICATIONS AND USAGE) and should not be introduced in acutely deteriorating asthma, which is a potentially life-threatening condition. There are no data demonstrating that SEREVENT DISKUS provides greater efficacy than or additional efficacy to inhaled, short-acting beta₂-agonists in patients with worsening asthma. Serious acute respiratory events, including fatalities, have been reported both in the United States and worldwide in patients receiving SEREVENT. In most cases, these have occurred in patients with severe asthma (e.g., patients with a history of corticosteroid dependence, low pulmonary function, intubation, mechanical ventilation, frequent hospitalizations, or previous life-threatening acute asthma exacerbations) and/or in some patients in whom asthma has been acutely deteriorating (e.g., unresponsive to usual medications; increasing need for inhaled, short-acting beta₂-agonists; increasing need for systemic corticosteroids; significant increase in symptoms; recent emergency room visits; sudden or progressive deterioration in pulmonary function). However, they have occurred in a few patients with less severe asthma as well. It was not possible from these reports to determine whether SEREVENT contributed to these events.

2. SEREVENT DISKUS should not be used to treat acute symptoms. An inhaled, short-acting beta₂-agonist, not SEREVENT DISKUS, should be used to relieve acute asthma or COPD symptoms. When prescribing SEREVENT DISKUS, the physician must also provide the patient with an inhaled, short-acting beta₂-agonist (e.g., albuterol) for treatment of symptoms that occur acutely, despite regular twice-daily (morning and evening) use of SEREVENT DISKUS.

When beginning treatment with SEREVENT DISKUS, patients who have been taking inhaled, short-acting beta₂-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief of acute asthma or COPD symptoms (see PRECAUTIONS: Information for Patients).

3. Increasing use of inhaled, short-acting beta₂-agonists is a marker of deteriorating asthma or COPD. The physician and patient should be alert to such changes. The patient's condition may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient's inhaled, short-acting beta₂-agonist becomes less effective, the patient needs more inhalations than usual, or the patient develops a significant decrease in PEF or lung function, these may be markers of destabilization of their disease. In this setting, the patient requires immediate reevaluation with reassessment of the treatment regimen, giving special consideration to the possible need for corticosteroids. If the patient uses 4 or more inhalations per day of an inhaled, short-acting beta₂-agonist for 2 or more consecutive days, or if more than 1 canister (200 inhalations per canister) of inhaled, short-acting beta₂-agonist is used in an 8-week period in conjunction with SEREVENT DISKUS, then the patient should consult the physician for reevaluation. **Increasing the daily dosage of SEREVENT DISKUS in this situation is not appropriate. SEREVENT DISKUS should not be used more frequently than twice daily (morning and evening) at the recommended dose of 1 inhalation.**

4. SEREVENT DISKUS should not be used in conjunction with an inhaled, long-acting beta₂-agonist. SEREVENT DISKUS should not be used with other medications containing long-acting beta₂-agonists.

5. SEREVENT DISKUS is not a substitute for oral or inhaled corticosteroids. There are no data demonstrating that SEREVENT DISKUS has a clinical anti-inflammatory effect and could be expected to take the place of corticosteroids. When initiating SEREVENT DISKUS in patients receiving oral or inhaled corticosteroids for treatment of asthma, patients should be continued on a suitable dose of corticosteroids to maintain clinical stability even if they feel better as a result of initiating SEREVENT DISKUS. Any change in corticosteroid dosage should be made ONLY after clinical evaluation (see PRECAUTIONS: Information for Patients).

6. The recommended dosage should not be exceeded. As with other inhaled beta₂-adrenergic drugs, SEREVENT DISKUS should not be used more often or at higher doses than recommended. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Large doses of inhaled or oral salmeterol (12 to 20 times the recommended dose) have been associated with clinically significant prolongation of the QTc interval, which has the potential for producing ventricular arrhythmias.

7. Paradoxical bronchospasm. As with other inhaled asthma and COPD medications, SEREVENT DISKUS can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with SEREVENT DISKUS, it should be treated immediately with a short-acting, inhaled bronchodilator; SEREVENT DISKUS should be discontinued immediately; and alternative therapy should be instituted.

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

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

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

11. Potential drug interactions. Because of the potential for drug interactions and the potential for increased risk of cardiovascular adverse events, the concomitant use of SEREVENT DISKUS with strong CYP 3A4 inhibitors (e.g., ketoconazole, ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) is not recommended (see CLINICAL PHARMACOLOGY: Pharmacokinetics: *Drug Interactions*).

PRECAUTIONS

General: Cardiovascular Effects: No effect on the cardiovascular system is usually seen after the administration of inhaled salmeterol at recommended doses, but the cardiovascular and central nervous system effects seen with all sympathomimetic drugs (e.g., increased blood pressure, heart rate, excitement) can occur after use of salmeterol and may require discontinuation of SEREVENT DISKUS. SEREVENT DISKUS, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive disorders or thyrotoxicosis; and in patients who are unusually responsive to sympathomimetic amines.

As has been described with other beta-adrenergic agonist bronchodilators, clinically significant changes in systolic and/or diastolic blood pressure, pulse rate, and ECGs have been seen infrequently in individual patients in controlled clinical studies with salmeterol.

Metabolic Effects: Doses of the related beta₂-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis. Beta-adrenergic agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation.

Clinically significant changes in blood glucose and/or serum potassium were seen rarely during clinical studies with long-term administration of SEREVENT DISKUS at recommended doses.

Information for Patients: Patients should be instructed to read the accompanying Medication Guide with each new prescription and refill. The complete text of the Medication Guide is reprinted at the end of this document.

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

It is important that patients understand how to use the DISKUS appropriately and how to use SEREVENT DISKUS in relation to other asthma or COPD medications they are taking. Patients should be given the following information:

- Patients should be informed that salmeterol may increase the risk of asthma-related death.
- 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).
- The physician should be notified immediately if any of the following signs of seriously worsening asthma or COPD occur:
 - decreasing effectiveness of inhaled, short-acting beta₂-agonists;
 - need for more inhalations than usual of inhaled, short-acting beta₂-agonists;
 - significant decrease in PEF or lung function as outlined by the physician;
 - use of 4 or more inhalations per day of a short-acting beta₂-agonist for 2 or more days consecutively;
 - use of more than 1 canister (200 inhalations per canister) of an inhaled, short-acting beta₂-agonist in an 8-week period.
- Patients should not stop therapy with SEREVENT DISKUS for asthma or COPD without physician/provider guidance since symptoms may worsen after discontinuation.
- 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.
- Patients should be cautioned regarding adverse effects associated with beta₂-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.
- When patients are prescribed SEREVENT DISKUS, other medications for asthma and COPD should be used only as directed by the physician.
- SEREVENT DISKUS should not be used with a spacer device.
- Patients who are pregnant or nursing should contact the physician about the use of SEREVENT DISKUS.
- 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.
- 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.
- 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.
- For the proper use of SEREVENT DISKUS and to attain maximum benefit, the patient should read and follow carefully the Instructions for Using SEREVENT DISKUS in the Medication Guide accompanying the product.
- Most patients are able to taste or feel a dose delivered from SEREVENT DISKUS. However, whether or not patients are able to sense delivery of a dose, they should not exceed the recommended dose of 1 inhalation twice daily, morning and evening. Patients should contact a physician or pharmacist if they have questions.

Drug Interactions: Inhibitors of Cytochrome P450 3A4: In a drug interaction study in 20 healthy subjects, coadministration of salmeterol (50 mcg twice daily) and ketoconazole (400 mg once daily) for 7 days resulted in greater systemic exposure to salmeterol (AUC increased 16-fold and C_{max} increased 1.4-fold). Three (3) subjects were withdrawn due to beta₂-agonist side effects (2 with prolonged QTc and 1 with palpitations and sinus tachycardia). Although there was no statistical effect on the mean QTc, coadministration of salmeterol and ketoconazole was associated with more frequent increases in QTc duration compared with salmeterol and placebo administration. Due to the potential increased risk of car-

SEREVENT® DISKUS® (salmeterol xinafoate inhalation powder)

diovascular adverse events, the concomitant use of salmeterol with strong CYP3A4 inhibitors (e.g., ketoconazole, ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) is not recommended.

Short-Acting Beta₂-Agonists: In two 12-week, repetitive-dose adolescent and adult clinical trials in patients with asthma (N = 149), the mean daily need for additional beta₂-agonist in patients using SEREVENT DISKUS was approximately 1 1/2 inhalations/day. Twenty-six percent (26%) of the patients in these trials used between 8 and 24 inhalations of short-acting beta-agonist per day on 1 or more occasions. Nine percent (9%) of the patients in these trials averaged over 4 inhalations/day over the course of the 12-week trials. No increase in frequency of cardiovascular events was observed among the 3 patients who averaged 8 to 11 inhalations/day; however, the safety of concomitant use of more than 8 inhalations/day of short-acting beta₂-agonist with SEREVENT DISKUS has not been established. In 29 patients who experienced worsening of asthma while receiving SEREVENT DISKUS during these trials, albuterol therapy administered via either nebulizer or inhalation aerosol (1 dose in most cases) led to improvement in FEV₁ and no increase in occurrence of cardiovascular adverse events.

In 2 clinical trials in patients with COPD, the mean daily need for additional beta₂-agonist for patients using SEREVENT DISKUS was approximately 4 inhalations/day. Twenty-four percent (24%) of the patients using SEREVENT DISKUS in these trials averaged 6 or more inhalations of albuterol per day over the course of the 24-week trials. No increase in frequency of cardiovascular events was observed among patients who averaged 6 or more inhalations per day.

Monoamine Oxidase Inhibitors and Tricyclic Antidepressants: Salmeterol should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of salmeterol on the vascular system may be potentiated by these agents.

Corticosteroids and Cromoglycate: In clinical trials, inhaled corticosteroids and/or inhaled cromolyn sodium did not alter the safety profile of salmeterol when administered concurrently.

Methylxanthines: The concurrent use of intravenously or orally administered methylxanthines (e.g., aminophylline, theophylline) by patients receiving salmeterol has not been completely evaluated. In 1 clinical asthma trial, 87 patients receiving SEREVENT Inhalation Aerosol 42 mcg twice daily concurrently with a theophylline product had adverse event rates similar to those in 71 patients receiving SEREVENT Inhalation Aerosol without theophylline. Resting heart rates were slightly higher in the patients on theophylline but were little affected by therapy with SEREVENT Inhalation Aerosol.

In 2 clinical trials in patients with COPD, 39 subjects receiving SEREVENT DISKUS concurrently with a theophylline product had adverse event rates similar to those in 302 patients receiving SEREVENT DISKUS without theophylline. Based on the available data, the concomitant administration of methylxanthines with SEREVENT DISKUS did not alter the observed adverse event profile.

Beta-Adrenergic Receptor Blocking Agents: Beta-blockers not only block the pulmonary effect of beta-agonists, such as SEREVENT DISKUS, but may also produce severe bronchospasm in patients with asthma or COPD. Therefore, patients with asthma or COPD should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with asthma or COPD. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

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

Carcinogenesis, Mutagenesis, Impairment of Fertility: In an 18-month oral carcinogenicity study in CD-mice, salmeterol xinafoate caused a dose-related increase in the incidence of smooth muscle hyperplasia, cystic glandular hyperplasia, leiomyomas of the uterus, and ovarian cysts at doses of 1.4 mg/kg and above (approximately 20 times the maximum recommended daily inhalation dose in adults and children based on comparison of the area under the plasma concentration versus time curves [AUCs]). The incidence of leiomyosarcomas was not statistically significant. No tumors were seen at 0.2 mg/kg (approximately 3 times the maximum recommended daily inhalation doses in adults and children based on comparison of the AUCs).

In a 24-month oral and inhalation carcinogenicity study in Sprague Dawley rats, salmeterol caused a dose-related increase in the incidence of mesovarian leiomyomas and ovarian cysts at doses of 0.68 mg/kg and above (approximately 55 times the maximum recommended daily inhalation dose in adults and approximately 25 times the maximum recommended daily inhalation dose in children on a mg/m² basis). No tumors were seen at 0.21 mg/kg (approximately 15 times the maximum recommended daily inhalation dose in adults and approximately 8 times the maximum recommended daily inhalation dose in children on a mg/m² basis). These findings in rodents are similar to those reported previously for other beta-adrenergic agonist drugs. The relevance of these findings to human use is unknown.

Salmeterol produced no detectable or reproducible increases in microbial and mammalian gene mutation in vitro. No clastogenic activity occurred in vitro in human lymphocytes or in vivo in a rat micronucleus test. No effects on fertility were identified in male and female rats treated with salmeterol at oral doses up to 2 mg/kg (approximately 160 times the maximum recommended daily inhalation dose in adults on a mg/m² basis).

Pregnancy: Teratogenic Effects: Pregnancy Category C. No teratogenic effects occurred in rats at oral doses up to 2 mg/kg (approximately 160 times the maximum recommended daily inhalation dose in adults on a mg/m² basis). In pregnant Dutch rabbits administered oral doses of 1 mg/kg and above (approximately 50 times the maximum recommended daily inhalation dose in adults based on comparison of the AUCs), salmeterol exhibited fetal toxic effects characteristically resulting from beta-adrenoceptor stimulation. These included precocious eyelid openings, cleft palate, sternal fusion, limb and paw flexures, and delayed ossification of the frontal cranial bones. No significant effects occurred at an oral dose of 0.6 mg/kg (approximately 20 times the maximum recommended daily inhalation dose in adults based on comparison of the AUCs).

New Zealand White rabbits were less sensitive since only delayed ossification of the frontal bones was seen at an oral dose of 10 mg/kg (approximately 1,600 times the maximum recommended daily inhalation dose in adults on a mg/m² basis). Extensive use of other beta-agonists has provided no evidence that these class effects in animals are relevant to their use in humans. There are no adequate and well-controlled studies with SEREVENT DISKUS in pregnant women. SEREVENT DISKUS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Salmeterol xinafoate crossed the placenta following oral administration of 10 mg/kg to mice and rats (approximately 410 and 810 times, respectively, the maximum recommended daily inhalation dose in adults on a mg/m² basis).

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

Nursing Mothers: Plasma levels of salmeterol after inhaled therapeutic doses are very low. In rats, salmeterol xinafoate is excreted in the milk. However, since there are no data from controlled trials on the use of salmeterol by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue SEREVENT DISKUS, taking into account the importance of SEREVENT DISKUS to the mother. Caution should be exercised when SEREVENT DISKUS is administered to a nursing woman.

Pediatric Use: The safety and efficacy of SEREVENT DISKUS has been evaluated in over 2,500 patients aged 4 to 11 years with asthma, 346 of whom were administered SEREVENT DISKUS for 1 year. Based on available data, no adjustment of dosage of SEREVENT DISKUS in pediatric patients is warranted for either asthma or EIB (see DOSAGE AND ADMINISTRATION).

In 2 randomized, double-blind, controlled clinical trials of 12 weeks' duration, SEREVENT DISKUS 50 mcg was administered to 211 pediatric patients with asthma who did and who did not receive concurrent inhaled corticosteroids. The efficacy of SEREVENT DISKUS was demonstrated over the 12-week treatment period with respect to PEF and FEV₁. SEREVENT DISKUS was effective in demographic subgroups (gender and age) of the population. SEREVENT DISKUS was effective when coadministered with other inhaled asthma medications, such as short-acting bronchodilators and inhaled corticosteroids. SEREVENT DISKUS was well tolerated in the pediatric population, and there were no safety issues identified specific to the administration of SEREVENT DISKUS to pediatric patients.

In 2 randomized studies in children 4 to 11 years old with asthma and EIB, a single 50-mcg dose of SEREVENT DISKUS prevented EIB when dosed 30 minutes prior to exercise, with protection lasting up to 11.5 hours in repeat testing following this single dose in many patients.

Geriatric Use: Of the total number of adolescent and adult patients with asthma who received SEREVENT DISKUS in chronic dosing clinical trials, 209 were 65 years of age and older. Of the total number of patients with COPD who received SEREVENT DISKUS in chronic dosing clinical trials, 167 were 65 years of age or older and 45 were 75 years of age or older. No apparent differences in the safety of SEREVENT DISKUS were observed when geriatric patients were compared with younger patients in clinical trials. As with other beta₂-agonists, however, special caution should be observed when using SEREVENT DISKUS in geriatric patients who have concomitant cardiovascular disease that could be adversely affected by this class of drug. Data from the trials in patients with COPD suggested a greater effect on FEV₁ of SEREVENT DISKUS in the <65 years age-group, as compared with the ≥65 years age-group. However, based on available data, no adjustment of dosage of SEREVENT DISKUS in geriatric patients is warranted.

ADVERSE REACTIONS

Data from a large, 28-week, placebo-controlled US study that compared the safety of salmeterol (SEREVENT Inhalation Aerosol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol (see WARNINGS and CLINICAL TRIALS: Asthma: *Salmeterol Multi-center Asthma Research Trial*).

Asthma: Two multicenter, 12-week, controlled studies have evaluated twice-daily doses of SEREVENT DISKUS in patients 12 years of age and older with asthma. Table 4 reports the incidence of adverse events in these 2 studies.

Table 4. Adverse Event Incidence in Two 12-Week Adolescent and Adult Clinical Trials in Patients With Asthma

Adverse Event	Percent of Patients		
	Placebo (N=152)	SEREVENT DISKUS 50 mcg Twice Daily (N = 149)	Albuterol Inhalation Aerosol 180 mcg 4 Times Daily (N = 150)
Ear, nose, and throat Nasal/sinus congestion, pallor Rhinitis	6 4	9 5	8 4
Neurological Headache	9	13	12
Respiratory Asthma Tracheitis/bronchitis Influenza	1 4 2	3 7 5	<1 3 5

Table 4 includes all events (whether considered drug-related or nondrug-related by the investigator) that occurred at a rate of 3% or greater in the group receiving SEREVENT DISKUS and were more common than in the placebo group.

Pharyngitis, sinusitis, upper respiratory tract infection, and cough occurred at ≥3% but were more common in the placebo group. However, throat irritation has been described at rates exceeding that of placebo in other controlled clinical trials.

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

Ear, Nose, and Throat: Sinus headache.

Gastrointestinal: Nausea.

Mouth and Teeth: Oral mucosal abnormality.

Musculoskeletal: Pain in joint.

Neurological: Sleep disturbance, paresthesia.

Skin: Contact dermatitis, eczema.

Miscellaneous: Localized aches and pains, pyrexia of unknown origin.

Two multicenter, 12-week, controlled studies have evaluated twice-daily doses of SEREVENT DISKUS in patients aged 4 to 11 years with asthma. Table 5 includes all events (whether considered drug-related or nondrug-related by the investigator) that occurred at a rate of 3% or greater in the group receiving SEREVENT DISKUS and were more common than in the placebo group.

Table 5. Adverse Event Incidence in Two 12-Week Pediatric Clinical Trials in Patients With Asthma

Adverse Event	Percent of Patients		
	Placebo (N = 215)	SEREVENT DISKUS 50 mcg Twice Daily (N = 211)	Albuterol Inhalation Powder 200 mcg 4 Times Daily (N = 115)
Ear, nose, and throat Ear signs and symptoms Pharyngitis	3 3	4 6	9 3
Neurological Headache	14	17	20
Respiratory Asthma	2	4	<1
Skin Skin rashes Urticaria	3 0	4 3	2 2

The following events were reported at an incidence of 1% to 2% (3 to 4 patients) in the salmeterol group and with a higher incidence than in the albuterol and placebo groups: gastrointestinal signs and symptoms, lower respiratory signs and symptoms, photodermatitis, and arthralgia and articular rheumatism.

In clinical trials evaluating concurrent therapy of salmeterol with inhaled corticosteroids, adverse events were consistent with those previously reported for salmeterol, or with events that would be expected with the used of inhaled corticosteroids.

Chronic Obstructive Pulmonary Disease: Two multicenter, 24-week, controlled studies have evaluated twice-daily doses of SEREVENT DISKUS in patients with COPD. For presentation (Table 6), the placebo data from a third trial, identical in design, patient entrance criteria, and overall conduct but comparing fluticasone propionate with placebo, were integrated with the placebo data from these 2 studies (total N = 341 for salmeterol and 576 for placebo).

Table 6. Adverse Events With ≥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 Nasal congestion/blockage Sinusitis Ear signs and symptoms	6 3 2 1	7 4 4 3
Gastrointestinal Nausea and vomiting	3	3
Lower respiratory Cough Rhinitis Viral respiratory infection	4 2 4	5 4 5
Musculoskeletal Musculoskeletal pain Muscle cramps and spasms	10 1	12 3
Neurological Headache Dizziness	11 2	14 4
Average duration of exposure (days)	128.9	138.5

*Table 6 includes all events (whether considered drug-related or nondrug-related by the investigator) that occurred at a rate of 3% or greater in the group receiving SEREVENT DISKUS and were more common in the group receiving SEREVENT DISKUS than in the placebo group.

Other events occurring in the group receiving SEREVENT DISKUS that occurred at a frequency of 1% to <3% and were more common than in the placebo group were as follows:

Endocrine and Metabolic: Hyperglycemia.

Eye: Keratitis and conjunctivitis.

Gastrointestinal: Candidiasis mouth/throat, dyspeptic symptoms, hyposalivation, dental discomfort and pain, gastrointestinal infections.

Lower Respiratory: Lower respiratory signs and symptoms.

Musculoskeletal: Arthralgia and articular rheumatism; muscle pain; bone and skeletal pain; musculoskeletal inflammation; muscle stiffness, tightness, and rigidity.

Neurology: Migraines.

Non-Site Specific: Pain, edema and swelling.

Psychiatry: Anxiety.

Skin: Skin rashes.

Adverse reactions to salmeterol are similar in nature to those seen with other selective beta₂-adrenoceptor agonists, i.e., tachycardia; palpitations; immediate hypersensitivity reactions, including urticaria, angioedema, rash, bronchospasm (see WARNINGS); headache; tremor; nervousness; and paradoxical bronchospasm (see WARNINGS).

Observed During Clinical Practice: In addition to adverse events reported from clinical trials, the following events have been identified during postapproval use of salmeterol. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, or causal connection to salmeterol or a combination of these factors.

In extensive US and worldwide postmarketing experience with salmeterol, serious exacerbations of asthma, including some that have been fatal, have been reported. In most cases, these have occurred in patients with severe asthma and/or in some patients in whom asthma has been acutely deteriorating (see WARNINGS), but they have also occurred in a few patients with less severe asthma. It was not possible from these reports to determine whether salmeterol contributed to these events.

Respiratory: Reports of upper airway symptoms of laryngeal spasm, irritation, or swelling such as stridor or choking; oropharyngeal irritation.

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

Non-Site Specific: Very rare anaphylactic reaction in patients with severe milk protein allergy.

OVERDOSAGE

The expected signs and symptoms with overdosage of SEREVENT DISKUS are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and symptoms listed under ADVERSE REACTIONS, e.g., seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, and insomnia. Overdosage with SEREVENT DISKUS may be expected to result in exaggeration of the pharmacologic adverse effects associated with beta-adrenoceptor agonists, including tachycardia and/or arrhythmia, tremor, headache, and muscle cramps. Overdosage with SEREVENT DISKUS can lead to clinically significant prolongation of the QTc interval, which can produce ventricular arrhythmias. Other signs of overdosage may include hypokalemia and hyperglycemia.

As with all sympathomimetic medications, cardiac arrest and even death may be associated with abuse of SEREVENT DISKUS.

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

No deaths were seen in rats at an inhalation dose of 2.9 mg/kg (approximately 240 times the maximum recommended daily inhalation dose in adults and approximately 110 times the maximum recommended daily inhalation dose in children on a mg/m² basis) and in dogs at an inhalation dose of 0.7 mg/kg (approximately 190 times the maximum recommended daily inhalation dose in adults and approximately 90 times the maximum recommended daily inhalation dose in children on a mg/m² basis). By the oral route, no deaths occurred in mice at 150 mg/kg (approximately 6,100 times the maximum recommended daily inhalation dose in adults and approximately 2,900 times the maximum recommended daily inhalation dose in children on a mg/m² basis) and in rats at 1,000 mg/kg (approximately 81,000 times the maximum recommended daily inhalation dose in adults and approximately 38,000 times the maximum recommended daily inhalation dose in children on a mg/m² basis).

DOSAGE AND ADMINISTRATION

SEREVENT DISKUS should be administered by the orally inhaled route only (see Instructions for Using SEREVENT DISKUS in the Medication Guide accompanying the product). The patient must not exhale into the DISKUS and the DISKUS should only be activated and used in a level, horizontal position.

Asthma: Long-acting beta₂-adrenergic agonists, such as salmeterol, the active ingredient in SEREVENT DISKUS, may increase the risk of asthma-related death (see WARNINGS). Therefore, when treating patients with asthma, SEREVENT DISKUS should only be used as additional therapy for patients not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies, including SEREVENT DISKUS. It is not indicated for patients whose asthma can be managed by occasional use of inhaled, short-acting beta₂-agonists or for patients whose asthma can be successfully managed by inhaled corticosteroids or other controller medications along with occasional use of inhaled, short-acting beta₂-agonists.

For maintenance of bronchodilatation and prevention of symptoms of asthma, including the symptoms of nocturnal asthma, the usual dosage for adults and children 4 years of age and older is 1 inhalation (50 mcg) twice daily (morning and evening, approximately 12 hours apart). If a previously effective dosage regimen fails to provide the usual response, medical advice should be sought immediately as this is often a sign of destabilization of asthma. Under these circumstances, the therapeutic regimen should be reevaluated. If symptoms arise in the period between doses, an inhaled, short-acting beta₂-agonist should be taken for immediate relief.

Chronic Obstructive Pulmonary Disease: For maintenance treatment of bronchospasm associated with COPD (including chronic bronchitis and emphysema), the usual dosage for adults is 1 inhalation (50 mcg) twice daily (morning and evening, approximately 12 hours apart).

For both asthma and COPD, adverse effects are more likely to occur with higher doses of salmeterol, and more frequent administration or administration of a larger number of inhalations is not recommended.

To gain full therapeutic benefit, SEREVENT DISKUS should be administered twice daily (morning and evening) in the treatment of reversible airway obstruction.

Geriatric Use: Based on available data for SEREVENT DISKUS, no dosage adjustment is recommended.

Prevention of Exercise-Induced Bronchospasm: One inhalation of SEREVENT DISKUS at least 30 minutes before exercise has been shown to protect patients against EIB. When used intermittently as needed for prevention of EIB, this protection may last up to 9 hours in adolescents and adults and up to 12 hours in patients 4 to 11 years of age. Additional doses of SEREVENT should not be used for 12 hours after the administration of this drug. Patients who are receiving SEREVENT DISKUS twice daily should not use additional SEREVENT for prevention of EIB. If regular, twice-daily dosing is not effective in preventing EIB, other appropriate therapy for EIB should be considered.

HOW SUPPLIED

SEREVENT DISKUS is supplied as a disposable teal green unit containing 60 blisters. The drug product is packaged within a teal green, plastic-coated, moisture-protective foil pouch (NDC 0173-0521-00).

SEREVENT DISKUS is also supplied in an institutional pack of 1 disposable teal green unit containing 28 blisters. The drug product is packaged within a teal green, plastic-coated, moisture-protective foil pouch (NDC 0173-0520-00).

Store at controlled room temperature (see USP), 20° to 25°C (68° to 77°F) in a dry place away from direct heat or sunlight. Keep out of reach of children. SEREVENT DISKUS should be discarded 6 weeks after removal from the moisture-protective foil pouch or after all blisters have been used (when the dose indicator reads "0"), whichever comes first. The DISKUS is not reusable. Do not attempt to take the DISKUS apart.

MEDICATION GUIDE

SEREVENT® [ser' uh-venf] DISKUS® (salmeterol xinafoate inhalation powder)

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

What is the most important information I should know about SEREVENT DISKUS?

SEREVENT DISKUS is a medicine called a long-acting beta₂-agonist or LABA. LABA medicines are used in patients with asthma, exercise-induced bronchospasm (EIB), and chronic obstructive pulmonary disease (COPD). LABA medicines help the muscles around the airways in your lungs stay relaxed to prevent symptoms, such as wheezing and shortness of breath. These symptoms can happen when the muscles around the airways tighten. This makes it hard to breathe. In severe cases, wheezing can stop your breathing and cause death if not treated right away.

• **In patients with asthma, LABA medicines, such as SEREVENT DISKUS, may increase the chance of death from asthma problems.** In a large asthma study, more patients who used salmeterol (SEREVENT) died from asthma problems compared with patients who did not use salmeterol (SEREVENT). Talk with your healthcare provider about this risk and the benefits of treating your asthma with SEREVENT DISKUS.

• **SEREVENT DISKUS does not relieve sudden symptoms. Always have a short-acting beta₂-agonist medicine with you to treat sudden symptoms.** If you do not have an inhaled, short-acting bronchodilator, contact your healthcare provider to have one prescribed for you.

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

• **SEREVENT DISKUS:**

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

• **Call your healthcare provider if breathing problems worsen over time while using SEREVENT DISKUS. You may need different treatment.**

• **Get emergency medical care if:**

- breathing problems worsen quickly, and
- you use your short-acting beta₂-agonist medicine, but it does not relieve your breathing problems

What is SEREVENT DISKUS?

SEREVENT DISKUS is a long-acting beta₂-agonist medicine (LABA). SEREVENT DISKUS is used for asthma, exercise-induced bronchospasm (EIB), and chronic obstructive pulmonary disease (COPD) as follows:

Asthma

SEREVENT DISKUS is used long term, twice a day, to control symptoms of asthma, and prevent symptoms such as wheezing in adults and children ages 4 and older.

Because LABA medicines, such as SEREVENT DISKUS, may increase the chance of death from asthma problems, SEREVENT DISKUS is not for adults and children with asthma who:

- are well controlled with another asthma-controller medicine, such as a low to medium dose of an inhaled corticosteroid medicine
- only need short-acting beta₂-agonist medicines once in awhile

Exercise-Induced Bronchospasm (EIB)

SEREVENT DISKUS is used for the prevention of wheezing caused by exercise in adults and children 4 years of age and older.

Chronic Obstructive Pulmonary Disease (COPD)

SEREVENT DISKUS is used long term, twice a day in controlling symptoms of COPD and preventing wheezing in adults with COPD.

What should I tell my healthcare provider before using SEREVENT DISKUS?

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

- have heart problems
- have high blood pressure
- have seizures
- have thyroid problems
- have diabetes
- have liver problems
- are pregnant or planning to become pregnant. It is not known if SEREVENT DISKUS may harm your unborn baby.
- are breastfeeding. It is not known if SEREVENT DISKUS passes into your milk and if it can harm your baby.
- are allergic to SEREVENT DISKUS, any other medicines, or food products

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

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

How do I use SEREVENT DISKUS?

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

- Children should use SEREVENT DISKUS with an adult's help, as instructed by the child's healthcare provider.
- Use SEREVENT DISKUS exactly as prescribed. **Do not use SEREVENT DISKUS more often than prescribed.**
- For asthma and COPD, the usual dose is 1 inhalation twice a day (morning and evening). The 2 doses should be about 12 hours apart.
- For preventing exercise-induced bronchospasm, take 1 inhalation at least 30 minutes before exercise. Do not use SEREVENT DISKUS more often than every 12 hours. Do not use extra SEREVENT DISKUS before exercise if you already use it twice a day.
- If you miss a dose of SEREVENT DISKUS, just skip that dose. Take your next dose at your usual time. Do not take 2 doses at one time.

• Do not use a spacer device with SEREVENT DISKUS.

• Do not breathe into SEREVENT DISKUS.

• **While you are using SEREVENT DISKUS twice a day, do not use other medicines that contain a long-acting beta₂-agonist or LABA for any reason.** Other LABA medicines include ADVAIR DISKUS® (fluticasone propionate and salmeterol inhalation powder), ADVAIR® HFA (fluticasone propionate and salmeterol) Inhalation Aerosol, FORADIL® AEROLIZER® (formoterol fumarate inhalation powder), SYMBICORT® (budesonide and formoterol fumarate dihydrate) Inhalation Aerosol, PERFORMIST™ (formoterol fumarate) Inhalation Solution, and BROVANA™ (arformoterol tartrate) Inhalation Solution.

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

• Make sure you always have a short-acting beta₂-agonist medicine with you. Use your short-acting beta₂-agonist medicine if you have breathing problems between doses of SEREVENT DISKUS.

• **Call your healthcare provider or get medical care right away if:**

- your breathing problems worsen with SEREVENT DISKUS
- you need to use your short-acting beta₂-agonist medicine more often than usual
- your short-acting beta₂-agonist medicine does not work as well for you at relieving symptoms
- you need to use 4 or more inhalations of your short-acting beta₂-agonist medicine for 2 or more days in a row
- you use 1 whole canister of your short-acting beta₂-agonist medicine in 8 weeks' time
- your peak flow meter results decrease. Your healthcare provider will tell you the numbers that are right for you.
- you have asthma and your symptoms do not improve after using SEREVENT DISKUS regularly for 1 week.



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Research Triangle Park, NC 27709

What are the possible side effects with SEREVENT DISKUS?

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

Other possible side effects with SEREVENT DISKUS include:

- serious allergic reactions including rash; hives; swelling of the face, mouth, and tongue; and breathing problems. Call your healthcare provider or get emergency medical care if you get any symptoms of a serious allergic reaction.
- increased blood pressure
- a fast and irregular heartbeat
- chest pain
- headache
- tremor
- nervousness
- throat irritation

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

These are not all the side effects with SEREVENT DISKUS. Ask your healthcare provider or pharmacist for more information. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How do I store SEREVENT DISKUS?

- Store SEREVENT DISKUS at room temperature between 68° to 77° F (20° to 25° C). Keep in a dry place away from heat and sunlight.
- Safely discard SEREVENT DISKUS 6 weeks after you remove it from the foil pouch, or after the dose indicator reads "0", whichever comes first.
- Keep SEREVENT DISKUS and all medicines out of the reach of children.

General Information about SEREVENT DISKUS

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

This Medication Guide summarizes the most important information about SEREVENT DISKUS. If you would like more information, talk with your healthcare provider or pharmacist. You can ask your healthcare provider or pharmacist for information about SEREVENT DISKUS that was written for healthcare professionals. You can also contact the company that makes SEREVENT DISKUS (toll free) at 1-888-825-5249 or at www.serevent.com.

Instructions for Using SEREVENT DISKUS

Follow the instructions below for using your SEREVENT DISKUS. **You will breathe in (inhale) the medicine from the DISKUS.** If you have any questions, ask your healthcare provider or pharmacist.



Take the SEREVENT DISKUS out of the box and foil pouch. Write the "Pouch opened" and "Use by" dates on the label on top of the DISKUS. **The "Use by" date is 6 weeks from date of opening the pouch.**

- The DISKUS will be in the closed position when the pouch is opened.
- The **dose indicator** on the top of the DISKUS tells you how many doses are left. The dose indicator number will decrease each time you use the DISKUS. After you have used 55 doses from the DISKUS, the numbers 5 to 0 will appear in **red** to warn you that there are only a few doses left (see Figure 1).



Figure 1

Taking a dose from the DISKUS requires the following 3 simple steps: Open, Click, Inhale.

1. OPEN

Hold the DISKUS in one hand and put the thumb of your other hand on the **thumbgrip**. Push your thumb away from you as far as it will go until the mouthpiece appears and snaps into position (see Figure 2).



Figure 2

2. CLICK

Hold the DISKUS in a level, flat position with the mouthpiece towards you. Slide the **lever** away from you as far as it will go until it **clicks** (see Figure 3). The DISKUS is now ready to use.



Figure 3

Every time the **lever** is pushed back, a dose is ready to be inhaled. This is shown by a decrease in numbers on the dose counter. **To avoid releasing or wasting doses once the DISKUS is ready:**

- Do not close the DISKUS.
- Do not tilt the DISKUS.
- Do not play with the lever.
- Do not move the lever more than once.

3. INHALE

Before inhaling your dose from the DISKUS, breathe out (exhale) fully while holding the DISKUS level and away from your mouth (see Figure 4). **Remember, never breathe out into the DISKUS mouthpiece.**



Figure 4

Put the mouthpiece to your lips (see Figure 5). Breathe in quickly and deeply through the DISKUS. Do not breathe in through your nose.



Figure 5

Remove the DISKUS from your mouth. Hold your breath for about 10 seconds, or for as long as is comfortable. Breathe out slowly.

The DISKUS delivers your dose of medicine as a very fine powder. Most patients can taste or feel the powder. Do not use another dose from the DISKUS if you do not feel or taste the medicine.

4. **Close the DISKUS when you are finished taking a dose so that the DISKUS will be ready for you to take your next dose.** Put your thumb on the thumbgrip and slide the thumbgrip back towards you as far as it will go (see Figure 6). The DISKUS will click shut. The lever will automatically return to its original position. The DISKUS is now ready for you to take your next scheduled dose, due in about 12 hours. (Repeat steps 1 to 4.)



Figure 6

Remember:

- Never breathe into the DISKUS.
- Never take the DISKUS apart.
- Always ready and use the DISKUS in a level, flat position.
- Do not use the DISKUS with a spacer device.
- Never wash the mouthpiece or any part of the DISKUS. **Keep it dry.**
- Always keep the DISKUS in a dry place.
- Never take an extra dose, even if you did not taste or feel the medicine.

Rx only



GlaxoSmithKline
Research Triangle Park, NC 27709

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

March 2008 SRD:2MG

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

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

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

FOR ORAL INHALATION

Initial U.S. Approval: 2000

WARNING: RISK OF ASTHMA-RELATED DEATH

See full prescribing information for complete boxed warning.

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

RECENT MAJOR CHANGES

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

INDICATIONS AND USAGE

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

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

Important limitations:

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

DOSAGE AND ADMINISTRATION

For oral inhalation only.

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

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- Asthma-related death: Long-acting beta₂-adrenergic agonists may increase the risk. Prescribe only for recommended patient populations. (5.1)
- Deterioration of disease and acute episodes: Do not initiate in acutely deteriorating asthma or to treat acute symptoms. (5.2)
- Use with additional long-acting beta₂-agonist: Do not use in combination because of risk of overdose. (5.3)
- Localized infections: *Candida albicans* infection of the mouth and throat may occur. Monitor patients periodically for signs of adverse effects on the oral cavity. Advise patients to rinse the mouth following inhalation. (5.4)
- Pneumonia: Increased risk in patients with COPD. Monitor patients for signs and symptoms of pneumonia. (5.5)
- Immunosuppression: Potential worsening of infections (e.g., existing tuberculosis, fungal, bacterial, viral, or parasitic infection; or ocular herpes simplex). Use with caution in patients with these infections. More serious or even fatal course of chickenpox or measles can occur in susceptible patients. (5.6)
- Transferring patients from systemic corticosteroids: Risk of impaired adrenal function when transferring from oral steroids. Taper patients slowly from systemic corticosteroids if transferring to ADVAIR DISKUS. (5.7)
- Hypercorticism and adrenal suppression: May occur with very high dosages or at the regular dosage in susceptible individuals. If such changes occur, discontinue ADVAIR DISKUS slowly. (5.8)
- Strong cytochrome P450 3A4 inhibitors: (e.g., ritonavir) Risk of increased systemic corticosteroid and cardiovascular effects. Use not recommended with ADVAIR DISKUS. (5.9)
- Paradoxical bronchospasm: Discontinue ADVAIR DISKUS and institute alternative therapy if paradoxical bronchospasm occurs. (5.10)
- Patients with cardiovascular or central nervous system disorders: Use with caution because of beta-adrenergic stimulation. (5.12)
- Decreases in bone mineral density: Assess bone mineral density initially and periodically thereafter. (5.13)
- Effects on growth: Monitor growth of pediatric patients. (5.14)
- Glaucoma and cataracts: Close monitoring is warranted. (5.15)
- Metabolic effects: Be alert to eosinophilic conditions, hypokalemia, and hyperglycemia. (5.16, 5.18)
- Coexisting conditions: Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis. (5.17)

ADVERSE REACTIONS

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

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

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

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

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

See 17 for PATIENT COUNSELING INFORMATION and MEDICATION GUIDE.

Revised: August 2008

ADD:4PI

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)

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FULL PRESCRIBING INFORMATION

WARNING: RISK OF ASTHMA-RELATED DEATH

Long-acting beta₂-adrenergic agonists, such as salmeterol, one of the active ingredients in ADVAIR DISKUS, may increase the risk of asthma-related death. Therefore, when treating patients with asthma, physicians should only prescribe ADVAIR DISKUS for patients not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies. Data from a large placebo-controlled US study that compared the safety of salmeterol (SEREVENT® Inhalation Aerosol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176 patients treated for 28 weeks on salmeterol versus 3 deaths out of 13,179 patients on placebo) [see Warnings and Precautions (5.1)].

1 INDICATIONS AND USAGE

1.1 Maintenance Treatment of Asthma

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

Long-acting beta₂-adrenergic agonists, such as salmeterol, one of the active ingredients in ADVAIR DISKUS, may increase the risk of asthma-related death [see Warnings and Precautions (5.1)]. Therefore, when treating patients with asthma, physicians should only prescribe ADVAIR DISKUS for patients not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies.

Important Limitations of Use:

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

1.2 Maintenance Treatment of Chronic Obstructive Pulmonary Disease

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

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

2 DOSAGE AND ADMINISTRATION

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

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

2.1 Asthma

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

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

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

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

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

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

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

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

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

2.2 Chronic Obstructive Pulmonary Disease

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

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

3 DOSAGE FORMS AND STRENGTHS

Disposable purple device with 60 blisters containing a combination of fluticasone propionate (100, 250, or 500 mcg) and salmeterol (50 mcg) as an oral inhalation powder formulation. An institutional pack containing 14 blisters is also available.

4 CONTRAINDICATIONS

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

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

5 WARNINGS AND PRECAUTIONS

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

Long-acting beta₂-adrenergic agonists, such as salmeterol, one of the active ingredients in ADVAIR DISKUS, may increase the risk of asthma-related death. Therefore, when treating patients with asthma, physicians should only prescribe ADVAIR DISKUS for patients not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies.

A large placebo-controlled US study that compared the safety of salmeterol with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in patients receiving salmeterol. The Salmeterol Multi-center Asthma Research Trial (SMART) was a randomized, double-blind study that enrolled long-acting beta₂-agonist-naïve patients with asthma to assess the

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)

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

Post-hoc subpopulation analyses were performed. In Caucasians, asthma-related death occurred at a higher rate in patients treated with salmeterol than in patients treated with placebo (0.07% vs. 0.01%, relative risk 5.82 [95% CI: 0.70, 48.37]). In African Americans also, asthma-related death occurred at a higher rate in patients treated with salmeterol than those treated with placebo (0.31% vs. 0.04%, relative risk 7.26 [95% CI: 0.89, 58.94]). Although the relative risks of asthma-related death were similar in Caucasians and African Americans, the estimate of excess deaths in patients treated with salmeterol was greater in African Americans because there was a higher overall rate of asthma-related death in African American patients (see Table 1). Given the similar basic mechanisms of action of beta₂-agonists, it is possible that the findings seen in the SMART study represent a class effect.

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

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

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

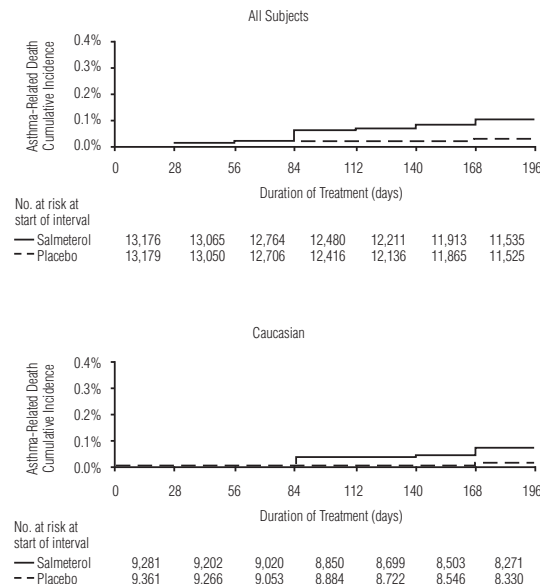
* Life-table 28-week estimate, adjusted according to the patients' actual lengths of exposure to study treatment to account for early withdrawal of patients from the study.

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

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

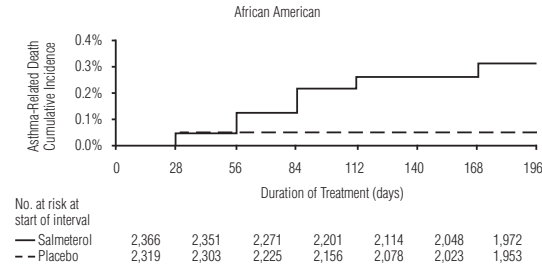
§ The Total Population includes the following ethnic origins listed on the case report form: Caucasian, African American, Hispanic, Asian, and "Other." In addition, the Total Population includes those patients whose ethnic origin was not reported. The results for Caucasian and African American subpopulations are shown above. No asthma-related deaths occurred in the Hispanic (salmeterol n = 996, placebo n = 999), Asian (salmeterol n = 173, placebo n = 149), or "Other" (salmeterol n = 230, placebo n = 224) subpopulations. One asthma-related death occurred in the placebo group in the subpopulation whose ethnic origin was not reported (salmeterol n = 130, placebo n = 127).

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



(cont.)

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



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

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

5.2 Deterioration of Disease and Acute Episodes

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

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

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

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

When beginning treatment with ADVAIR DISKUS, patients who have been taking oral or inhaled, short-acting beta₂-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs.

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

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

5.4 Local Effects

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

5.5 Pneumonia

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

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

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

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5.6 Immunosuppression

Persons who are using drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible children or adults using corticosteroids. In such children or adults who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If a patient is exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If a patient is exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered.

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

5.7 Transferring Patients From Systemic Corticosteroid Therapy

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

Patients who have been previously maintained on 20 mg or more per day of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although ADVAIR DISKUS may provide control of asthma symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of glucocorticoid systemically and does NOT provide the mineralocorticoid activity that is necessary for coping with these emergencies.

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

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

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

5.8 Hypercorticism and Adrenal Suppression

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

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

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

5.9 Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors

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

5.10 Paradoxical Bronchospasm and Upper Airway Symptoms

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

5.11 Immediate Hypersensitivity Reactions

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

5.12 Cardiovascular and Central Nervous System Effects

Excessive beta-adrenergic stimulation has been associated with seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, palpitation, nausea, dizziness, fatigue, malaise, and insomnia [see *Overdosage* (10)].

Therefore, ADVAIR DISKUS, like all products containing sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Salmeterol, a component of ADVAIR DISKUS, can produce a clinically significant cardiovascular effect in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of salmeterol at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Large doses of inhaled or oral salmeterol (12 to 20 times the recommended dose) have been associated with clinically significant prolongation of the QTc interval, which has the potential for producing ventricular arrhythmias. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

5.13 Reduction in Bone Mineral Density

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

A 2-year study of 160 patients (females 18 to 40 years of age, males 18 to 50) with asthma receiving CFC-propelled fluticasone propionate inhalation aerosol 88 or 440 mcg twice daily demonstrated no statistically significant changes in BMD at any time point (24, 52, 76, and 104 weeks of double-blind treatment) as assessed by dual-energy x-ray absorptiometry at lumbar regions L1 through L4.

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

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

5.14 Effect on Growth

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

5.15 Glaucoma and Cataracts

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

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

5.16 Eosinophilic Conditions and Churg-Strauss Syndrome

In rare cases, patients on inhaled fluticasone propionate may present with systemic eosinophilic conditions. Some of these patients have clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of fluticasone propionate. Cases of serious eosinophilic conditions have also been reported with other inhaled corticosteroids in this clinical setting. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal relationship between fluticasone propionate and these underlying conditions has not been established.

5.17 Coexisting Conditions

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

5.18 Hypokalemia and Hyperglycemia

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

6 ADVERSE REACTIONS

Long-acting beta₂-adrenergic agonists, such as salmeterol, may increase the risk of asthma-related death. Data from a large, placebo-controlled US study that compared the safety of salmeterol (SEREVENT Inhalation Aerosol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients

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receiving salmeterol [see Warnings and Precautions (5.1)]. Salmeterol is a component of ADVAIR DISKUS. However, the data from this study are not adequate to determine whether concurrent use of inhaled corticosteroids, such as fluticasone propionate, the other component of ADVAIR DISKUS, or other asthma-controller therapy modifies the risk of asthma-related death.

Systemic and local corticosteroid use may result in the following:

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

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

6.1 Clinical Trials Experience in Asthma

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

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

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

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

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

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

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

6.2 Clinical Trials Experience in Chronic Obstructive Pulmonary Disease

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

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

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

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

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

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

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

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

6.3 Postmarketing Experience

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

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

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

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Eye Disorders: Glaucoma.

Gastrointestinal Disorders: Abdominal pain, dyspepsia, xerostomia.

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

Metabolic and Nutrition Disorders: Hyperglycemia, weight gain.

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

Nervous System Disorders: Paresthesia, restlessness.

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

Reproductive System and Breast Disorders: Dysmenorrhea.

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

Skin and Subcutaneous Tissue Disorders: Ecchymoses, photodermatitis.

Vascular Disorders: Pallor.

7 DRUG INTERACTIONS

ADVAIR DISKUS has been used concomitantly with other drugs, including short-acting β_2 -agonists, methylxanthines, and intranasal corticosteroids, commonly used in patients with asthma or COPD, without adverse drug reactions. No formal drug interaction studies have been performed with ADVAIR DISKUS.

7.1 Inhibitors of Cytochrome P450 3A4

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

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

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

Salmeterol: In a drug interaction study in 20 healthy subjects, coadministration of inhaled salmeterol (50 mcg twice daily) and oral ketoconazole (400 mg once daily) for 7 days resulted in greater systemic exposure to salmeterol (AUC increased 16-fold and C_{max} increased 1.4-fold). Three (3) subjects were withdrawn due to β_2 -agonist side effects (2 with prolonged QTc and 1 with palpitations and sinus tachycardia). Although there was no statistical effect on the mean QTc, coadministration of salmeterol and ketoconazole was associated with more frequent increases in QTc duration compared with salmeterol and placebo administration.

7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

ADVAIR DISKUS should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of salmeterol, a component of ADVAIR DISKUS, on the vascular system may be potentiated by these agents.

7.3 Beta-Adrenergic Receptor Blocking Agents

Beta-blockers not only block the pulmonary effect of beta-agonists, such as salmeterol, a component of ADVAIR DISKUS, but may produce severe bronchospasm in patients with reversible obstructive airways disease. Therefore, patients with asthma and COPD should not normally be treated with beta-blockers. However, under certain circumstances, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents for these patients; cardioselective beta-blockers could be considered, although they should be administered with caution.

7.4 Diuretics

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

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

ADVAIR DISKUS: In the mouse reproduction assay, fluticasone propionate by the subcutaneous route at a dose approximately 3/5 the maximum recommended human daily inhalation dose (MRHD) on a mg/m² basis combined with oral salmeterol at a dose approximately 410 times the MRHD on a mg/m² basis produced cleft palate, fetal death, increased implantation loss, and delayed ossification. These observations are characteristic of glucocorticoids. No developmental toxicity was observed at combination doses of fluticasone propionate subcutaneously up to approximately 1/6 the MRHD on a mg/m² basis and oral doses of salmeterol up to approximately 55 times the MRHD on a mg/m² basis. In rats, combining fluticasone propionate subcutaneously at a dose equivalent to the MRHD on a mg/m² basis and an oral dose of salmeterol at approximately 810 times the MRHD on a mg/m² basis produced decreased fetal weight, umbilical hernia, delayed ossification, and changes in the occipital bone. No such effects were seen when combining flutica-

sone propionate subcutaneously at a dose less than the MRHD on a mg/m² basis and an oral dose of salmeterol at approximately 80 times the MRHD on a mg/m² basis.

Fluticasone Propionate: Subcutaneous studies in the mouse at a dose less than the MRHD on a mg/m² basis and in the rat at a dose equivalent to the MRHD on a mg/m² basis revealed fetal toxicity characteristic of potent corticosteroid compounds, including embryonic growth retardation, omphalocele, cleft palate, and retarded cranial ossification.

In the rabbit, fetal weight reduction and cleft palate were observed at a subcutaneous dose less than the MRHD on a mg/m² basis. However, no teratogenic effects were reported at oral doses up to approximately 5 times the MRHD on a mg/m² basis. No fluticasone propionate was detected in the plasma in this study, consistent with the established low bioavailability following oral administration [see *Clinical Pharmacology* (12.3)].

Experience with oral corticosteroids since their introduction in pharmacologic, as opposed to physiologic, doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans. In addition, because there is a natural increase in corticosteroid production during pregnancy, most women will require a lower exogenous corticosteroid dose and many will not need corticosteroid treatment during pregnancy.

Salmeterol: No teratogenic effects occurred in rats at oral doses approximately 160 times the MRHD on a mg/m² basis. In Dutch rabbits administered oral doses approximately 50 times the MRHD based on comparison of the AUCs, salmeterol exhibited fetal toxic effects characteristically resulting from beta-adrenoceptor stimulation. These included precocious eyelid openings, cleft palate, sternebral fusion, limb and paw flexures, and delayed ossification of the frontal cranial bones. No such effects occurred at an oral dose approximately 20 times the MRHD based on comparison of the AUCs.

New Zealand White rabbits were less sensitive since only delayed ossification of the frontal bones was seen at an oral dose approximately 1,600 times the MRHD on a mg/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.

8.2 Labor and Delivery

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

8.3 Nursing Mothers

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

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

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

8.4 Pediatric Use

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

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

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

If a child or adolescent on any corticosteroid appears to have growth suppression, the possibility that he/she is particularly sensitive to this effect of corticosteroids should be considered. The potential growth effects of prolonged treatment should be weighed against the clinical benefits obtained. To minimize the systemic effects of orally inhaled corticosteroids, including ADVAIR DISKUS, each patient should be titrated to the lowest strength that effectively controls his/her asthma [see *Dosage and Administration* (2.1)].

8.5 Geriatric Use

Clinical studies of ADVAIR DISKUS for asthma did not include sufficient numbers of patients aged 65 years and older to determine whether older patients with asthma respond differently than younger patients.

Of the total number of patients in clinical studies receiving ADVAIR DISKUS for COPD, 1,621 were 65 years of age or older and 379 were 75 years of age or older. Patients with COPD 65 years of age and older had a higher incidence of serious adverse events compared with patients less than 65 years of age. Although the distribution of adverse events was similar in the 2 age-groups, patients over 65 years of age experienced more severe events. In two 1-year studies, the excess risk of pneumonia that was seen in patients treated with ADVAIR DISKUS compared with those treated with salmeterol was greater in patients over 65 years of age than in patients less than 65 years of age. 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.

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)

No relationship between fluticasone propionate systemic exposure and age was observed in 57 patients with COPD (aged 40 to 82 years) given 250 or 500 mcg twice daily.

8.6 Hepatic Impairment

Formal pharmacokinetic studies using ADVAIR DISKUS have not been conducted in patients with hepatic impairment. However, since both fluticasone propionate and salmeterol are predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of fluticasone propionate and salmeterol in plasma. Therefore, patients with hepatic disease should be closely monitored.

8.7 Renal Impairment

Formal pharmacokinetic studies using ADVAIR DISKUS have not been conducted in patients with renal impairment.

10 OVERDOSAGE

No human overdosage data has been reported for ADVAIR DISKUS.

No deaths occurred in rats given an inhaled single-dose combination of salmeterol 3.6 mg/kg (approximately 290 and 140 times the MRHD for adults and children, respectively, on a mg/m² basis) and 1.9 mg/kg of fluticasone propionate (approximately 15 and 35 times the MRHD for adults and children, respectively, on a mg/m² basis).

Fluticasone Propionate: Chronic overdosage with fluticasone propionate may result in signs/symptoms of hypercorticism [see *Warnings and Precautions* (5.7)]. Inhalation by healthy volunteers of a single dose of 4,000 mcg of fluticasone propionate inhalation powder or single doses of 1,760 or 3,520 mcg of fluticasone propionate inhalation aerosol was well tolerated. Fluticasone propionate given by inhalation aerosol at dosages of 1,320 mcg twice daily for 7 to 15 days to healthy human volunteers was also well tolerated. Repeat oral doses up to 80 mg daily for 10 days in healthy volunteers and repeat oral doses up to 20 mg daily for 42 days in patients were well tolerated. Adverse reactions were of mild or moderate severity, and incidences were similar in active and placebo treatment groups.

No deaths were seen in mice given an oral dose of 1,000 mg/kg (4,100 and 9,600 times the MRHD dose for adults and children, respectively, on a mg/m² basis). No deaths were seen in rats given an oral dose of 1,000 mg/kg (8,100 and 19,200 times the MRHD for adults and children, respectively, on a mg/m² basis).

Salmeterol: The expected signs and symptoms with overdosage of salmeterol are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the following: seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, and insomnia. Overdosage with salmeterol can lead to clinically significant prolongation of the QTc interval, which can produce ventricular arrhythmias. Other signs of overdosage may include hypokalemia and hyperglycemia.

As with all sympathomimetic medications, cardiac arrest and even death may be associated with abuse of salmeterol.

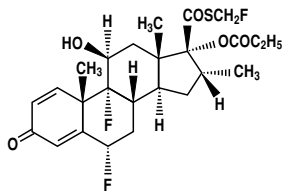
Treatment consists of discontinuation of salmeterol together with appropriate symptomatic therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is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

No deaths were seen in rats given salmeterol at an inhalation dose of 2.9 mg/kg (approximately 240 and 110 times the MRHD for adults and children, respectively, on a mg/m² basis) and in dogs at an inhalation dose of 0.7 mg/kg (approximately 190 and 90 times the MRHD for adults and children, respectively, on a mg/m² basis). By the oral route, no deaths occurred in mice at 150 mg/kg (approximately 6,100 and 2,900 times the MRHD for adults and children, respectively, on a mg/m² basis) and in rats at 1,000 mg/kg (approximately 81,000 and 38,000 times the MRHD for adults and children, respectively, on a mg/m² basis).

11 DESCRIPTION

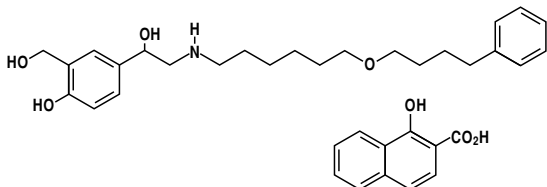
ADVAIR DISKUS 100/50, ADVAIR DISKUS 250/50, and ADVAIR DISKUS 500/50 are combinations of fluticasone propionate and salmeterol xinafoate.

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



Fluticasone propionate is a white powder with a molecular weight of 500.6, and the empirical formula is C₂₅H₃₇F₃O₅S. 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 -[[(6-(4-phenylbutoxy)hexyl)amino]methyl]-1,3-benzenedimethanol, 1-hydroxy-2-naphthalenecarboxylate, and it has the following chemical structure:



Salmeterol xinafoate is a white powder with a molecular weight of 603.8, and the empirical

formula is C₂₅H₃₇NO₄•C₁₁H₉O₃. It is freely soluble in methanol; slightly soluble in ethanol, chloroform, and isopropanol; and sparingly soluble in water.

ADVAIR DISKUS 100/50, ADVAIR DISKUS 250/50, and ADVAIR DISKUS 500/50 are specially designed plastic devices containing a double-foil blister strip of a powder formulation of fluticasone propionate and salmeterol xinafoate intended for oral inhalation only. Each blister on the double-foil strip within the device contains 100, 250, or 500 mcg of microfine fluticasone propionate and 72.5 mcg of microfine salmeterol xinafoate salt, equivalent to 50 mcg of salmeterol base, in 12.5 mg of formulation containing lactose (which contains milk proteins). Each blister contains 1 complete dose of both medications. After a blister containing medication is opened by activating the device, the medication is dispersed into the airstream created by the patient inhaling through the mouthpiece.

Under standardized in vitro test conditions, ADVAIR DISKUS delivers 93, 233, and 465 mcg of fluticasone propionate and 45 mcg of salmeterol base per blister from ADVAIR DISKUS 100/50, 250/50, and 500/50, respectively, when tested at a flow rate of 60 L/min for 2 seconds. In adult patients with obstructive lung disease and severely compromised lung function (mean FEV₁ 20% to 30% of predicted), mean peak inspiratory flow (PIF) through a DISKUS inhalation device was 82.4 L/min (range, 46.1 to 115.3 L/min).

Inhalation profiles for adolescent (N = 13, aged 12 to 17 years) and adult (N = 17, aged 18 to 50 years) patients with asthma inhaling maximally through the DISKUS® device show mean PIF of 122.2 L/min (range, 81.6 to 152.1 L/min). Inhalation profiles for pediatric patients with asthma inhaling maximally through the DISKUS device show a mean PIF of 75.5 L/min (range, 49.0 to 104.8 L/min) for the 4-year-old patient set (N = 20) and 107.3 L/min (range, 82.8 to 125.6 L/min) for the 8-year-old patient set (N = 20).

The actual amount of drug delivered to the lung will depend on patient factors, such as inspiratory flow profile.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

ADVAIR DISKUS: Since ADVAIR DISKUS contains both fluticasone propionate and salmeterol, the mechanisms of action described below for the individual components apply to ADVAIR DISKUS. These drugs represent 2 classes of medications (a synthetic corticosteroid and a selective, long-acting beta-adrenergic receptor agonist) that have different effects on clinical and physiological indices.

Fluticasone Propionate: Fluticasone propionate is a synthetic trifluorinated corticosteroid with potent anti-inflammatory activity. In vitro assays using human lung cytosol preparations have established fluticasone propionate as a human glucocorticoid receptor agonist with an affinity 18 times greater than dexamethasone, almost twice that of beclomethasone-17-monopropionate (BMP), the active metabolite of beclomethasone dipropionate, and over 3 times that of budesonide. Data from the McKenzie vasoconstrictor assay in man are consistent with these results.

Inflammation is an important component in the pathogenesis of asthma. Corticosteroids have been shown to inhibit multiple cell types (e.g., mast cells, eosinophils, basophils, lymphocytes, macrophages, neutrophils) and mediator production or secretion (e.g., histamine, eicosanoids, leukotrienes, cytokines) involved in the asthmatic response. These anti-inflammatory actions of corticosteroids contribute to their efficacy in asthma.

Inflammation is also a component in the pathogenesis of COPD. In contrast to asthma, however, the predominant inflammatory cells in COPD include neutrophils, CD8+ T-lymphocytes, and macrophages. The effects of corticosteroids in the treatment of COPD are not well defined and inhaled corticosteroids and fluticasone propionate when used apart from ADVAIR DISKUS are not indicated for the treatment of COPD.

Salmeterol Xinafoate: Salmeterol is a selective, long-acting beta₂-adrenergic agonist. In vitro studies show salmeterol to be at least 50 times more selective for beta₂-adrenoceptors than albuterol. Although beta₂-adrenoceptors are the predominant adrenergic receptors in bronchial smooth muscle and 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.

12.2 Pharmacodynamics

ADVAIR DISKUS: Healthy Subjects: Cardiovascular Effects: Since systemic pharmacodynamic effects of salmeterol are not normally seen at the therapeutic dose, higher doses were used to produce measurable effects. Four (4) studies were conducted in healthy adult subjects: (1) a single-dose crossover study using 2 inhalations of ADVAIR DISKUS 500/50, fluticasone propionate powder 500 mcg and salmeterol powder 50 mcg given concurrently, or fluticasone propionate powder 500 mcg given alone, (2) a cumulative dose study using 50 to 400 mcg of salmeterol powder given alone or as ADVAIR DISKUS 500/50, (3) a repeat-dose study for 11 days using 2 inhalations twice daily of ADVAIR DISKUS 250/50, fluticasone propionate powder 250 mcg, or salmeterol powder 50 mcg, and (4) a single-dose study using 5 inhalations of ADVAIR DISKUS 100/50, fluticasone propionate powder 100 mcg alone, or placebo. In these studies no significant differences were observed in the pharmacodynamic effects of salmeterol (pulse rate, blood pressure, QTc interval, potassium, and glucose) whether the salmeterol was given as ADVAIR DISKUS, concurrently with fluticasone propionate from separate inhalers, or as salmeterol alone. The systemic pharmacodynamic effects of salmeterol were not altered by the presence of fluticasone propionate in ADVAIR DISKUS. The potential effect of salmeterol on the effects of fluticasone propionate on the HPA axis was also evaluated in these studies.

HPA Axis Effects: No significant differences across treatments were observed in 24-hour urinary cortisol excretion and, where measured, 24-hour plasma cortisol AUC. The systemic pharmacodynamic effects of fluticasone propionate were not altered by the presence of salmeterol in ADVAIR DISKUS in healthy subjects.

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

Asthma: Adults and Adolescent Patients: Cardiovascular Effects: In clinical studies with ADVAIR DISKUS in adult and adolescent patients 12 years of age and older with asthma, no significant differences were observed in the systemic pharmacodynamic effects of salmeterol (pulse rate, blood pressure, QTc interval, potassium, and glucose) whether the salmeterol was given alone or as ADVAIR DISKUS. In 72 adolescent and adult patients with asthma given either ADVAIR DISKUS 100/50 or ADVAIR DISKUS 250/50, continuous 24-hour electrocardiographic monitoring was performed after the first dose and after 12 weeks of therapy, and no clinically significant dysrhythmias were noted.

HPA Axis Effects: In a 28-week study in adolescent and adult patients with asthma, ADVAIR DISKUS 500/50 twice daily was compared with the concurrent use of salmeterol powder 50 mcg plus fluticasone propionate powder 500 mcg from separate inhalers or fluticasone propionate powder 500 mcg alone. No significant differences across treatments were observed in serum cortisol AUC after 12 weeks of dosing or in 24-hour urinary cortisol excretion after 12 and 28 weeks.

In a 12-week study in adolescent and adult patients with asthma, ADVAIR DISKUS 250/50 twice daily was compared with fluticasone propionate powder 250 mcg alone, salmeterol powder 50 mcg alone, and placebo. For most patients, the ability to increase cortisol production in response to stress, as assessed by 30-minute cosyntropin stimulation, remained intact with ADVAIR DISKUS. One patient (3%) who received ADVAIR DISKUS 250/50 had an abnormal response (peak serum cortisol <18 mcg/dL) after dosing, compared with 2 patients (6%) who received placebo, 2 patients (6%) who received fluticasone propionate 250 mcg, and no patients who received salmeterol.

In a repeat-dose, 3-way crossover study, 1 inhalation twice daily of ADVAIR DISKUS 100/50, FLOVENT® DISKUS® 100 mcg (fluticasone propionate inhalation powder, 100 mcg), or placebo was administered to 20 adolescent and adult patients with asthma. After 28 days of treatment, geometric mean serum cortisol AUC over 12 hours showed no significant difference between ADVAIR DISKUS and FLOVENT DISKUS or between either active treatment and placebo.

Pediatric Patients: HPA Axis Effects: In a 12-week study in patients with asthma aged 4 to 11 years who were receiving inhaled corticosteroids at study entry, ADVAIR DISKUS 100/50 twice daily was compared with fluticasone propionate inhalation powder 100 mcg administered twice daily via the DISKUS. The values for 24-hour urinary cortisol excretion at study entry and after 12 weeks of treatment were similar within each treatment group. After 12 weeks, 24-hour urinary cortisol excretion was also similar between the 2 groups.

Chronic Obstructive Pulmonary Disease: Cardiovascular Effects: In clinical studies with ADVAIR DISKUS in patients with COPD, no significant differences were seen in pulse rate, blood pressure, potassium, and glucose between ADVAIR DISKUS, the individual components of ADVAIR DISKUS, and placebo. In a study of ADVAIR DISKUS 250/50, 8 patients (2 [1.1%] in the group given ADVAIR DISKUS 250/50, 1 [0.5%] in the fluticasone propionate 250-mcg group, 3 [1.7%] in the salmeterol group, and 2 [1.1%] in the placebo group) had QTc intervals >470 msec at least 1 time during the treatment period. Five (5) of these 8 patients had a prolonged QTc interval at baseline.

In a 24-week study, 130 patients with COPD received continuous 24-hour electrocardiographic monitoring prior to the first dose and after 4 weeks of twice-daily treatment with either ADVAIR DISKUS 500/50, fluticasone propionate powder 500 mcg, salmeterol powder 50 mcg, or placebo. No significant differences in ventricular or supraventricular arrhythmias and heart rate were observed among the groups treated with ADVAIR DISKUS 500/50, the individual components, or placebo. One (1) subject in the fluticasone propionate group experienced atrial flutter/atrial fibrillation, and 1 subject in the group given ADVAIR DISKUS 500/50 experienced heart block. There were 3 cases of nonsustained ventricular tachycardia (1 each in the placebo, salmeterol, and fluticasone propionate 500-mcg treatment groups).

In 24-week clinical studies in patients with COPD, the incidence of clinically significant electrocardiogram (ECG) abnormalities (myocardial ischemia, ventricular hypertrophy, clinically significant conduction abnormalities, clinically significant arrhythmias) was lower for patients who received salmeterol (1%, 9 of 688 patients who received either salmeterol 50 mcg or ADVAIR DISKUS) compared with placebo (3%, 10 of 370 patients).

No significant differences with salmeterol 50 mcg alone or in combination with fluticasone propionate as ADVAIR DISKUS 500/50 were observed on pulse rate and systolic and diastolic blood pressure in a subset of patients with COPD who underwent 12-hour serial vital sign measurements after the first dose (N = 183) and after 12 weeks of therapy (N = 149). Median changes from baseline in pulse rate and systolic and diastolic blood pressure were similar to those seen with placebo.

HPA Axis Effects: Short-cosyntropin stimulation testing was performed both at Day 1 and Endpoint in 101 patients with COPD receiving twice-daily ADVAIR DISKUS 250/50, fluticasone propionate powder 250 mcg, salmeterol powder 50 mcg, or placebo. For most patients, the ability to increase cortisol production in response to stress, as assessed by short cosyntropin stimulation, remained intact with ADVAIR DISKUS 250/50. One (1) patient (3%) who received ADVAIR DISKUS 250/50 had an abnormal stimulated cortisol response (peak cortisol <14.5 mcg/dL assessed by high-performance liquid chromatography) after dosing, compared with 2 patients (9%) who received fluticasone propionate 250 mcg, 2 patients (7%) who received salmeterol 50 mcg, and 1 patient (4%) who received placebo following 24 weeks of treatment or early discontinuation from study.

After 36 weeks of dosing, serum cortisol concentrations in a subset of patients with COPD (n = 83) were 22% lower in patients receiving ADVAIR DISKUS 500/50 and 21% lower in patients receiving fluticasone propionate 500 mcg than in patients receiving placebo.

Other Fluticasone Propionate Products: Asthma: HPA Axis Effects: In clinical trials with fluticasone propionate inhalation powder using doses up to and including 250 mcg twice daily, occasional abnormal short cosyntropin tests (peak serum cortisol <18 mcg/dL assessed by radioimmunoassay) were noted both in patients receiving fluticasone propionate and in patients receiving placebo. The incidence of abnormal tests at 500 mcg twice daily was greater than placebo. In a 2-year study carried out with the DISKHALER® inhalation device in 64 patients with mild, persistent asthma (mean FEV₁ 91% of predicted) randomized to fluticasone propionate 500 mcg twice daily or placebo, no patient receiving fluticasone propionate had an abnormal response to 6-hour cosyntropin infusion (peak serum cortisol <18 mcg/dL). With a peak cortisol threshold of <35 mcg/dL, 1 patient receiving fluticasone propionate (4%) had an abnormal response at 1 year; repeat testing at 18 months and 2 years was normal. Another patient receiving fluticasone propionate (5%) had an abnormal response at 2 years. No patient on placebo had an abnormal response at 1 or 2 years.

Chronic Obstructive Pulmonary Disease: HPA Axis Effects: After 4 weeks of dosing, the steady-state fluticasone propionate pharmacokinetics and serum cortisol levels were described in a subset of patients with COPD (n = 86) randomized to twice-daily fluticasone propionate inhalation powder via the DISKUS 500 mcg, fluticasone propionate inhalation powder 250 mcg, or placebo.

Serial serum cortisol concentrations were measured across a 12-hour dosing interval. Serum cortisol concentrations following 250- and 500-mcg twice-daily dosing were 10% and 21% lower than placebo, respectively, indicating a dose-dependent increase in systemic exposure to fluticasone propionate.

Other Salmeterol Xinafoate Products: Asthma: Cardiovascular Effects: Inhaled salmeterol, like other beta-adrenergic agonist drugs, can produce dose-related cardiovascular effects and effects on blood glucose and/or serum potassium [see *Warnings and Precautions* (5.12, 5.18)]. The cardiovascular effects (heart rate, blood pressure) associated with salmeterol occur with similar frequency, and are of similar type and severity, as those noted following albuterol administration.

The effects of rising doses of salmeterol and standard inhaled doses of albuterol were studied in volunteers and in patients with asthma. Salmeterol doses up to 84 mcg administered as inhalation aerosol resulted in heart rate increases of 3 to 16 beats/min, about the same as albuterol dosed at 180 mcg by inhalation aerosol (4 to 10 beats/min). Adolescent and adult patients receiving 50-mcg doses of salmeterol inhalation powder (N = 60) underwent continuous electrocardiographic monitoring during two 12-hour periods after the first dose and after 1 month of therapy, and no clinically significant dysrhythmias were noted.

Concomitant Use of ADVAIR DISKUS With Other Respiratory Medications: Short-Acting Beta₂-Agonists: In clinical trials with patients with asthma, the mean daily need for albuterol by 166 adult and adolescent patients 12 years of age and older using ADVAIR DISKUS was approximately 1.3 inhalations/day, and ranged from 0 to 9 inhalations/day. Five percent (5%) of patients using ADVAIR DISKUS in these trials averaged 6 or more inhalations per day over the course of the 12-week trials. No increase in frequency of cardiovascular adverse reactions was observed among patients who averaged 6 or more inhalations per day.

In a COPD clinical trial, the mean daily need for albuterol for patients using ADVAIR DISKUS 250/50 was 4.1 inhalations/day. Twenty-six percent (26%) of patients using ADVAIR DISKUS 250/50 averaged 6 or more inhalations per day over the course of the 24-week trial. No increase in frequency of cardiovascular adverse reactions was observed among patients who averaged 6 or more inhalations of albuterol per day.

Methylxanthines: The concurrent use of intravenously or orally administered methylxanthines (e.g., aminophylline, theophylline) by adult and adolescent patients 12 years of age and older receiving ADVAIR DISKUS has not been completely evaluated. In clinical trials with patients with asthma, 39 patients receiving ADVAIR DISKUS 100/50, 250/50, or 500/50 twice daily concurrently with a theophylline product had adverse event rates similar to those in 304 patients receiving ADVAIR DISKUS without theophylline. Similar results were observed in patients receiving salmeterol 50 mcg plus fluticasone propionate 500 mcg twice daily concurrently with a theophylline product (n = 39) or without theophylline (n = 132).

In a COPD clinical trial, 17 patients receiving ADVAIR DISKUS 250/50 twice daily concurrently with a theophylline product had adverse event rates similar to those in 161 patients receiving ADVAIR DISKUS without theophylline. Based on the available data, the concomitant administration of methylxanthines with ADVAIR DISKUS did not alter the observed adverse event profile.

Fluticasone Propionate Nasal Spray: In adult and adolescent patients 12 years of age and older taking ADVAIR DISKUS in clinical trials, no difference in the profile of adverse events or HPA axis effects was noted between patients who were taking FLONASE® (fluticasone propionate) Nasal Spray, 50 mcg concurrently (n = 46) and those who were not (n = 130).

12.3 Pharmacokinetics

Absorption: Fluticasone Propionate: Healthy Subjects: Fluticasone propionate acts locally in the lung; therefore, plasma levels do not predict therapeutic effect. Studies using oral dosing of labeled and unlabeled drug have demonstrated that the oral systemic bioavailability of fluticasone propionate is negligible (<1%), primarily due to incomplete absorption and presystemic metabolism in the gut and liver. In contrast, the majority of the fluticasone propionate delivered to the lung is systemically absorbed.

Following administration of ADVAIR DISKUS to healthy adult subjects, peak plasma concentrations of fluticasone propionate were achieved in 1 to 2 hours. In a single-dose crossover study, a higher-than-recommended dose of ADVAIR DISKUS was administered to 14 healthy adult subjects. Two (2) inhalations of the following treatments were administered: ADVAIR DISKUS 500/50, fluticasone propionate powder 500 mcg and salmeterol powder 50 mcg given concurrently, and fluticasone propionate powder 500 mcg alone. Mean peak plasma concentrations of fluticasone propionate averaged 107, 94, and 120 pg/mL, respectively, indicating no significant changes in systemic exposures of fluticasone propionate.

In 15 healthy subjects, systemic exposure to fluticasone propionate from 4 inhalations of ADVAIR® HFA 230/21 (fluticasone propionate 230 mcg and salmeterol 21 mcg) Inhalation Aerosol (920/84 mcg) and 2 inhalations of ADVAIR DISKUS 500/50 (1,000/100 mcg) were similar between the 2 inhalers (i.e., 799 vs. 832 pg•hr/mL, respectively), but approximately half the systemic exposure from 4 inhalations of fluticasone propionate CFC inhalation aerosol 220 mcg (880 mcg, AUC = 1,543 pg•hr/mL). Similar results were observed for peak fluticasone propionate plasma concentrations (186 and 182 pg/mL from ADVAIR HFA and ADVAIR DISKUS, respectively, and 307 pg/mL from the fluticasone propionate CFC inhalation aerosol). Absolute bioavailability of fluticasone propionate was 5.3% and 5.5% following administration of ADVAIR HFA and ADVAIR DISKUS, respectively.

Asthma and COPD Patients: Peak steady-state fluticasone propionate plasma concentrations in adult patients with asthma (N = 11) ranged from undetectable to 266 pg/mL after a 500-mcg twice-daily dose of fluticasone propionate inhalation powder using the DISKUS device. The mean fluticasone propionate plasma concentration was 110 pg/mL.

Full pharmacokinetic profiles were obtained from 9 female and 16 male patients with asthma given fluticasone propionate inhalation powder 500 mcg twice daily using the DISKUS device and from 14 female and 43 male patients with COPD given 250 or 500 mcg twice daily. No overall differences in fluticasone propionate pharmacokinetics were observed.

Peak steady-state fluticasone propionate plasma concentrations in patients with COPD averaged 53 pg/mL (range, 19.3 to 159.3 pg/mL) after treatment with 250 mcg twice daily (N = 30) and 84 pg/mL (range, 24.3 to 197.1 pg/mL) after treatment with 500 mcg twice daily (N = 27) via the fluticasone propionate DISKUS device. In another study in patients with COPD, peak steady-state fluticasone propionate plasma concentrations averaged 115 pg/mL (range, 52.6 to 366.0 pg/mL) after treatment with 500 mcg twice daily via the fluticasone propionate DISKUS device (N = 15) and 105 pg/mL (range, 22.5 to 299.0 pg/mL) via ADVAIR DISKUS (N = 24).

Salmeterol Xinafoate: Healthy Subjects: Salmeterol xinafoate, an ionic salt, dissociates in solution so that the salmeterol and 1-hydroxy-2-naphthoic acid (xinafoate) moieties are absorbed, distributed, metabolized, and eliminated independently. Salmeterol acts locally in the lung; therefore, plasma levels do not predict therapeutic effect.

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)

Following administration of ADVAIR DISKUS to healthy adult subjects, peak plasma concentrations of salmeterol were achieved in about 5 minutes.

In 15 healthy subjects receiving ADVAIR HFA 230/21 Inhalation Aerosol (920/84 mcg) and ADVAIR DISKUS 500/50 (1,000/100 mcg), systemic exposure to salmeterol was higher (317 vs. 169 pg•hr/mL) and peak salmeterol concentrations were lower (196 vs. 223 pg/mL) following ADVAIR HFA compared with ADVAIR DISKUS, although pharmacodynamic results were comparable.

Asthma Patients: Because of the small therapeutic dose, systemic levels of salmeterol are low or undetectable after inhalation of recommended doses (50 mcg of salmeterol inhalation powder twice daily). Following chronic administration of an inhaled dose of 50 mcg of salmeterol inhalation powder twice daily, salmeterol was detected in plasma within 5 to 45 minutes in 7 patients with asthma; plasma concentrations were very low, with mean peak concentrations of 167 pg/mL at 20 minutes and no accumulation with repeated doses.

Distribution: Fluticasone Propionate: Following intravenous administration, the initial disposition phase for fluticasone propionate was rapid and consistent with its high lipid solubility and tissue binding. The volume of distribution averaged 4.2 L/kg.

The percentage of fluticasone propionate bound to human plasma proteins averages 91%. Fluticasone propionate is weakly and reversibly bound to erythrocytes and is not significantly bound to human transferrin.

Salmeterol: The percentage of salmeterol bound to human plasma proteins averages 96% in vitro over the concentration range of 8 to 7,722 ng of salmeterol base per milliliter, much higher concentrations than those achieved following therapeutic doses of salmeterol.

Metabolism: Fluticasone Propionate: The total clearance of fluticasone propionate is high (average, 1,093 mL/min), with renal clearance accounting for less than 0.02% of the total. The only circulating metabolite detected in man is the 17 β -carboxylic acid derivative of fluticasone propionate, which is formed through the CYP 3A4 pathway. This metabolite had less affinity (approximately 1/2,000) than the parent drug for the glucocorticoid receptor of human lung cytosol in vitro and negligible pharmacological activity in animal studies. Other metabolites detected in vitro using cultured human hepatoma cells have not been detected in man.

Salmeterol: Salmeterol base is extensively metabolized by hydroxylation, with subsequent elimination predominantly in the feces. No significant amount of unchanged salmeterol base was detected in either urine or feces.

An in vitro study using human liver microsomes showed that salmeterol is extensively metabolized to α -hydroxysalmeterol (aliphatic oxidation) by CYP 3A4. Ketoconazole, a strong inhibitor of CYP 3A4, essentially completely inhibited the formation of α -hydroxysalmeterol in vitro.

Elimination: Fluticasone Propionate: Following intravenous dosing, fluticasone propionate showed polyexponential kinetics and had a terminal elimination half-life of approximately 7.8 hours. Less than 5% of a radiolabeled oral dose was excreted in the urine as metabolites, with the remainder excreted in the feces as parent drug and metabolites. Terminal half-life estimates of fluticasone propionate for ADVAIR HFA, ADVAIR DISKUS, and fluticasone propionate CFC inhalation aerosol were similar and averaged 5.6 hours.

Salmeterol: In 2 healthy adult subjects who received 1 mg of radiolabeled salmeterol (as salmeterol xinafoate) orally, approximately 25% and 60% of the radiolabeled salmeterol was eliminated in urine and feces, respectively, over a period of 7 days. The terminal elimination half-life was about 5.5 hours (1 volunteer only).

The xinafoate moiety has no apparent pharmacologic activity. The xinafoate moiety is highly protein bound (>99%) and has a long elimination half-life of 11 days. No terminal half-life estimates were calculated for salmeterol following administration of ADVAIR DISKUS.

Special Populations: A population pharmacokinetic analysis was performed for fluticasone propionate and salmeterol utilizing data from 9 controlled clinical trials that included 350 patients with asthma aged 4 to 77 years who received treatment with ADVAIR DISKUS, the combination of HFA-propelled fluticasone propionate and salmeterol inhalation aerosol (ADVAIR HFA), fluticasone propionate inhalation powder (FLOVENT DISKUS), HFA-propelled fluticasone propionate inhalation aerosol (FLOVENT® HFA), or CFC-propelled fluticasone propionate inhalation aerosol. The population pharmacokinetic analyses for fluticasone propionate and salmeterol showed no clinically relevant effects of age, gender, race, body weight, body mass index, or percent of predicted FEV₁ on apparent clearance and apparent volume of distribution.

Age: When the population pharmacokinetic analysis for fluticasone propionate was divided into subgroups based on fluticasone propionate strength, formulation, and age (adolescents/adults and children), there were some differences in fluticasone propionate exposure. Higher fluticasone propionate exposure from ADVAIR DISKUS 100/50 compared with FLOVENT DISKUS 100 mcg was observed in adolescents and adults (ratio 1.52 [90% CI: 1.08, 2.13]). However, in clinical studies of up to 12 weeks' duration comparing ADVAIR DISKUS 100/50 and FLOVENT DISKUS 100 mcg in adolescents and adults, no differences in systemic effects of corticosteroid treatment (e.g., HPA axis effects) were observed. Similar fluticasone propionate exposure was observed from ADVAIR DISKUS 500/50 and FLOVENT DISKUS 500 mcg (ratio 0.83 [90% CI: 0.65, 1.07]) in adolescents and adults.

Steady-state systemic exposure to salmeterol when delivered as ADVAIR DISKUS 100/50, ADVAIR DISKUS 250/50, or ADVAIR HFA 115/21 (fluticasone propionate 115 mcg and salmeterol 21 mcg) Inhalation Aerosol was evaluated in 127 patients aged 4 to 57 years. The geometric mean AUC was 325 pg•hr/mL [90% CI: 309, 341] in adolescents and adults.

The population pharmacokinetic analysis included 160 patients with asthma aged 4 to 11 years who received ADVAIR DISKUS 100/50 or FLOVENT DISKUS 100 mcg. Higher fluticasone propionate exposure (AUC) was observed in children from ADVAIR DISKUS 100/50 compared with FLOVENT DISKUS 100 mcg (ratio 1.20 [90% CI: 1.06, 1.37]). Higher fluticasone propionate exposure (AUC) from ADVAIR DISKUS 100/50 was observed in children compared with adolescents and adults (ratio 1.63 [90% CI: 1.35, 1.96]). However, in clinical studies of up to 12 weeks' duration comparing ADVAIR DISKUS 100/50 and FLOVENT DISKUS 100 mcg in both adolescents and adults and in children, no differences in systemic effects of corticosteroid treatment (e.g., HPA axis effects) were observed.

Exposure to salmeterol was higher in children compared with adolescents and adults who received ADVAIR DISKUS 100/50 (ratio 1.23 [90% CI: 1.10, 1.38]). However, in clinical studies of up to 12 weeks' duration with ADVAIR DISKUS 100/50 in both adolescents and adults and in children, no differences in systemic effects of beta₂-agonist treatment (e.g., cardiovascular effects, tremor) were observed.

Gender: The population pharmacokinetic analysis involved 202 males and 148 females with asthma who received fluticasone propionate alone or in combination with salmeterol and showed no gender differences for fluticasone propionate pharmacokinetics.

The population pharmacokinetic analysis involved 76 males and 51 females with asthma who

received salmeterol in combination with fluticasone propionate and showed no gender differences for salmeterol pharmacokinetics.

Hepatic and Renal Impairment: Formal pharmacokinetic studies using ADVAIR DISKUS have not been conducted in patients with hepatic or renal impairment. However, since both fluticasone propionate and salmeterol are predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of fluticasone propionate and salmeterol in plasma. Therefore, patients with hepatic disease should be closely monitored.

Drug Interactions: In the repeat- and single-dose studies, there was no evidence of significant drug interaction in systemic exposure between fluticasone propionate and salmeterol when given as ADVAIR DISKUS. The population pharmacokinetic analysis from 9 controlled clinical trials in 350 patients with asthma showed no significant effects on fluticasone propionate or salmeterol pharmacokinetics following co-administration with beta₂-agonists, corticosteroids, antihistamines, or theophyllines.

Inhibitors of Cytochrome P450 3A4: Ritonavir: Fluticasone Propionate: Fluticasone propionate is a substrate of CYP 3A4. Coadministration of fluticasone propionate and the strong CYP 3A4 inhibitor ritonavir is not recommended based upon a multiple-dose, crossover drug interaction study in 18 healthy subjects. Fluticasone propionate aqueous nasal spray (200 mcg once daily) was coadministered for 7 days with ritonavir (100 mg twice daily). Plasma fluticasone propionate concentrations following fluticasone propionate aqueous nasal spray alone were undetectable (<10 pg/mL) in most subjects, and when concentrations were detectable peak levels (C_{max}) averaged 11.9 pg/mL (range, 10.8 to 14.1 pg/mL) and AUC₍₀₋₁₂₎ averaged 8.43 pg•hr/mL (range, 4.2 to 18.8 pg•hr/mL). Fluticasone propionate C_{max} and AUC₍₀₋₁₂₎ increased to 318 pg/mL (range, 110 to 648 pg/mL) and 3,102.6 pg•hr/mL (range, 1,207.1 to 5,662.0 pg•hr/mL), respectively, after coadministration of ritonavir with fluticasone propionate aqueous nasal spray. This significant increase in plasma fluticasone propionate exposure resulted in a significant decrease (86%) in serum cortisol AUC.

Ketoconazole: Fluticasone Propionate: In a placebo-controlled, crossover study in 8 healthy adult volunteers, coadministration of a single dose of orally inhaled fluticasone propionate (1,000 mcg) with multiple doses of ketoconazole (200 mg) to steady state resulted in increased plasma fluticasone propionate exposure, a reduction in plasma cortisol AUC, and no effect on urinary excretion of cortisol.

Salmeterol: In a placebo-controlled, crossover drug interaction study in 20 healthy male and female subjects, coadministration of salmeterol (50 mcg twice daily) and the strong CYP 3A4 inhibitor ketoconazole (400 mg once daily) for 7 days resulted in a significant increase in plasma salmeterol exposure as determined by a 16-fold increase in AUC (ratio with and without ketoconazole 15.76 [90% CI: 10.66, 23.31]) mainly due to increased bioavailability of the swallowed portion of the dose. Peak plasma salmeterol concentrations were increased by 1.4-fold [90% CI: 1.23, 1.68]. Three (3) out of 20 subjects (15%) were withdrawn from salmeterol and ketoconazole coadministration due to beta-agonist-mediated systemic effects (2 with QTc prolongation and 1 with palpitations and sinus tachycardia). Coadministration of salmeterol and ketoconazole did not result in a clinically significant effect on mean heart rate, mean blood potassium, or mean blood glucose. Although there was no statistical effect on the mean QTc, coadministration of salmeterol and ketoconazole was associated with more frequent increases in QTc duration compared with salmeterol and placebo administration.

Erythromycin: Fluticasone Propionate: In a multiple-dose drug interaction study, coadministration of orally inhaled fluticasone propionate (500 mcg twice daily) and erythromycin (333 mg 3 times daily) did not affect fluticasone propionate pharmacokinetics.

Salmeterol: In a repeat-dose study in 13 healthy subjects, concomitant administration of erythromycin (a moderate CYP 3A4 inhibitor) and salmeterol inhalation aerosol resulted in a 40% increase in salmeterol C_{max} at steady state (ratio with and without erythromycin 1.4 [90% CI: 0.96, 2.03], p = 0.12), a 3.6-beat/min increase in heart rate [95% CI: 0.19, 7.03], p < 0.04), a 5.8-msec increase in QTc interval [95% CI: -6.14, 17.77], p = 0.34), and no change in plasma potassium.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Fluticasone Propionate: Fluticasone propionate demonstrated no tumorigenic potential in mice at oral doses up to 1,000 mcg/kg (approximately 4 and 10 times the MRHD for adults and children, respectively, on a mg/m² basis) for 78 weeks or in rats at inhalation doses up to 57 mcg/kg (less than and approximately equivalent to the MRHD for adults and children, respectively, on a mg/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 in vivo mouse micronucleus test.

No evidence of impairment of fertility was observed in reproductive studies conducted in rats at subcutaneous doses up to 50 mcg/kg (less than the MRHD on a mg/m² basis). Prostate weight was significantly reduced.

Salmeterol: In an 18-month carcinogenicity study in CD-mice, salmeterol at oral doses of 1.4 mg/kg and above (approximately 20 times the MRHD for adults and children based on comparison of the plasma AUCs) caused a dose-related increase in the incidence of smooth muscle hyperplasia, cystic glandular hyperplasia, leiomyomas of the uterus, and cysts in the ovaries. No tumors were seen at 0.2 mg/kg (approximately 3 times the MRHD for adults and children based on comparison of the AUCs).

In a 24-month oral and inhalation carcinogenicity study in Sprague Dawley rats, salmeterol caused a dose-related increase in the incidence of mesovarian leiomyomas and ovarian cysts at doses of 0.68 mg/kg and above (approximately 55 and 25 times the MRHD for adults and children, respectively, on a mg/m² basis). No tumors were seen at 0.21 mg/kg (approximately 15 and 8 times the MRHD for adults and children, respectively, on a mg/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 rats treated with salmeterol at oral doses up to 2 mg/kg (approximately 160 times the MRHD for adults on a mg/m² basis).

13.2 Animal Toxicology and/or Pharmacology

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

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)

Reproductive Toxicology Studies: *ADVAIR DISKUS:* In mice, combining 150 mcg/kg subcutaneously of fluticasone propionate (less than the MRHD on a mg/m² basis) with 10 mg/kg orally of salmeterol (approximately 410 times the MRHD on a mg/m² basis) produced cleft palate, fetal death, increased implantation loss, and delayed ossification. No such effects were observed at combination subcutaneous doses up to 40 mcg/kg subcutaneously of fluticasone propionate (less than the MRHD on a mg/m² basis) and up to 1.4 mg/kg orally doses of salmeterol (approximately 55 times the MRHD on a mg/m² basis).

In rats, combining 100 mcg/kg subcutaneously of fluticasone propionate (equivalent to the MRHD on a mg/m² basis) and 10 mg/kg orally of salmeterol (approximately 810 times the MRHD on a mg/m² basis) produced decreased fetal weight, umbilical hernia, delayed ossification, and changes in the occipital bone. No such effects were observed at combination doses up to 30 mcg/kg subcutaneously of fluticasone propionate (less than the MRHD on a mg/m² basis) and up to 1 mg/kg orally of salmeterol (approximately 80 times the MRHD on a mg/m² basis).

Fluticasone Propionate: Subcutaneous studies in the mouse and rat at 45 and 100 mcg/kg (less than and equivalent to the MRHD on a mg/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 MRHD on a mg/m² basis). However, no teratogenic effects were reported at oral doses up to 300 mcg/kg (approximately 5 times the MRHD on a mg/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* (12.3)].

Fluticasone propionate crossed the placenta following subcutaneous administration to mice and rats and oral administration to rabbits.

Salmeterol: No teratogenic effects occurred in rats at oral doses up to 2 mg/kg (approximately 160 times the MRHD on a mg/m² basis).

In Dutch rabbits administered oral doses of 1 mg/kg and above (approximately 50 times and above the MRHD based on comparison of the AUCs), salmeterol exhibited fetal toxic effects characteristically resulting from beta-adrenoceptor stimulation. These included precocious eyelid openings, cleft palate, sternalbone fusion, limb and paw flexures, and delayed ossification of the frontal cranial bones. No such effects occurred at an oral dose of 0.6 mg/kg (approximately 20 times the MRHD based on comparison of the AUCs). New Zealand White rabbits were less sensitive since only delayed ossification of the frontal bones was seen at an oral dose of 10 mg/kg (approximately 1,600 times the MRHD on a mg/m² basis).

Salmeterol crossed the placenta following oral administration to mice and rats.

14 CLINICAL STUDIES

14.1 Asthma

Adult and Adolescent Patients 12 Years of Age and Older: In clinical trials comparing ADVAIR DISKUS with its individual components, improvements in most efficacy endpoints were greater with ADVAIR DISKUS than with the use of either fluticasone propionate or salmeterol alone. In addition, clinical trials showed similar results between ADVAIR DISKUS and the concurrent use of fluticasone propionate plus salmeterol at corresponding doses from separate inhalers.

Studies Comparing ADVAIR DISKUS to Fluticasone Propionate Alone or Salmeterol Alone: Three (3) double-blind, parallel-group clinical trials were conducted with ADVAIR DISKUS in 1,208 adolescent and adult patients (≥12 years, baseline FEV₁ 63% to 72% of predicted normal) with asthma that was not optimally controlled on their current therapy. All treatments were inhalation powders given as 1 inhalation from the DISKUS device twice daily, and other maintenance therapies were discontinued.

Study 1: Clinical Trial With ADVAIR DISKUS 100/50: This placebo-controlled, 12-week, US study compared ADVAIR DISKUS 100/50 with its individual components, fluticasone propionate 100 mcg and salmeterol 50 mcg. The study was stratified according to baseline asthma maintenance therapy; patients were using either inhaled corticosteroids (N = 250) (daily doses of beclomethasone dipropionate 252 to 420 mcg; flunisolide 1,000 mcg; fluticasone propionate inhalation aerosol 176 mcg; or triamcinolone acetonide 600 to 1,000 mcg) or salmeterol (N = 106). Baseline FEV₁ measurements were similar across treatments: ADVAIR DISKUS 100/50, 2.17 L; fluticasone propionate 100 mcg, 2.11 L; salmeterol, 2.13 L; and placebo, 2.15 L.

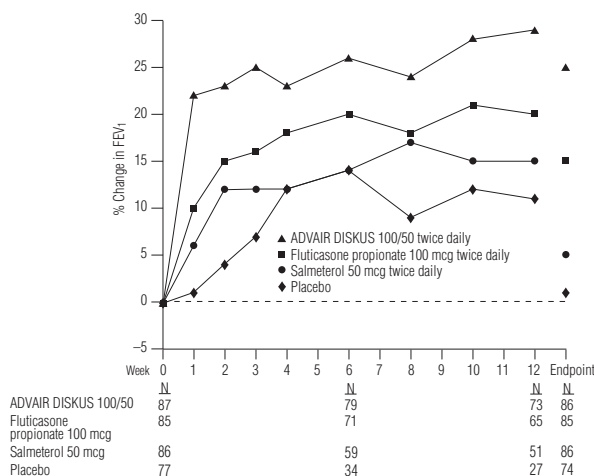
Predefined withdrawal criteria for lack of efficacy, an indicator of worsening asthma, were utilized for this placebo-controlled study. Worsening asthma was defined as a clinically important decrease in FEV₁ or PEF, increase in use of VENTOLIN® (albuterol, USP) Inhalation Aerosol, increase in night awakenings due to asthma, emergency intervention or hospitalization due to asthma, or requirement for asthma medication not allowed by the protocol. As shown in Table 4, statistically significantly fewer patients receiving ADVAIR DISKUS 100/50 were withdrawn due to worsening asthma compared with fluticasone propionate, salmeterol, and placebo.

Table 4. Percent of Patients Withdrawn Due to Worsening Asthma in Patients Previously Treated With Either Inhaled Corticosteroids or Salmeterol (Study 1)

ADVAIR DISKUS 100/50 (N = 87)	Fluticasone Propionate 100 mcg (N = 85)	Salmeterol 50 mcg (N = 86)	Placebo (N = 77)
3%	11%	35%	49%

The FEV₁ results are displayed in Figure 2. Because this trial used predetermined criteria for worsening asthma, which caused more patients in the placebo group to be withdrawn, FEV₁ results at Endpoint (last available FEV₁ result) are also provided. Patients receiving ADVAIR DISKUS 100/50 had significantly greater improvements in FEV₁ (0.51 L, 25%) compared with fluticasone propionate 100 mcg (0.28 L, 15%), salmeterol (0.11 L, 5%), and placebo (0.01 L, 1%). These improvements in FEV₁ with ADVAIR DISKUS were achieved regardless of baseline asthma maintenance therapy (inhaled corticosteroids or salmeterol).

Figure 2. Mean Percent Change From Baseline in FEV₁ in Patients With Asthma Previously Treated With Either Inhaled Corticosteroids or Salmeterol (Study 1)



The effect of ADVAIR DISKUS 100/50 on morning and evening PEF endpoints is shown in Table 5.

Table 5. Peak Expiratory Flow Results for Patients With Asthma Previously Treated With Either Inhaled Corticosteroids or Salmeterol (Study 1)

Efficacy Variable*	ADVAIR DISKUS 100/50 (N = 87)	Fluticasone Propionate 100 mcg (N = 85)	Salmeterol 50 mcg (N = 86)	Placebo (N = 77)
AM PEF (L/min)				
Baseline	393	374	369	382
Change from baseline	53	17	-2	-24
PM PEF (L/min)				
Baseline	418	390	396	398
Change from baseline	35	18	-7	-13

*Change from baseline = change from baseline at Endpoint (last available data).

The subjective impact of asthma on patients' perception of health was evaluated through use of an instrument called the Asthma Quality of Life Questionnaire (AQLQ) (based on a 7-point scale where 1 = maximum impairment and 7 = none). Patients receiving ADVAIR DISKUS 100/50 had clinically meaningful improvements in overall asthma-specific quality of life as defined by a difference between groups of ≥0.5 points in change from baseline AQLQ scores (difference in AQLQ score of 1.25 compared with placebo).

Study 2: Clinical Trial With ADVAIR DISKUS 250/50: This placebo-controlled, 12-week, US study compared ADVAIR DISKUS 250/50 with its individual components, fluticasone propionate 250 mcg and salmeterol 50 mcg, in 349 patients with asthma using inhaled corticosteroids (daily doses of beclomethasone dipropionate 462 to 672 mcg; flunisolide 1,250 to 2,000 mcg; fluticasone propionate inhalation aerosol 440 mcg; or triamcinolone acetonide 1,100 to 1,600 mcg). Baseline FEV₁ measurements were similar across treatments: ADVAIR DISKUS 250/50, 2.23 L; fluticasone propionate 250 mcg, 2.12 L; salmeterol, 2.20 L; and placebo, 2.19 L.

Efficacy results in this study were similar to those observed in Study 1. Patients receiving ADVAIR DISKUS 250/50 had significantly greater improvements in FEV₁ (0.48 L, 23%) compared with fluticasone propionate 250 mcg (0.25 L, 13%), salmeterol (0.05 L, 4%), and placebo (decrease of 0.11 L, decrease of 5%). Statistically significantly fewer patients receiving ADVAIR DISKUS 250/50 were withdrawn from this study for worsening asthma (4%) compared with fluticasone propionate (22%), salmeterol (38%), and placebo (62%). In addition, ADVAIR DISKUS 250/50 was superior to fluticasone propionate, salmeterol, and placebo for improvements in morning and evening PEF. Patients receiving ADVAIR DISKUS 250/50 also had clinically meaningful improvements in overall asthma-specific quality of life as described in Study 1 (difference in AQLQ score of 1.29 compared with placebo).

Study 3: Clinical Trial With ADVAIR DISKUS 500/50: This 28-week, non-US study compared ADVAIR DISKUS 500/50 with fluticasone propionate 500 mcg alone and concurrent therapy (salmeterol 50 mcg plus fluticasone propionate 500 mcg administered from separate inhalers) twice daily in 503 patients with asthma using inhaled corticosteroids (daily doses of beclomethasone dipropionate 1,260 to 1,680 mcg; budesonide 1,500 to 2,000 mcg; flunisolide 1,500 to 2,000 mcg; or fluticasone propionate inhalation aerosol 660 to 880 mcg [750 to 1,000 mcg inhalation powder]). The primary efficacy parameter, morning PEF, was collected daily for the first 12 weeks of the study. The primary purpose of weeks 13 to 28 was to collect safety data.

Baseline PEF measurements were similar across treatments: ADVAIR DISKUS 500/50, 359 L/min; fluticasone propionate 500 mcg, 351 L/min; and concurrent therapy, 345 L/min. Morning PEF improved significantly with ADVAIR DISKUS 500/50 compared with fluticasone propionate 500 mcg over the 12-week treatment period. Improvements in morning PEF observed with ADVAIR DISKUS 500/50 were similar to improvements observed with concurrent therapy.

Onset of Action and Progression of Improvement in Asthma Control: The onset of action and progression of improvement in asthma control were evaluated in the 2 placebo-controlled US trials. Following the first dose, the median time to onset of clinically significant bronchodilation (≥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

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)

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)

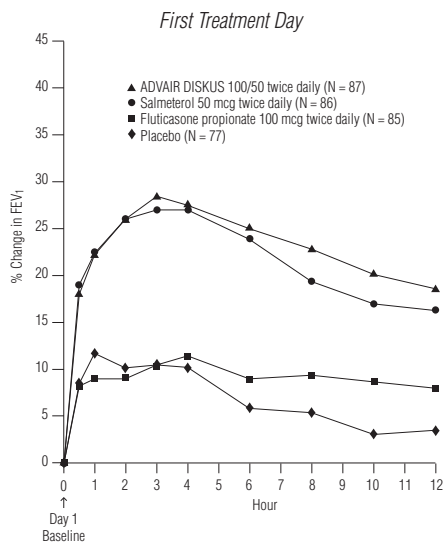
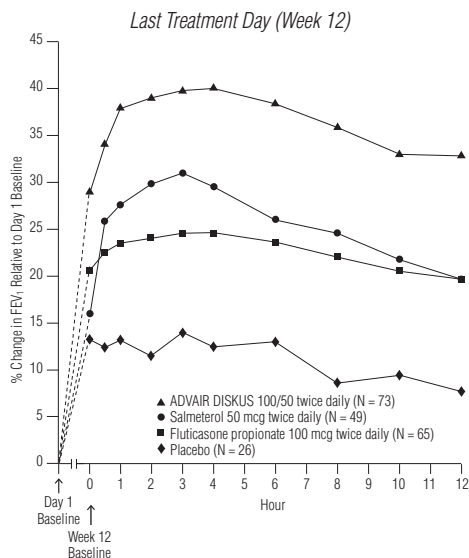


Figure 4. Percent Change in Serial 12-hour FEV₁ in Patients With Asthma Previously Using Either Inhaled Corticosteroids or Salmeterol (Study 1)



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.

14.2 Chronic Obstructive Pulmonary Disease

The efficacy of ADVAIR DISKUS 250/50 and ADVAIR DISKUS 500/50 in the treatment of patients with COPD was evaluated in 6 randomized, double-blind, parallel-group clinical trials in adult patients 40 years of age and older. These trials were primarily designed to evaluate the efficacy of ADVAIR DISKUS on lung function (3 trials), exacerbations (2 trials), and survival (1 trial).

Lung Function: Two of the 3 clinical trials primarily designed to evaluate the efficacy of ADVAIR DISKUS on lung function were conducted in 1,414 patients with COPD associated with chronic bronchitis. In these 2 trials, all the patients had a history of cough productive of sputum that was not attributable to another disease process on most days for at least 3 months of the year for at least 2 years. The trials were randomized, double-blind, parallel-group, 24-week treatment duration. One trial evaluated the efficacy of ADVAIR DISKUS 250/50 compared with its components fluticasone propionate 250 mcg and salmeterol 50 mcg and to placebo, and the other trial evaluated the efficacy of ADVAIR DISKUS 500/50 compared with its components fluticasone propionate 500 mcg salmeterol 50 mcg and to placebo. Study treatments were inhalation powders given as 1 inhalation from the DISKUS device twice daily. Maintenance COPD therapies were discontinued, with the exception of theophylline. The patients had a mean pre-bronchodilator FEV₁ of 41% and 20% reversibility at study entry. Percent reversibility was calculated as 100 times (FEV₁ post-albuterol minus FEV₁ pre-albuterol)/FEV₁ pre-albuterol.

Improvements in lung function (as defined by predose and postdose FEV₁) were significantly greater with ADVAIR DISKUS than with fluticasone propionate, salmeterol, or placebo. The improvement in lung function with ADVAIR DISKUS 500/50 was similar to the improvement seen with ADVAIR DISKUS 250/50.

Figures 5 and 6 display predose and 2-hour postdose, respectively, FEV₁ results for the study with ADVAIR DISKUS 250/50. To account for patient withdrawals during the study, FEV₁ at Endpoint (last evaluable FEV₁) was evaluated. Patients receiving ADVAIR DISKUS 250/50 had significantly greater improvements in predose FEV₁ at Endpoint (165 mL, 17%) compared with salmeterol 50 mcg (91 mL, 9%) and placebo (1 mL, 1%), demonstrating the contribution of fluticasone propionate to the improvement in lung function with ADVAIR DISKUS (Figure 5). Patients receiving ADVAIR DISKUS 250/50 had significantly greater improvements in postdose FEV₁ at Endpoint (281 mL, 27%) compared with fluticasone propionate 250 mcg (147 mL, 14%) and placebo (58 mL, 6%), demonstrating the contribution of salmeterol to the improvement in lung function with ADVAIR DISKUS (Figure 6).

Figure 5. Predose FEV₁: Mean Percent Change From Baseline in Patients With Chronic Obstructive Pulmonary Disease

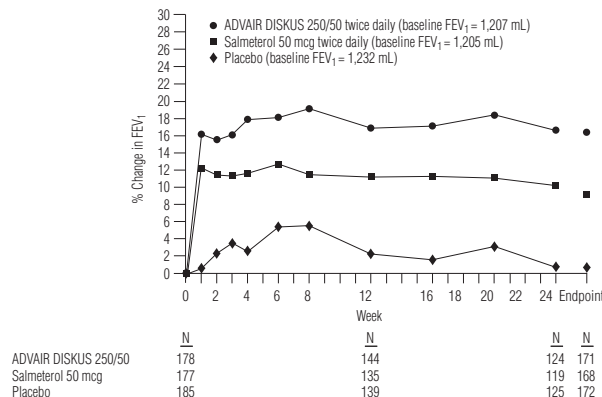
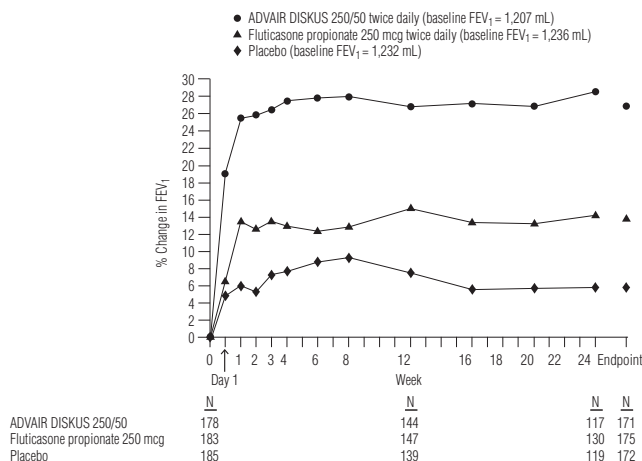


Figure 6. Two-Hour Postdose FEV₁: Mean Percent Changes From Baseline Over Time in Patients With Chronic Obstructive Pulmonary Disease



The third trial was a 1-year study that evaluated ADVAIR DISKUS 500/50, fluticasone propionate 500 mcg, salmeterol 50 mcg, and placebo in 1,465 patients. The patients had an established history of COPD and exacerbations, a pre-bronchodilator FEV₁ <70% of predicted at study entry, and 8.3% reversibility. The primary endpoint was the comparison of pre-bronchodilator FEV₁ in the groups receiving ADVAIR DISKUS 500/50 or placebo. Patients treated with ADVAIR DISKUS 500/50 had greater improvements in FEV₁ (113 mL, 10%) compared with fluticasone propionate 500 mcg (7 mL, 2%), salmeterol (15 mL, 2%), and placebo (-60 mL, -3%).

Exacerbations: Two studies were primarily designed to evaluate the effect of ADVAIR DISKUS 250/50 on exacerbations. In these 2 studies, exacerbations were defined as worsening of 2 or more major symptoms (dyspnea, sputum volume, and sputum purulence) or worsening of any 1 major symptom together with any 1 of the following minor symptoms: sore throat, colds (nasal discharge and/or nasal congestion), fever without other cause, and increased cough or wheeze for at least 2 consecutive days. COPD exacerbations were considered of moderate severity if treatment with sys-

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)

temic corticosteroids and/or antibiotics was required and were considered severe if hospitalization was required.

Exacerbations were also evaluated as a secondary outcome in the 1- and 3-year trials with ADVAIR DISKUS 500/50. There was not a symptomatic definition of exacerbation in these 2 trials. Exacerbations were defined in terms of severity requiring treatment with antibiotics and/or systemic corticosteroids (moderately severe) or requiring hospitalization (severe).

The 2 exacerbation trials with ADVAIR DISKUS 250/50 were identical studies designed to evaluate the effect of ADVAIR DISKUS 250/50 and salmeterol 50 mcg, each given twice daily, on exacerbations of COPD over a 12-month period. A total of 1,579 patients had an established history of COPD (but no other significant respiratory disorders). Patients had a pre-bronchodilator FEV₁ of 33% of predicted, a mean reversibility of 23% at baseline, and a history of ≥1 COPD exacerbation in the previous year that was moderate or severe. All patients were treated with ADVAIR DISKUS 250/50 twice daily during a 4-week run-in period prior to being assigned study treatment with twice-daily ADVAIR DISKUS 250/50 or salmeterol 50 mcg. In both studies, treatment with ADVAIR DISKUS 250/50 resulted in a significantly lower annual rate of moderate/severe COPD exacerbations compared with salmeterol (30.5% reduction [95% CI: 17.0, 41.8], p<0.001) in the first study and (30.4% reduction [95% CI: 16.9, 41.7], p<0.001) in the second study. Patients treated with ADVAIR DISKUS 250/50 also had a significantly lower annual rate of exacerbations requiring treatment with oral corticosteroids compared with patients treated with salmeterol (39.7% reduction [95% CI: 22.8, 52.9], p<0.001) in the first study, and (34.3% reduction [95% CI: 18.6, 47.0], p<0.001) in the second study. Secondary endpoints including pulmonary function and symptom scores improved more in patients treated with ADVAIR DISKUS 250/50 than with salmeterol 50 mcg in both studies.

Exacerbations were evaluated in the 1- and the 3-year trials with ADVAIR DISKUS 500/50 as 1 of the secondary efficacy endpoints. In the 1-year trial, the group receiving ADVAIR DISKUS 500/50 had a significantly lower rate of moderate and severe exacerbations compared with placebo (25.4% reduction compared with placebo [95% CI: 13.5, 35.7]) but not when compared with its components (7.5% reduction compared with fluticasone propionate [95% CI: -7.3, 20.3] and 7% reduction compared with salmeterol [95% CI: -8.0, 19.9]). In the 3-year trial, the group receiving ADVAIR DISKUS 500/50 had a significantly lower rate of moderate and severe exacerbations compared with each of the other treatment groups (25.1% reduction compared with placebo [95% CI: 18.6, 31.1], 9.0% reduction compared with fluticasone propionate [95% CI: 1.2, 16.2], and 12.2% reduction compared with salmeterol [95% CI: 4.6, 19.2]).

There were no studies conducted to directly compare the efficacy of ADVAIR DISKUS 250/50 with ADVAIR DISKUS 500/50 on exacerbations. Across studies, the reduction in exacerbations seen with ADVAIR DISKUS 500/50 was not greater than the reduction in exacerbations seen with ADVAIR DISKUS 250/50.

Survival: A 3-year multicenter, international study evaluated the efficacy of ADVAIR DISKUS 500/50 compared with fluticasone propionate 500 mcg, salmeterol 50 mcg, and placebo on survival in 6,112 patients with COPD. During the study patients were permitted usual COPD therapy with the exception of other inhaled corticosteroids and long-acting bronchodilators. The patients were 40 to 80 years of age with an established history of COPD, a pre-bronchodilator FEV₁ <60% of predicted at study entry, and <10% of predicted reversibility. Each patient who withdrew from double-blind treatment for any reason was followed for the full 3-year study period to determine survival status. The primary efficacy endpoint was all-cause mortality. Survival with ADVAIR DISKUS 500/50 was not significantly improved compared with placebo, or the individual components (all-cause mortality rate 12.6% ADVAIR DISKUS vs. 15.2% placebo). The rates for all-cause mortality were 13.5% and 16.0% in the groups treated with salmeterol 50 mcg and fluticasone propionate 500 mcg, respectively. Secondary outcomes, including pulmonary function (post-bronchodilator FEV₁), improved with ADVAIR DISKUS 500/50, salmeterol, and fluticasone propionate 500/50 compared with placebo.

16 HOW SUPPLIED/STORAGE AND HANDLING

ADVAIR DISKUS 100/50 is supplied as a disposable purple device containing 60 blisters. The DISKUS inhalation device is packaged within a purple, plastic-coated, moisture-protective foil pouch (NDC 0173-0695-00). ADVAIR DISKUS 100/50 is also supplied in an institutional pack of 1 disposable purple device containing 14 blisters. The DISKUS inhalation device is packaged within a purple, plastic-coated, moisture-protective foil pouch (NDC 0173-0695-04).

ADVAIR DISKUS 250/50 is supplied as a disposable purple device containing 60 blisters. The DISKUS inhalation device is packaged within a purple, plastic-coated, moisture-protective foil pouch (NDC 0173-0696-00). ADVAIR DISKUS 250/50 is also supplied in an institutional pack of 1 disposable purple device containing 14 blisters. The DISKUS inhalation device is packaged within a purple, plastic-coated, moisture-protective foil pouch (NDC 0173-0696-04).

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Store at controlled room temperature (see USP), 20° to 25°C (68° to 77°F), in a dry place away from direct heat or sunlight. Keep out of reach of children. The DISKUS inhalation device is not reusable. The device should be discarded 1 month after removal from the moisture-protective foil overwrap pouch or after all blisters have been used (when the dose indicator reads “0”), whichever comes first. Do not attempt to take the device apart.

17 PATIENT COUNSELING INFORMATION

See Medication Guide (17.6).

17.1 Asthma-Related Death

Patients with asthma should be informed that salmeterol, one of the active ingredients in ADVAIR DISKUS, may increase the risk of asthma-related death. They should also be informed that data are not adequate to determine whether the concurrent use of inhaled corticosteroids, such as fluticasone propionate, the other component of ADVAIR DISKUS, or other asthma-controller therapy modifies this risk.

17.2 Not for Acute Symptoms

ADVAIR DISKUS is not meant to relieve acute asthma symptoms or exacerbations of COPD and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting beta₂-agonist such as albuterol. (The physician should provide the patient with such medication and instruct the patient in how it should be used.)

Patients should be instructed to notify their physician immediately if they experience any of the following:

- Decreasing effectiveness of inhaled, short-acting beta₂-agonists
- Need for more inhalations than usual of inhaled, short-acting beta₂-agonists
- Significant decrease in lung function as outlined by the physician

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

17.3 Do Not Use Additional Long-Acting Beta₂-Agonists

When patients are prescribed ADVAIR DISKUS, other long-acting beta₂-agonists for asthma and COPD should not be used.

17.4 Risks Associated With Corticosteroid Therapy

Local Effects: Patients should be advised that localized infections with *Candida albicans* occurred in the mouth and pharynx in some patients. If oropharyngeal candidiasis develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while still continuing therapy with ADVAIR DISKUS, but at times therapy with ADVAIR DISKUS may need to be temporarily interrupted under close medical supervision. Rinsing the mouth after inhalation is advised.

Pneumonia: Patients with COPD have a higher risk of pneumonia and should be instructed to contact their healthcare provider if they develop symptoms of pneumonia.

Immunosuppression: Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles and, if exposed, to consult their physician without delay. Patients should be informed of potential worsening of existing tuberculosis, fungal, bacterial, viral, or parasitic infections, or ocular herpes simplex.

Hypercorticism and Adrenal Suppression: Patients should be advised that ADVAIR DISKUS may cause systemic corticosteroid effects of hypercorticism and adrenal suppression. Additionally, patients should be instructed that deaths due to adrenal insufficiency have occurred during and after transfer from systemic corticosteroids. Patients should taper slowly from systemic corticosteroids if transferring to ADVAIR DISKUS.

Reduction in Bone Mineral Density: Patients who are at an increased risk for decreased BMD should be advised that the use of corticosteroids may pose an additional risk.

Reduced Growth Velocity: Patients should be informed that orally inhaled corticosteroids, including fluticasone propionate, a component of ADVAIR DISKUS, may cause a reduction in growth velocity when administered to pediatric patients. Physicians should closely follow the growth of children and adolescents taking corticosteroids by any route.

Ocular Effects: Long-term use of inhaled corticosteroids may increase the risk of some eye problems (cataracts or glaucoma); regular eye examinations should be considered.

17.5 Risks Associated With Beta-Agonist Therapy

Patients should be informed of adverse effects associated with beta₂-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.

**Please see the Medication Guide for
ADVAIR DISKUS on the following pages.**

17.6 Medication Guide

MEDICATION GUIDE

ADVAIR [ad´vair] DISKUS® 100/50
(fluticasone propionate 100 mcg and salmeterol 50 mcg inhalation powder)

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

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

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

What is the most important information I should know about ADVAIR DISKUS?

- **ADVAIR DISKUS contains 2 medicines:**
 - **fluticasone propionate (the same medicine found in FLOVENT®),** an inhaled corticosteroid medicine. Inhaled corticosteroids help to decrease inflammation in the lungs. Inflammation in the lungs can lead to asthma symptoms.
 - **salmeterol (the same medicine found in SEREVENT®),** a long-acting beta₂-agonist medicine or LABA. LABA medicines are used in patients with asthma and chronic obstructive pulmonary disease (COPD). LABA medicines help the muscles around the airways in your lungs stay relaxed to prevent symptoms, such as wheezing and shortness of breath. These symptoms can happen when the muscles around the airways tighten. This makes it hard to breathe. In severe cases, wheezing can stop your breathing and cause death if not treated right away.
- **In patients with asthma, LABA medicines, such as salmeterol (one of the medicines in ADVAIR DISKUS), may increase the chance of death from asthma problems.** In a large asthma study, more patients who used salmeterol died from asthma problems compared with patients who did not use salmeterol. It is not known whether fluticasone propionate, the other medicine in ADVAIR DISKUS, changes your chance of death from asthma problems seen with salmeterol. Talk with your healthcare provider about this risk and the benefits of treating your asthma with ADVAIR DISKUS.
- **ADVAIR DISKUS does not relieve sudden symptoms. Always have a short-acting beta₂-agonist medicine with you to treat sudden symptoms. If you do not have an inhaled, short-acting bronchodilator, contact your healthcare provider to have one prescribed for you.**
- **Do not stop using ADVAIR DISKUS unless told to do so by your healthcare provider because your symptoms might get worse.**
- **ADVAIR DISKUS should be used only if your healthcare provider decides that another asthma-controller medicine alone does not control your asthma or that you need 2 asthma-controller medicines.**
- **Call your healthcare provider if breathing problems worsen over time while using ADVAIR DISKUS. You may need different treatment.**
- **Get emergency medical care if:**
 - **breathing problems worsen quickly, and**
 - **you use your short-acting beta₂-agonist medicine, but it does not relieve your breathing problems.**

What is ADVAIR DISKUS?

ADVAIR DISKUS combines an inhaled corticosteroid medicine, fluticasone propionate (the same medicine found in FLOVENT) and a long-acting beta₂-agonist medicine, salmeterol (the same medicine found in SEREVENT). ADVAIR DISKUS is used for asthma and chronic obstructive pulmonary disease (COPD) as follows:

Asthma

ADVAIR DISKUS is used long term, twice a day to control symptoms of asthma and to prevent symptoms such as wheezing in adults and children ages 4 and older.

ADVAIR DISKUS contains salmeterol (the same medicine found in SEREVENT). Because LABA medicines, such as salmeterol, may increase the chance of death from asthma problems, ADVAIR DISKUS is not for adults and children with asthma who:

- are well controlled with another asthma-controller medicine such as a low to medium dose of an inhaled corticosteroid medicine
- only need short-acting beta₂-agonist medicines once in awhile

Chronic Obstructive Pulmonary Disease

COPD is a chronic lung disease that includes chronic bronchitis, emphysema, or both. ADVAIR DISKUS 250/50 is used long term, twice a day to help improve lung function for better breathing in adults with COPD. ADVAIR DISKUS 250/50 has been shown to decrease the number of flare-ups and worsening of COPD symptoms (exacerbations).

Who should not use ADVAIR DISKUS?

Do not use ADVAIR DISKUS:

- to treat sudden, severe symptoms of asthma or COPD
- if you have a severe allergy to milk proteins. Ask your doctor if you are not sure.

What should I tell my healthcare provider before using ADVAIR DISKUS?

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

- have heart problems
- have high blood pressure
- have seizures
- have thyroid problems
- have diabetes
- have liver problems
- have osteoporosis

- **have an immune system problem**
- **are pregnant or planning to become pregnant.** It is not known if ADVAIR DISKUS may harm your unborn baby.
- **are breastfeeding.** It is not known if ADVAIR DISKUS passes into your milk and if it can harm your baby.
- **are allergic to any of the ingredients in ADVAIR DISKUS, any other medicines, or food products. See the end of this Medication Guide for a complete list of the ingredients in ADVAIR DISKUS.**
- **are exposed to chickenpox or measles**

Tell your healthcare provider about all the medicines you take including prescription and non-prescription medicines, vitamins, and herbal supplements. ADVAIR DISKUS and certain other medicines may interact with each other. This may cause serious side effects. Especially, tell your healthcare provider if you take ritonavir. The anti-HIV medicines NORVIR® (ritonavir capsules) Soft Gelatin, NORVIR (ritonavir oral solution), and KALETRA® (lopinavir/ritonavir) Tablets contain ritonavir.

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

How do I use ADVAIR DISKUS?

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

- Children should use ADVAIR DISKUS with an adult's help, as instructed by the child's healthcare provider.
- Use ADVAIR DISKUS exactly as prescribed. **Do not use ADVAIR DISKUS more often than prescribed.** ADVAIR DISKUS comes in 3 strengths. Your healthcare provider will prescribe the one that is best for your condition.
- The usual dosage of ADVAIR DISKUS is 1 inhalation twice a day (morning and evening). The 2 doses should be about 12 hours apart. Rinse your mouth with water after using ADVAIR DISKUS.
- If you take more ADVAIR DISKUS than your doctor has prescribed, get medical help right away if you have any unusual symptoms, such as worsening shortness of breath, chest pain, increased heart rate, or shakiness.
- If you miss a dose of ADVAIR DISKUS, just skip that dose. Take your next dose at your usual time. Do not take 2 doses at one time.
- Do not use a spacer device with ADVAIR DISKUS.
- Do not breathe into ADVAIR DISKUS.
- **While you are using ADVAIR DISKUS twice a day, do not use other medicines that contain a long-acting beta₂-agonist or LABA for any reason. Ask your healthcare provider or pharmacist if any of your other medicines are LABA medicines.**
- Do not change or stop any of your medicines used to control or treat your breathing problems. Your healthcare provider will adjust your medicines as needed.
- Make sure you always have a short-acting beta₂-agonist medicine with you. Use your short-acting beta₂-agonist medicine if you have breathing problems between doses of ADVAIR DISKUS.
- **Call your healthcare provider or get medical care right away if:**
 - your breathing problems worsen with ADVAIR DISKUS
 - you need to use your short-acting beta₂-agonist medicine more often than usual
 - your short-acting beta₂-agonist medicine does not work as well for you at relieving symptoms
 - you need to use 4 or more inhalations of your short-acting beta₂-agonist medicine for 2 or more days in a row
 - you use 1 whole canister of your short-acting beta₂-agonist medicine in 8 weeks' time
 - your peak flow meter results decrease. Your healthcare provider will tell you the numbers that are right for you.
 - you have asthma and your symptoms do not improve after using ADVAIR DISKUS regularly for 1 week

What are the possible side effects with ADVAIR DISKUS?

- **ADVAIR DISKUS contains salmeterol (the same medicine found in SEREVENT). In patients with asthma, LABA medicines, such as salmeterol, may increase the chance of death from asthma problems.** See "What is the most important information I should know about ADVAIR DISKUS?"
- Patients with COPD have a higher chance of getting pneumonia. ADVAIR DISKUS may increase the chance of getting pneumonia. **Call your healthcare provider if you notice any of the following symptoms:**
 - increase in mucus (sputum) production
 - change in mucus color
 - fever
 - chills
 - increased cough
 - increased breathing problems.

Other possible side effects with ADVAIR DISKUS include:

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

Medication Guide: ADVAIR DISKUS® (fluticasone propionate and salmeterol inhalation powder)

- **increased blood pressure**
- **a fast and irregular heartbeat**
- **chest pain**
- **headache**
- **tremor**
- **nervousness**
- **weakened immune system and a higher chance of infections**
- **lower bone mineral density.** This may be a problem for people who already have a higher chance of low bone density (osteoporosis).
- **eye problems including glaucoma and cataracts.** You should have regular eye exams while using ADVAIR DISKUS.
- **slowed growth in children.** A child's growth should be checked often.

The most common side effects with ADVAIR DISKUS include:

Asthma in adults and children:

- upper respiratory tract infection
- throat irritation
- hoarseness and voice changes
- thrush in the mouth and throat
- bronchitis
- cough
- headache
- nausea and vomiting

In children with asthma, infections in the ear, nose, and throat are also common.

COPD:

- thrush in the mouth and throat
- throat irritation
- hoarseness and voice changes
- viral respiratory infections
- headache
- muscle and bone pain

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

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

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How do I store ADVAIR DISKUS?

- Store ADVAIR DISKUS at room temperature between 68° to 77° F (20° to 25° C). Keep in a dry place away from heat and sunlight.
- Safely discard ADVAIR DISKUS 1 month after you remove it from the foil pouch, or after the dose indicator reads "0", whichever comes first.
- **Keep ADVAIR DISKUS and all medicines out of the reach of children.**

General Information about ADVAIR DISKUS

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

This Medication Guide summarizes the most important information about ADVAIR DISKUS. If you would like more information, talk with your healthcare provider or pharmacist. You can ask your healthcare provider or pharmacist for information about ADVAIR DISKUS that was written for healthcare professionals. You can also contact the company that makes ADVAIR DISKUS (toll free) at 1-888-825-5249 or at www.advaair.com.

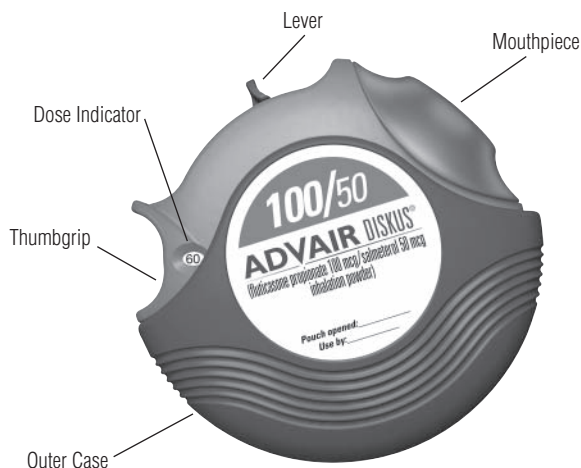
What are the ingredients in ADVAIR DISKUS?

Active ingredients: fluticasone propionate, salmeterol xinafoate

Inactive ingredient: lactose (contains milk proteins)

Instructions for Using ADVAIR DISKUS

Follow the instructions below for using your ADVAIR DISKUS. **You will breathe in (inhale) the medicine from the DISKUS®.** If you have any questions, ask your healthcare provider or pharmacist.



Take ADVAIR DISKUS out of the box and foil pouch. Write the **"Pouch opened"** and **"Use by"** dates on the label on top of the DISKUS. The **"Use by"** date is 1 month from date of opening the pouch.

- The DISKUS will be in the closed position when the pouch is opened.
- The **dose indicator** on the top of the DISKUS tells you how many doses are left. The dose indicator number will decrease each time you use the DISKUS. After you have used 55 doses from the DISKUS, the numbers 5 to 0 will appear in red to warn you that there are only a few doses left (see Figure 1). If you are using a "sample" DISKUS, the numbers 5 to 0 will appear in red after 23 doses.

Taking a dose from the DISKUS requires the following 3 simple steps: Open, Click, Inhale.



Figure 1

1. OPEN

Hold the DISKUS in one hand and put the thumb of your other hand on the **thumbgrip**. Push your thumb away from you as far as it will go until the mouthpiece appears and snaps into position (see Figure 2).



2. CLICK

Hold the DISKUS in a level, flat position with the mouthpiece towards you. Slide the **lever** away from you as far as it will go until it **clicks** (see Figure 3). The DISKUS is now ready to use.



Figure 3

Every time the **lever** is pushed back, a dose is ready to be inhaled. This is shown by a decrease in numbers on the dose counter. **To avoid releasing or wasting doses once the DISKUS is ready:**

- **Do not close the DISKUS.**
- **Do not tilt the DISKUS.**
- **Do not play with the lever.**
- **Do not move the lever more than once.**

Figure 2

3. INHALE

Before inhaling your dose from the DISKUS, breathe out (exhale) fully while holding the DISKUS level and away from your mouth (see Figure 4). **Remember, never breathe out into the DISKUS mouthpiece.**



Figure 4

Put the mouthpiece to your lips (see Figure 5). Breathe in quickly and deeply through the DISKUS. Do not breathe in through your nose.



Figure 5

Remove the DISKUS from your mouth. Hold your breath for about 10 seconds, or for as long as is comfortable. Breathe out slowly.

The DISKUS delivers your dose of medicine as a very fine powder. Most patients can taste or feel the powder. Do not use another dose from the DISKUS if you do not feel or taste the medicine.

Rinse your mouth with water after breathing-in the medicine. Spit the water out. Do not swallow.

4. Close the DISKUS when you are finished taking a dose so that the DISKUS will be ready for you to take your next dose. Put your thumb on the thumbgrip and slide the thumbgrip back towards you as far as it will go (see Figure 6). The DISKUS will click shut. The lever will automatically return to its original position. The DISKUS is now ready for you to take your next scheduled dose, due in about 12 hours. (Repeat steps 1 to 4.)



Figure 6

Medication Guide: ADVAIR DISKUS® (fluticasone propionate and salmeterol inhalation powder)

Remember:

- Never breathe into the DISKUS.
- Never take the DISKUS apart.
- Always ready and use the DISKUS in a level, flat position.
- Do not use the DISKUS with a spacer device.
- After each dose, rinse your mouth with water and spit the water out. Do not swallow.
- Never wash the mouthpiece or any part of the DISKUS. **Keep it dry.**
- Always keep the DISKUS in a dry place.
- Never take an extra dose, even if you did not taste or feel the medicine.

April 2008 ADD:4MG

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

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GlaxoSmithKline
Research Triangle Park, NC 27709

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ADVAIR® HFA 45/21

(fluticasone propionate 45 mcg and salmeterol 21 mcg*)
Inhalation Aerosol

ADVAIR® HFA 115/21

(fluticasone propionate 115 mcg and salmeterol 21 mcg*)
Inhalation Aerosol

ADVAIR® HFA 230/21

(fluticasone propionate 230 mcg and salmeterol 21 mcg*)
Inhalation Aerosol

*As salmeterol xinafoate salt 30.45 mcg, equivalent to salmeterol base 21 mcg

For Oral Inhalation Only

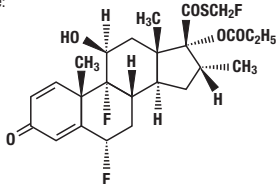
WARNING

Long-acting beta₂-adrenergic agonists, such as salmeterol, one of the active ingredients in ADVAIR HFA, may increase the risk of asthma-related death. Therefore, when treating patients with asthma, physicians should only prescribe ADVAIR HFA for patients not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies. Data from a large placebo-controlled US study that compared the safety of salmeterol (SEREVENT® Inhalation Aerosol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176 patients treated for 28 weeks on salmeterol versus 3 deaths out of 13,179 patients on placebo) (see WARNINGS).

DESCRIPTION

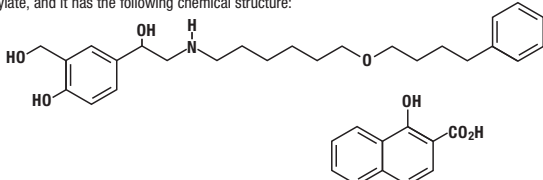
ADVAIR HFA 45/21 Inhalation Aerosol, ADVAIR HFA 115/21 Inhalation Aerosol, and ADVAIR HFA 230/21 Inhalation Aerosol are combinations of fluticasone propionate and salmeterol xinafoate.

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



Fluticasone propionate is a white powder with a molecular weight of 500.6, and the empirical formula is C₂₅H₃₁F₇O₅S. It is practically insoluble in water, freely soluble in dimethyl sulfoxide and dimethylformamide, and slightly soluble in methanol and 95% ethanol.

The other active component of ADVAIR HFA is salmeterol xinafoate, a 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 '-[[[4-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol, 1-hydroxy-2-naphthalenecarboxylate, and it has the following chemical structure:



Salmeterol xinafoate is a white powder with a molecular weight of 603.8, and the empirical formula is C₂₅H₃₁NO₆•C₁₁H₇O₃. It is freely soluble in methanol; slightly soluble in ethanol, chloroform, and isopropanol; and sparingly soluble in water.

ADVAIR HFA 45/21 Inhalation Aerosol, ADVAIR HFA 115/21 Inhalation Aerosol, and ADVAIR HFA 230/21 Inhalation Aerosol are pressurized, metered-dose aerosol units intended for oral inhalation only. Each unit contains a microcrystalline suspension of fluticasone propionate (micronized) and salmeterol xinafoate (micronized) in propellant HFA-134a (1,1,1,2-tetrafluoroethane). It contains no other excipients.

After priming, each actuation of the inhaler delivers 50, 125, or 250 mcg of fluticasone propionate and 25 mcg of salmeterol in 75 mg of suspension from the valve. Each actuation delivers 45, 115, or 230 mcg of fluticasone propionate and 21 mcg of salmeterol from the actuator. Twenty-one micrograms (21 mcg) of salmeterol base is equivalent to 30.45 mcg of salmeterol xinafoate. The actual amount of drug delivered to the lung may depend on patient factors, such as the coordination between the actuation of the device and inspiration through the delivery system.

Each 12-g canister provides 120 inhalations.

ADVAIR HFA should be primed before using for the first time by releasing 4 test sprays into the air away from the face, shaking well for 5 seconds before each spray. In cases where the inhaler has not been used for more than 4 weeks or when it has been dropped, prime the inhaler again by shaking well before each spray and releasing 2 test sprays into the air away from the face.

This product does not contain any chlorofluorocarbon (CFC) as the propellant.

CLINICAL PHARMACOLOGY

Mechanism of Action: ADVAIR HFA Inhalation Aerosol: Since ADVAIR HFA contains both fluticasone propionate and salmeterol, the mechanisms of action described below for the individual components apply to ADVAIR HFA. These drugs represent 2 classes of medications (a synthetic corticosteroid and a selective, long-acting beta₂-adrenergic receptor agonist) that have different effects on clinical, physiologic, and inflammatory indices of asthma.

Fluticasone Propionate: Fluticasone propionate is a synthetic trifluorinated corticosteroid with potent anti-inflammatory activity. In vitro assays using human lung cytosol preparations have established fluticasone propionate as a human glucocorticoid receptor agonist with an affinity 18 times greater than dexamethasone, almost twice that of beclomethasone-17-monopropionate (BMP), the active metabolite of beclomethasone dipropionate, and over 3 times that of budesonide. Data from the McKenzie vasoconstrictor assay in man are consistent with these results.

Inflammation is an important component in the pathogenesis of asthma. Corticosteroids have been shown to inhibit multiple cell types (e.g., mast cells, eosinophils, basophils, lymphocytes, macrophages, and neutrophils) and mediator production or secretion (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in the asthmatic response. These anti-inflammatory actions of corticosteroids contribute to their efficacy in asthma.

Salmeterol Xinafoate: Salmeterol is a long-acting beta₂-adrenergic agonist. In vitro studies and in vivo pharmacologic studies demonstrate that salmeterol is selective for beta₂-adrenoceptors compared with isoproterenol, which has approximately equal agonist activity on beta₁- and beta₂-adrenoceptors. In vitro studies show salmeterol to be at least 50 times more selective for beta₂-adrenoceptors than albuterol. Although beta₂-adrenoceptors are the predominant adrenergic receptors in bronchial smooth muscle and beta₂-adrenoceptors are the predominant receptors in the heart, there are also beta₂-adrenoceptors in the human heart comprising 10% to 50% of the total beta-adrenoceptors. The precise function of these receptors has not been established, but their presence raises the possibility that even selective beta₂-agonists may have cardiac effects.

The pharmacologic effects of beta₂-adrenoceptor agonist drugs, including salmeterol, are at least in part attributable to stimulation of intracellular adenylyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

In vitro tests show that salmeterol is a potent and long-lasting inhibitor of the release of mast cell mediators, such as histamine, leukotrienes, and prostaglandin D₂, from human lung. Salmeterol inhibits histamine-induced plasma protein extravasation and inhibits platelet activating factor-induced eosinophil accumulation in the lungs of guinea pigs when

administered by the inhaled route. In humans, single doses of salmeterol administered via inhalation aerosol attenuate allergen-induced bronchial hyper-responsiveness.

Preclinical: In animals and humans, propellant HFA-134a was found to be rapidly absorbed and rapidly eliminated, with an elimination half-life of 3 to 27 minutes in animals and 5 to 7 minutes in humans. Time to maximum plasma concentration (T_{max}) and mean residence time are both extremely short, leading to a transient appearance of HFA-134a in the blood with no evidence of accumulation.

Propellant HFA-134a is devoid of pharmacological activity except at very high doses in animals (i.e., 380 to 1,300 times the maximum human exposure based on comparisons of area under the plasma concentration versus time curve [AUC] values), primarily producing ataxia, tremors, dyspnea, or salivation. These events are similar to effects produced by the structurally related CFCs, which have been used extensively in metered-dose inhalers. In drug interaction studies in male and female dogs, there was a slight increase in the salmeterol-related effect on heart rate (a known effect of beta₂-agonists) when given in combination with high doses of fluticasone propionate. This effect was not observed in clinical studies.

Pharmacokinetics: ADVAIR HFA Inhalation Aerosol: Three single-dose, placebo-controlled, crossover studies were conducted in healthy subjects: (1) a study using 4 inhalations of ADVAIR HFA 230/21, salmeterol CFC inhalation aerosol 21 mcg, or fluticasone propionate CFC inhalation aerosol 220 mcg, (2) a study using 8 inhalations of ADVAIR HFA 45/21, ADVAIR HFA 115/21, or ADVAIR HFA 230/21, and (3) a study using 4 inhalations of ADVAIR HFA 230/21; 2 inhalations of ADVAIR DISKUS® 500/50 (fluticasone propionate 500 mcg and salmeterol 50 mcg inhalation powder); 4 inhalations of fluticasone propionate CFC inhalation aerosol 220 mcg; or 1,010 mcg of fluticasone propionate given intravenously. Peak plasma concentrations of fluticasone propionate were achieved in 0.33 to 1.5 hours and those of salmeterol were achieved in 5 to 10 minutes.

Peak plasma concentrations of fluticasone propionate (N = 20 subjects) following 8 inhalations of ADVAIR HFA 45/21, ADVAIR HFA 115/21, and ADVAIR HFA 230/21 averaged 41, 108, and 173 pg/mL, respectively. Peak plasma salmeterol concentrations ranged from 220 to 470 pg/mL.

Systemic exposure (N = 20 subjects) from 4 inhalations of ADVAIR HFA 230/21 was 53% of the value from the individual inhaler for fluticasone propionate CFC inhalation aerosol and 42% of the value from the individual inhaler for salmeterol CFC inhalation aerosol. Peak plasma concentrations from ADVAIR HFA for fluticasone propionate (86 vs. 120 pg/mL) and salmeterol (170 vs. 510 pg/mL) were significantly lower compared to individual inhalers.

In 15 healthy subjects, systemic exposure to fluticasone propionate from 4 inhalations of ADVAIR HFA 230/21 (920/84 mcg) and 2 inhalations of ADVAIR DISKUS 500/50 (1,000/100 mcg) were similar between the 2 inhalers (i.e., 799 vs. 632 pg•h/mL, respectively) but approximately half the systemic exposure from 4 inhalations of fluticasone propionate CFC inhalation aerosol 220 mcg (880 mcg, AUC = 1,543 pg•h/mL). Similar results were observed for peak fluticasone propionate plasma concentrations (186 and 182 pg/mL from ADVAIR HFA and ADVAIR DISKUS, respectively, and 307 pg/mL from the fluticasone propionate CFC inhalation aerosol). Systemic exposure to salmeterol was higher (317 vs. 169 pg•h/mL) and peak salmeterol concentrations were lower (196 vs. 223 pg/mL) following ADVAIR HFA compared to ADVAIR DISKUS, although pharmacodynamic results were comparable.

Absolute bioavailability of fluticasone propionate from ADVAIR HFA in 15 healthy subjects was 5.3%. Terminal half-life estimates of fluticasone propionate for ADVAIR HFA, ADVAIR DISKUS, and fluticasone propionate CFC inhalation aerosol were similar and averaged 5.6 hours. No terminal half-life estimates were calculated for salmeterol.

A double-blind crossover study was conducted in 13 adult patients with asthma to evaluate the steady-state pharmacokinetics of fluticasone propionate and salmeterol following administration of 2 inhalations of ADVAIR HFA 115/21 twice daily or 1 inhalation of ADVAIR DISKUS 250/50 twice daily for 4 weeks. Systemic exposure (AUC) to fluticasone propionate was similar for ADVAIR HFA (274 pg•h/mL [95% CI 150, 502]) and ADVAIR DISKUS (338 pg•h/mL [95% CI 197, 581]). Systemic exposure to salmeterol was also similar for ADVAIR HFA (53 pg•h/mL [95% CI 17, 164]) and ADVAIR DISKUS (70 pg•h/mL [95% CI 19, 254]).

Special Populations: Hepatic and Renal Impairment: Formal pharmacokinetic studies using ADVAIR HFA have not been conducted to examine gender differences or in special populations, such as elderly patients or patients with hepatic or renal impairment. However, since both fluticasone propionate and salmeterol are predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of fluticasone propionate and salmeterol in plasma. Therefore, patients with hepatic disease should be closely monitored.

Drug Interactions: In repeat- and single-dose studies, there was no evidence of significant drug interaction on systemic exposure to fluticasone propionate and salmeterol when given alone or in combination via the DISKUS. Similar definitive studies have not been performed with ADVAIR HFA.

Fluticasone Propionate: Absorption: Fluticasone propionate acts locally in the lung; therefore, plasma levels do not predict therapeutic effect. Studies using oral dosing of labeled and unlabeled drug have demonstrated that the oral systemic bioavailability of fluticasone propionate is negligible (<1%), primarily due to incomplete absorption and presystemic metabolism in the gut and liver. In contrast, the majority of the fluticasone propionate delivered to the lung is systemically absorbed.

Distribution: Following intravenous administration, the initial disposition phase for fluticasone propionate was rapid and consistent with its high lipid solubility and tissue binding. The volume of distribution averaged 4.2 L/kg.

The percentage of fluticasone propionate bound to human plasma proteins averages 99%. Fluticasone propionate is weakly and reversibly bound to erythrocytes and is not significantly bound to human transferrin.

Metabolism: The total clearance of fluticasone propionate is high (average, 1,093 mL/min), with renal clearance accounting for less than 0.02% of the total. The only circulating metabolite detected in man is the 17 β -carboxylic acid derivative of fluticasone propionate, which is formed through the cytochrome P450 3A4 pathway. This metabolite had less affinity (approximately 1/2,000) than the parent drug for the glucocorticoid receptor of human lung cytosol in vitro and negligible pharmacological activity in animal studies. Other metabolites detected in vitro using cultured human hepatoma cells have not been detected in man.

Elimination: Following intravenous dosing, fluticasone propionate showed polyexponential kinetics and had a terminal elimination half-life of approximately 7.8 hours. Less than 5% of a radiolabeled oral dose was excreted in the urine as metabolites, with the remainder excreted in the feces as parent drug and metabolites.

Special Populations: Gender: In 19 male and 33 female patients with asthma, systemic exposure was similar from 2 inhalations of fluticasone propionate CFC inhalation aerosol 44, 110, and 220 mcg twice daily.

Drug Interactions: Fluticasone propionate is a substrate of cytochrome P450 3A4. Coadministration of fluticasone propionate and the strong cytochrome P450 3A4 inhibitor ritonavir is not recommended based upon a multiple-dose, crossover drug interaction study in 18 healthy subjects. Fluticasone propionate aqueous nasal spray (200 mcg once daily) was coadministered for 7 days with ritonavir (100 mg twice daily). Plasma fluticasone propionate concentrations following fluticasone propionate aqueous nasal spray alone were undetectable (<10 pg/mL) in most subjects, and when concentrations were detectable, peak levels (C_{max}) averaged 11.9 pg/mL (range, 10.8 to 14.1 pg/mL) and AUC₀₋₂₄ averaged 8.43 pg•hr/mL (range, 4.2 to 18.8 pg•hr/mL). Fluticasone propionate C_{max} and AUC₀₋₂₄ increased to 318 pg/mL (range, 110 to 648 pg/mL) and 3,102.6 pg•hr/mL (range, 1,207.1 to 5,662.0 pg•hr/mL), respectively, after coadministration of ritonavir with fluticasone propionate aqueous nasal spray. This significant increase in systemic fluticasone propionate exposure resulted in a significant decrease (86%) in serum cortisol AUC.

Caution should be exercised when other strong cytochrome P450 3A4 inhibitors are coadministered with fluticasone propionate. In a drug interaction study, coadministration of orally inhaled fluticasone propionate (1,000 mcg) and ketoconazole (200 mg once daily) resulted in increased systemic fluticasone propionate exposure and reduced plasma cortisol AUC, but had no effect on urinary excretion of cortisol.

In another multiple-dose drug interaction study, coadministration of orally inhaled fluticasone propionate (500 mcg twice daily) and erythromycin (333 mg 3 times daily) did not affect fluticasone propionate pharmacokinetics.

Salmeterol Xinafoate: Salmeterol xinafoate, an ionic salt, dissociates in solution so that the salmeterol and 1-hydroxy-2-naphthoic acid (xinafoate) moieties are absorbed, distributed, metabolized, and excreted independently. Salmeterol acts locally in the lung; therefore, plasma levels do not predict therapeutic effect.

Absorption: Because of the small therapeutic dose, systemic levels of salmeterol are low or undetectable after inhalation of recommended doses (42 mcg of salmeterol inhalation aerosol twice daily). Following chronic administration of an inhaled dose of 42 mcg twice daily, salmeterol was detected in plasma within 5 to 10 minutes in 6 patients with asthma; plasma concentrations were very low, with mean peak concentrations of 150 pg/mL and no accumulation with repeated doses.

Distribution: The percentage of salmeterol bound to human plasma proteins averages 96% in vitro over the concentration range of 8 to 7,722 ng of salmeterol base per milliliter, much higher concentrations than those achieved following therapeutic doses of salmeterol.

Metabolism: Salmeterol base is extensively metabolized by hydroxylation, with subsequent elimination predominately in the feces. No significant amount of unchanged salmeterol base was detected in either urine or feces.

In an in vitro study using human liver microsomes showed that salmeterol is extensively metabolized to a hydroxysalmetrol (aliphatic oxidation) by cytochrome P450 3A4 (CYP3A4). Ketoconazole, a strong inhibitor of CYP3A4, essentially completely inhibited the formation of a hydroxysalmetrol in vitro.

Elimination: In 2 healthy adult subjects who received 1 mg of radiolabeled salmeterol (as salmeterol xinafoate) orally, approximately 25% and 60% of the radiolabeled salmeterol was eliminated in urine and feces, respectively, over a period of 7 days. The terminal elimination half-life was about 5.5 hours (1 volunteer only).

The xinafoate moiety has no apparent pharmacologic activity. The xinafoate moiety is highly protein bound (>99%) and has a long elimination half-life of 11 days.

Drug Interactions: Salmeterol is a substrate of CYP3A4.

Inhibitors of Cytochrome P450 3A4: Ketoconazole: In a placebo-controlled, crossover drug interaction study in 20 healthy male and female subjects, coadministration of salmeterol (50 mcg twice daily) and the strong CYP3A4 inhibitor ketoconazole (400 mg once daily) for 7 days resulted in a significant increase in plasma salmeterol exposure as determined by a 16-fold increase in AUC (ratio with and without ketoconazole 15.76; 90% CI: 10.66, 23.31) mainly due to increased bioavailability of the swallowed portion of the dose. Peak plasma salmeterol concentrations were increased by 1.4-fold

ADVAIR® HFA 45/21

(fluticasone propionate 45 mcg and salmeterol 21 mcg) Inhalation Aerosol

ADVAIR® HFA 115/21

(fluticasone propionate 115 mcg and salmeterol 21 mcg) Inhalation Aerosol

ADVAIR® HFA 230/21

(fluticasone propionate 230 mcg and salmeterol 21 mcg) Inhalation Aerosol

(90% CI: 1.23, 1.68). Three (3) out of 20 subjects (15%) were withdrawn from salmeterol and ketoconazole coadministration due to beta-agonist-mediated systemic effects (2 with QTC prolongation and 1 with palpitations and sinus tachycardia). Coadministration of salmeterol and ketoconazole did not result in a clinically significant effect on mean heart rate, mean blood potassium, or mean blood glucose. Although there was no statistical effect on the mean QTC, coadministration of salmeterol and ketoconazole was associated with more frequent increases in QTC duration compared with salmeterol and placebo administration. Due to the potential increased risk of cardiovascular adverse events, the concomitant use of salmeterol with strong CYP3A4 inhibitors (e.g., ketoconazole, ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, neflavin, saquinavir, telithromycin) is not recommended.

Erythromycin: In a repeat-dose study in 13 healthy subjects, concomitant administration of erythromycin (a moderate CYP3A4 inhibitor) and salmeterol inhalation aerosol resulted in a 40% increase in salmeterol Cmax at steady state (ratio with and without erythromycin 1.4; 90% CI: 0.96, 2.03; $p = 0.12$), a 3.6-beat/min increase in heart rate (95% CI: 0.19, 7.03; $p < 0.04$), a 5.8-msec increase in QTC interval (95% CI: -6.14, 17.77; $p = 0.34$), and no change in plasma potassium.

Pharmacodynamics: ADVAIR HFA Inhalation Aerosol: Since systemic pharmacodynamic effects of salmeterol are not normally seen at the therapeutic dose, higher doses were used to produce measurable effects. Four placebo-controlled, crossover studies were conducted in healthy subjects: (1) a cumulative-dose study using 42 to 336 mcg of salmeterol CFC inhalation aerosol given alone or as ADVAIR HFA 115/21, (2) a single-dose study using 4 inhalations of ADVAIR HFA 230/21, salmeterol CFC inhalation aerosol 21 mcg, or fluticasone propionate CFC inhalation aerosol 220 mcg, (3) a single-dose study using 8 inhalations of ADVAIR HFA 45/21, ADVAIR HFA 115/21, or ADVAIR HFA 230/21, and (4) a single-dose study using 4 inhalations of ADVAIR HFA 230/21; 2 inhalations of ADVAIR DISKUS 500/50; 4 inhalations of fluticasone propionate CFC inhalation aerosol 220 mcg; or 1,010 mcg of fluticasone propionate given intravenously. In these studies pulse rate, blood pressure, QTC interval, glucose, and/or potassium were measured. Comparable or lower effects were observed for ADVAIR HFA compared to ADVAIR DISKUS or salmeterol alone. The effect of salmeterol on pulse rate and potassium was not altered by the presence of different amounts of fluticasone propionate in ADVAIR HFA. The potential effect of salmeterol on the effects of fluticasone propionate on the hypothalamic-pituitary-adrenal (HPA) axis was also evaluated in 3 of these studies. Compared with fluticasone propionate CFC inhalation aerosol, ADVAIR HFA had less effect on 24-hour urinary cortisol excretion and less or comparable effect on 24-hour serum cortisol. In these crossover studies in healthy subjects, ADVAIR HFA and ADVAIR DISKUS had similar effects on urinary and serum cortisol.

In clinical studies with ADVAIR HFA in patients with asthma, systemic pharmacodynamic effects of salmeterol (pulse rate, blood pressure, QTC interval, potassium, and glucose) were similar to or slightly lower in patients treated with ADVAIR HFA compared with patients treated with salmeterol CFC inhalation aerosol 21 mcg. In 61 adolescent and adult patients with asthma given ADVAIR HFA (45/21 or 115/21 mcg), continuous 24-hour electrocardiographic monitoring was performed after the first dose and after 12 weeks of twice-daily therapy, and no clinically significant dysrhythmias were noted.

A 4-way crossover study in 13 patients with asthma compared pharmacodynamics at steady state following 4 weeks of twice-daily treatment with 2 inhalations of ADVAIR HFA 115/21, 1 inhalation of ADVAIR DISKUS 250/50 mcg, 2 inhalations of fluticasone propionate HFA inhalation aerosol 110 mcg, and placebo. No significant differences in serum cortisol AUC were observed between active treatments and placebo. Mean 12-hour serum cortisol AUC ratios comparing active treatment with placebo ranged from 0.9 to 1.2. No statistically or clinically significant increases in heart rate or QTC interval were observed for any active treatment compared with placebo.

In a 12-week study (see CLINICAL TRIALS: Studies Comparing ADVAIR HFA to Fluticasone Propionate Alone or Salmeterol Alone: Study 3) in patients with asthma, ADVAIR HFA 115/21 was compared with the individual components, fluticasone propionate CFC inhalation aerosol 110 mcg and salmeterol CFC inhalation aerosol 21 mcg, and placebo. All treatments were administered as 2 inhalations twice daily. After 12 weeks of treatment with these therapeutic doses, the geometric mean ratio of urinary cortisol excretion compared with baseline was 0.9 for ADVAIR HFA and fluticasone propionate and 1.0 for placebo and salmeterol. In addition, the ability to increase cortisol production in response to stress, as assessed by 30-minute cosyntropin stimulation in 23 to 32 patients per treatment group, remained intact for the majority of patients and was similar across treatments. Three patients who received ADVAIR HFA 115/21 had an abnormal response (peak serum cortisol <18 mcg/dL) after dosing, compared with 1 patient who received placebo, 2 patients who received fluticasone propionate 110 mcg, and 1 patient who received salmeterol.

In another 12-week study (see CLINICAL TRIALS: Studies Comparing ADVAIR HFA to Fluticasone Propionate Alone or Salmeterol Alone: Study 4) in patients with asthma, ADVAIR HFA 230/21 (2 inhalations twice daily) was compared with ADVAIR DISKUS 500/50 (1 inhalation twice daily) and fluticasone propionate CFC inhalation aerosol 220 mcg (2 inhalations twice daily). The geometric mean ratio of 24-hour urinary cortisol excretion at week 12 compared with baseline was 0.9 for all 3 treatment groups.

Fluticasone Propionate: In clinical trials with fluticasone propionate inhalation powder using doses up to and including 250 mcg twice daily, occasional abnormal short cosyntropin tests (peak serum cortisol <18 mcg/dL) were noted both in patients receiving fluticasone propionate and in patients receiving placebo. The incidence of abnormal tests at 500 mcg twice daily was greater than placebo. In a 2-year study carried out in 64 patients with mild, persistent asthma (mean FEV₁ 91% of predicted) randomized to fluticasone propionate 500 mcg twice daily or placebo, no patient receiving fluticasone propionate had an abnormal response to 6-hour cosyntropin infusion (peak serum cortisol <18 mcg/dL). With a peak cortisol threshold of <35 mcg/dL, 1 patient receiving fluticasone propionate (4%) had an abnormal response at 1 year; repeat testing at 18 months and 2 years was normal. Another patient receiving fluticasone propionate (5%) had an abnormal response at 2 years. No patient on placebo had an abnormal response at 1 or 2 years.

Salmeterol Xinafoate: Inhaled salmeterol, like other beta-adrenergic agonist drugs, can produce dose-related cardiovascular effects and effects on blood glucose and/or serum potassium in some patients (see PRECAUTIONS). The cardiovascular effects (heart rate, blood pressure) associated with salmeterol occur with similar frequency, and are of similar type and severity, as those noted following albuterol administration.

The effects of rising inhaled doses of salmeterol and standard inhaled doses of albuterol were studied in volunteers and in patients with asthma. Salmeterol doses up to 84 mcg resulted in heart rate increases of 3 to 16 beats/min, about the same as albuterol dosed at 180 mcg by inhalation aerosol (4 to 10 beats/min). In 2 double-blind asthma studies, patients receiving either 42 mcg of salmeterol inhalation aerosol twice daily ($n = 81$) or 180 mcg of albuterol inhalation aerosol 4 times daily ($n = 80$) underwent continuous electrocardiographic monitoring during four 24-hour periods; no clinically significant dysrhythmias were noted.

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

CLINICAL TRIALS

ADVAIR HFA has been studied in patients with asthma 12 years of age and older. ADVAIR HFA has not been studied in patients under 12 years of age or in patients with COPD. In clinical trials comparing ADVAIR HFA Inhalation Aerosol with the individual components, improvements in most efficacy endpoints were greater with ADVAIR HFA than with the use of either fluticasone propionate or salmeterol alone. In addition, clinical trials showed comparable results between ADVAIR HFA and ADVAIR DISKUS.

Studies Comparing ADVAIR HFA to Fluticasone Propionate Alone or Salmeterol Alone: Four (4) double-blind, parallel-group clinical trials were conducted with ADVAIR HFA in 1,517 adolescent and adult patients (≥ 12 years, mean baseline forced expiratory volume in 1 second [FEV₁] 65% to 75% of predicted normal) with asthma that was not optimally controlled on their current therapy. All metered-dose inhaler treatments were inhalation aerosols given as 2 inhalations twice daily, and other maintenance therapies were discontinued.

Study 1: Clinical Trial With ADVAIR HFA 45/21 Inhalation Aerosol: This placebo-controlled, 12-week, US study compared ADVAIR HFA 45/21 with fluticasone propionate CFC inhalation aerosol 44 mcg or salmeterol CFC inhalation aerosol 21 mcg, each given as 2 inhalations twice daily. The primary efficacy endpoints were predose FEV₁ and withdrawals due to worsening asthma. This study was stratified according to baseline asthma therapy: patients using beta-agonists (albuterol alone [$n = 142$], salmeterol [$n = 84$], or inhaled corticosteroids [$n = 134$] daily doses of beclomethasone dipropionate 252 to 336 mcg; budesonide 400 to 600 mcg; flunisolide 1,000 mcg; fluticasone propionate inhalation aerosol 176 mcg; fluticasone propionate inhalation powder 200 mcg; or triamcinolone acetonide 600 to 800 mcg). Baseline FEV₁ measurements were similar across treatments: ADVAIR HFA 45/21, 2.29 L; fluticasone propionate 44 mcg, 2.20 L; salmeterol, 2.33 L; and placebo, 2.27 L.

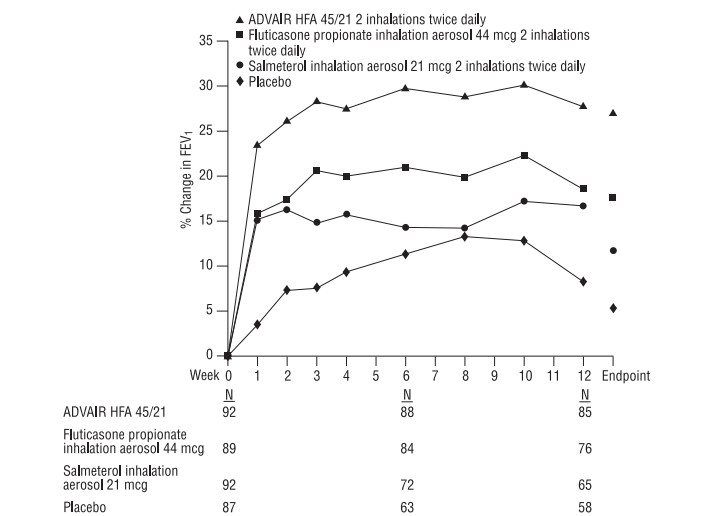
Predefined withdrawal criteria for lack of efficacy, an indicator of worsening asthma, were utilized for this placebo-controlled study. Worsening asthma was defined as a clinically important decrease in FEV₁ or peak expiratory flow (PEF), increase in use of VENTOLIN® (albuterol, USP) Inhalation Aerosol, increase in night awakenings due to asthma, emergency intervention or hospitalization due to asthma, or requirement for asthma medication not allowed by the protocol. As shown in Table 1, statistically significantly fewer patients receiving ADVAIR HFA 45/21 were withdrawn due to worsening asthma compared with salmeterol and placebo. Fewer patients receiving ADVAIR HFA 45/21 were withdrawn due to worsening asthma compared to fluticasone propionate 44 mcg; however, the difference was not statistically significant.

Table 1. Percent of Patients Withdrawn Due to Worsening Asthma in Patients Previously Treated With Beta₂-Agonists (Albuterol or Salmeterol) or Inhaled Corticosteroids (Study 1)

ADVAIR HFA 45/21 ($n = 92$)	Fluticasone Propionate CFC Inhalation Aerosol 44 mcg ($n = 89$)	Salmeterol CFC Inhalation Aerosol 21 mcg ($n = 92$)	Placebo HFA Inhalation Aerosol ($n = 87$)
2%	8%	25%	28%

The FEV₁ results are displayed in Figure 1. Because this trial used predetermined criteria for worsening asthma, which caused more patients in the placebo group to be withdrawn, FEV₁ results at Endpoint (last available FEV₁ result) are also provided. Patients receiving ADVAIR HFA 45/21 had significantly greater improvements in FEV₁ (0.58 L, 27%) compared with fluticasone propionate 44 mcg (0.36 L, 18%), salmeterol (0.25 L, 12%), and placebo (0.14 L, 5%). These improvements in FEV₁ with ADVAIR HFA 45/21 were achieved regardless of baseline asthma therapy (albuterol alone, salmeterol, or inhaled corticosteroids).

Figure 1. Mean Percent Change From Baseline in FEV₁ in Patients Previously Treated With Either Beta₂-Agonists (Albuterol or Salmeterol) or Inhaled Corticosteroids (Study 1)



The effect of ADVAIR HFA 45/21 on the secondary efficacy parameters, including morning and evening PEF, usage of VENTOLIN Inhalation Aerosol, and asthma symptoms over 24 hours on a scale of 0 to 5 is shown in Table 2.

Table 2. Secondary Efficacy Variable Results for Patients Previously Treated With Beta₂-Agonists (Albuterol or Salmeterol) or Inhaled Corticosteroids (Study 1)

Efficacy Variable*	ADVAIR HFA 45/21 ($n = 92$)	Fluticasone Propionate CFC Inhalation Aerosol 44 mcg ($n = 89$)	Salmeterol CFC Inhalation Aerosol 21 mcg ($n = 92$)	Placebo HFA Inhalation Aerosol ($n = 87$)
AM PEF (L/min)				
Baseline	377	369	381	382
Change from baseline	58	27	25	1
PM PEF (L/min)				
Baseline	397	387	402	407
Change from baseline	48	20	16	3
Use of VENTOLIN Inhalation Aerosol (inhalations/day)				
Baseline	3.1	2.4	2.7	2.7
Change from baseline	-2.1	-0.4	-0.8	0.2
Asthma symptom score/day				
Baseline	1.8	1.6	1.7	1.7
Change from baseline	-1.0	-0.3	-0.4	0

*Change from baseline = change from baseline at Endpoint (last available data).

The subjective impact of asthma on patients' perceptions of health was evaluated through use of an instrument called the Asthma Quality of Life Questionnaire (AQLQ) (based on a 7-point scale where 1 = maximum impairment and 7 = none). Patients receiving ADVAIR HFA 45/21 had clinically meaningful improvements in overall asthma-specific quality of life as defined by the difference between groups of ≥ 0.5 points in change from baseline AQLQ scores (difference in AQLQ score of 1.14 [95% CI 0.85, 1.44] compared to placebo).

Study 2: Clinical Trial With ADVAIR HFA 45/21 Inhalation Aerosol: This active-controlled, 12-week, US study compared ADVAIR HFA 45/21 with fluticasone propionate CFC inhalation aerosol 44 mcg and salmeterol CFC inhalation aerosol 21 mcg, each given as 2 inhalations twice daily, in 283 patients using as-needed albuterol alone. The primary efficacy endpoint was predose FEV₁. Baseline FEV₁ measurements were similar across treatments: ADVAIR HFA 45/21, 2.37 L; fluticasone propionate 44 mcg, 2.31 L; and salmeterol, 2.34 L.

Efficacy results in this study were similar to those observed in Study 1. Patients receiving ADVAIR HFA 45/21 had significantly greater improvements in FEV₁ (0.69 L, 33%) compared with fluticasone propionate 44 mcg (0.51 L, 25%) and salmeterol (0.47 L, 22%).

Study 3: Clinical Trial With ADVAIR HFA 115/21 Inhalation Aerosol: This placebo-controlled, 12-week, US study compared ADVAIR HFA 115/21 with fluticasone propionate CFC inhalation aerosol 110 mcg or salmeterol CFC inhalation aerosol 21 mcg, each given as 2 inhalations twice daily, in 365 patients using inhaled corticosteroids (daily doses of beclomethasone dipropionate 378 to 840 mcg; budesonide 800 to 1,200 mcg; flunisolide 1,250 to 2,000 mcg; fluticasone propionate inhalation aerosol 440 to 660 mcg; fluticasone propionate inhalation powder 400 to 600 mcg; or triamcinolone acetonide 900 to 1,600 mcg). The primary efficacy endpoints were predose FEV₁ and withdrawals due to worsening asthma. Baseline FEV₁ measurements were similar across treatments: ADVAIR HFA 115/21, 2.23 L; fluticasone propionate 110 mcg, 2.18 L; salmeterol, 2.22 L; and placebo, 2.17 L.

Efficacy results in this study were similar to those observed in Studies 1 and 2. Patients receiving ADVAIR HFA 115/21 had significantly greater improvements in FEV₁ (0.41 L, 20%) compared with fluticasone propionate 110 mcg (0.19 L, 9%), salmeterol (0.15 L, 8%), and placebo (-0.12 L, -6%). Significantly fewer patients receiving ADVAIR HFA 115/21 were withdrawn from this study for worsening asthma (7%) compared to salmeterol (24%) and placebo (54%). Fewer patients receiving ADVAIR HFA 115/21 were withdrawn due to worsening asthma (7%) compared to fluticasone propionate 110 mcg (11%); however, the difference was not statistically significant.

Study 4: Clinical Trial With ADVAIR HFA 230/21 Inhalation Aerosol: This active-controlled, 12-week, non-US study compared ADVAIR HFA 230/21 with fluticasone propionate CFC inhalation aerosol 220 mcg, each given as 2 inhalations twice daily, and with ADVAIR DISKUS 500/50 given as 1 inhalation twice daily in 509 patients using inhaled corticosteroids (daily doses of beclomethasone dipropionate CFC inhalation aerosol 1,500 to 2,000 mcg; budesonide 1,500 to 2,000 mcg; flunisolide 1,500 to 2,000 mcg; fluticasone propionate inhalation aerosol 600 to 880 mcg; or fluticasone propionate inhalation powder 750 to 1,000 mcg). The primary efficacy endpoint was morning PEF.

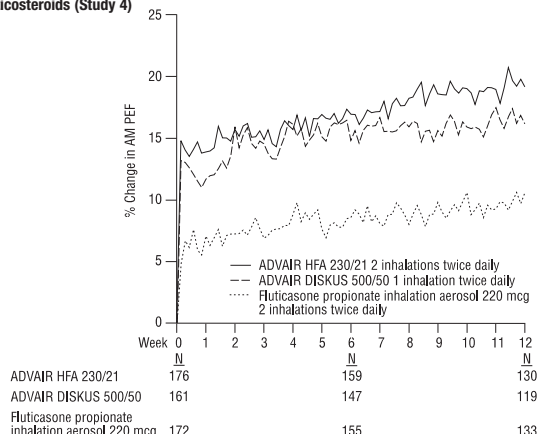
Baseline morning PEF measurements were similar across treatments: ADVAIR HFA 230/21, 327 L/min; ADVAIR DISKUS 500/50, 341 L/min; and fluticasone propionate 220 mcg, 345 L/min. As shown in Figure 2, morning PEF improved significantly with ADVAIR HFA 230/21 compared with fluticasone propionate 220 mcg over the 12-week treatment period. Improvements in morning PEF observed with ADVAIR HFA 230/21 were similar to improvements observed with ADVAIR DISKUS 500/50.

ADVAIR® HFA 45/21
(fluticasone propionate 45 mcg and salmeterol 21 mcg) Inhalation Aerosol

ADVAIR® HFA 115/21
(fluticasone propionate 115 mcg and salmeterol 21 mcg) Inhalation Aerosol

ADVAIR® HFA 230/21
(fluticasone propionate 230 mcg and salmeterol 21 mcg) Inhalation Aerosol

Figure 2. Mean Percent Change From Baseline in Morning Peak Expiratory Flow in Patients Previously Treated With Inhaled Corticosteroids (Study 4)



One-Year Safety Study: Clinical Trial With ADVAIR HFA 45/21, 115/21, and 230/21 Inhalation Aerosol: This 1-year, open-label, non-US study evaluated the safety of ADVAIR HFA 45/21, 115/21, and 230/21 given as 2 inhalations twice daily in 325 patients. This study was stratified into 3 groups according to baseline asthma therapy: patients using short-acting beta₂-agonists alone (n = 42), salmeterol (n = 91), or inhaled corticosteroids (n = 277). Patients treated with short-acting beta₂-agonists alone, salmeterol, or low doses of inhaled corticosteroids with or without concurrent salmeterol received ADVAIR HFA 45/21. Patients treated with moderate doses of inhaled corticosteroids with or without concurrent salmeterol received ADVAIR HFA 115/21. Patients treated with high doses of inhaled corticosteroids with or without concurrent salmeterol received ADVAIR HFA 230/21. Baseline FEV₁ measurements ranged from 2.3 to 2.6 L.

Improvements in FEV₁ (0.17 to 0.35 L at 4 weeks) were seen across all 3 treatments and were sustained throughout the 52-week treatment period. Few patients (3%) were withdrawn due to worsening asthma over 1 year.

Onset of Action and Progression of Improvement in Asthma Control: The onset of action and progression of improvement in asthma control were evaluated in 2 placebo-controlled US trials and 1 active-controlled US trial. Following the first dose, the median time to onset of clinically significant bronchodilation (>15% improvement in FEV₁) in most patients was seen within 30 to 60 minutes. Maximum improvement in FEV₁ occurred within 4 hours, and clinically significant improvement was maintained for 12 hours (see Figure 3).

Following the initial dose, predose FEV₁ relative to day 1 baseline improved markedly over the first week of treatment and continued to improve over the 12 weeks of treatment in all 3 studies.

No diminution in the 12-hour bronchodilator effect was observed with either ADVAIR HFA 45/21 (Figures 3 and 4) or ADVAIR HFA 230/21 as assessed by FEV₁ following 12 weeks of therapy.

Figure 3. Percent Change in Serial 12-Hour FEV₁ in Patients Previously Using Either Beta₂-Agonists (Albuterol or Salmeterol) or Inhaled Corticosteroids (Study 1)

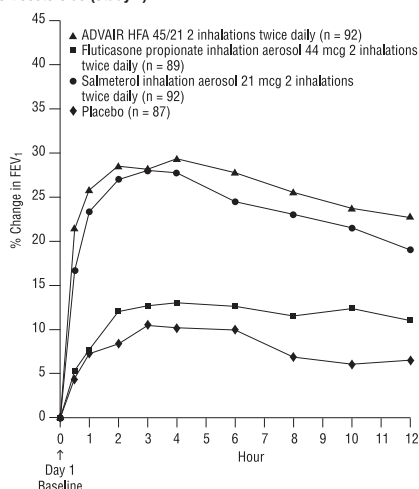
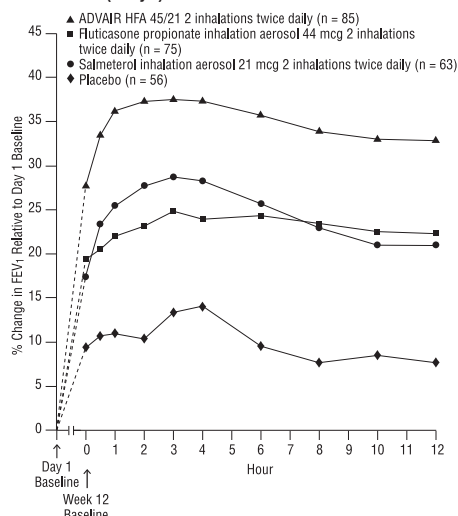


Figure 4. Percent Change in Serial 12-Hour FEV₁ in Patients Previously Using Either Beta₂-Agonists (Albuterol or Salmeterol) or Inhaled Corticosteroids (Study 1)



Reduction in asthma symptoms and use of rescue VENTOLIN Inhalation Aerosol and improvement in morning and evening PEF also occurred within the first day of treatment with ADVAIR HFA, and continued to improve over the 12 weeks of therapy in all 3 studies.

INDICATIONS AND USAGE

ADVAIR HFA is indicated for the long-term, twice-daily maintenance treatment of asthma in patients 12 years of age and older.

Long-acting beta₂-adrenergic agonists, such as salmeterol, one of the active ingredients in ADVAIR HFA, may increase the risk of asthma-related death (see WARNINGS). Therefore, when treating patients with asthma, physicians should only prescribe ADVAIR HFA for patients not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies. ADVAIR HFA is not indicated in patients whose asthma can be successfully managed by inhaled corticosteroids along with occasional use of inhaled, short-acting beta₂-agonists.

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

CONTRAINDICATIONS

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

Hypersensitivity to any of the ingredients of these preparations contraindicates their use.

WARNINGS

Long-acting beta₂-adrenergic agonists, such as salmeterol, one of the active ingredients in ADVAIR HFA, may increase the risk of asthma-related death. Therefore, when treating patients with asthma, physicians should only prescribe ADVAIR HFA for patients not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies.

A large placebo-controlled US study that compared the safety of salmeterol with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in patients receiving salmeterol. The Salmeterol Multi-center Asthma Research Trial (SMART) was a randomized, double-blind study that enrolled long-acting beta₂-agonist-naïve patients with asthma to assess the safety of salmeterol (SREVENTH Inhalation Aerosol) 42 mcg twice daily over 28 weeks compared to placebo when added to usual asthma therapy. A planned interim analysis was conducted when approximately half of the intended number of patients had been enrolled (N = 26,355), which led to premature termination of the study. The results of the interim analysis showed that patients receiving salmeterol were at increased risk for fatal asthma events (see Table 3 and Figure 5). In the total population, a higher rate of asthma-related death occurred in patients treated with salmeterol than those treated with placebo (0.10% vs. 0.02%; relative risk 4.37 [95% CI 1.25, 15.34]).

Post-hoc subpopulation analyses were performed. In Caucasians, asthma-related death occurred at a higher rate in patients treated with salmeterol than in patients treated with placebo (0.07% vs. 0.01%; relative risk 5.82 [95% CI 0.70, 48.37]). In African Americans also, asthma-related death occurred at a higher rate in patients treated with salmeterol than those treated with placebo (0.31% vs. 0.04%; relative risk 7.26 [95% CI 0.89, 58.94]). Although the relative risks of asthma-related death were similar in Caucasians and African Americans, the estimate of excess deaths in patients treated with salmeterol was greater in African Americans because there was a higher overall rate of asthma-related death in African American patients (see Table 3). Given the similar basic mechanisms of action of beta₂-agonists, it is possible that the findings seen in the SMART study represent a class effect.

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

Table 3: Asthma-Related Deaths in the 28-Week Salmeterol Multi-center Asthma Research Trial (SMART)

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

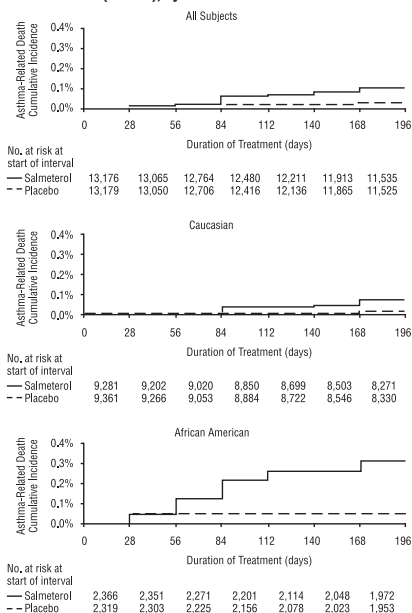
* Life-table 28-week estimate, adjusted according to the patients' actual lengths of exposure to study treatment to account for early withdrawal of patients from the study.

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

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

§ The Total Population includes the following ethnic origins listed on the case report form: Caucasian, African American, Hispanic, Asian, and "Other." In addition, the Total Population includes those patients whose ethnic origin was not reported. The results for Caucasian and African American subpopulations are shown above. No asthma-related deaths occurred in the Hispanic (salmeterol n = 996, placebo n = 999), Asian (salmeterol n = 173, placebo n = 149), or "Other" (salmeterol n = 230, placebo n = 224) subpopulations. One asthma-related death occurred in the placebo group in the subpopulation whose ethnic origin was not reported (salmeterol n = 130, placebo n = 127).

Figure 5. Cumulative Incidence of Asthma-Related Deaths in the 28-Week Salmeterol Multi-center Asthma Research Trial (SMART), by Duration of Treatment



ADVAIR® HFA 115/21
(fluticasone propionate 115 mcg and salmeterol 21 mcg) Inhalation Aerosol

ADVAIR® HFA 45/21
(fluticasone propionate 45 mcg and salmeterol 21 mcg) Inhalation Aerosol

ADVAIR® HFA 230/21
(fluticasone propionate 230 mcg and salmeterol 21 mcg) Inhalation Aerosol

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

The following additional WARNINGS about ADVAIR HFA should be noted.

ADVAIR HFA should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of asthma. Serious acute respiratory events, including fatalities, have been reported both in the United States and worldwide when salmeterol, a component of ADVAIR HFA, has been initiated in patients with significantly worsening or acutely deteriorating asthma. In most cases, these have occurred in patients with severe asthma (e.g., patients with a history of corticosteroid dependence, low pulmonary function, intubation, mechanical ventilation, frequent hospitalizations, or previous life-threatening acute asthma exacerbations) and/or in some patients in whom asthma has been acutely deteriorating (e.g., unresponsive to usual medications; increasing need for inhaled, short-acting beta₂-agonists; increasing need for systemic corticosteroids; significant increase in symptoms; recent emergency room visits; sudden or progressive deterioration in pulmonary function). However, they have occurred in a few patients with less severe asthma as well. It was not possible from these reports to determine whether salmeterol contributed to these events.

ADVAIR HFA should not be used to treat acute symptoms. An inhaled, short-acting beta₂-agonist, not ADVAIR HFA, should be used to relieve acute symptoms of shortness of breath. When prescribing ADVAIR HFA, the physician must also provide the patient with an inhaled, short-acting beta₂-agonist (e.g., albuterol) for treatment of shortness of breath that occurs acutely, despite regular twice-daily (morning and evening) use of ADVAIR HFA.

When beginning treatment with ADVAIR HFA, patients who have been taking oral or inhaled, short-acting beta₂-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs. For patients taking ADVAIR HFA, inhaled, short-acting beta₂-agonists should only be used for symptomatic relief of acute symptoms of shortness of breath (see PRECAUTIONS: Information for Patients).

Increasing use of inhaled, short-acting beta₂-agonists is a marker of deteriorating asthma. The physician and patient should be alert to such changes. The patient's condition may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient's inhaled, short-acting beta₂-agonist becomes less effective, the patient needs more inhalations than usual, or the patient develops a significant decrease in lung function, this may be a marker of destabilization of the disease. In this setting, the patient requires immediate reevaluation with reassessment of the treatment regimen, giving special consideration to the possible need for replacing the current strength of ADVAIR HFA with a higher strength, adding additional inhaled corticosteroid, or initiating systemic corticosteroids. Patients should not use more than 2 inhalations twice daily (morning and evening) of ADVAIR HFA.

ADVAIR HFA should not be used for transferring patients from systemic corticosteroid therapy. Particular care is needed for patients who have been transferred from systemically active corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of HPA function.

Patients who have been previously maintained on 20 mg or more per day of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although inhaled corticosteroids may provide control of asthma symptoms during these episodes, in recommended doses they supply less than normal physiologic amounts of glucocorticoid (cortisol) systemically and do NOT provide the mineralocorticoid activity that is necessary for coping with these emergencies.

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

ADVAIR HFA should not be used in conjunction with an inhaled, long-acting beta₂-agonist. Patients who are receiving ADVAIR HFA twice daily should not use additional salmeterol or other long-acting beta₂-agonists (e.g., formoterol) for prevention of exercise-induced bronchospasm (EIB) or the maintenance treatment of asthma. Additional benefit would not be gained from using supplemental salmeterol or formoterol for prevention of EIB since ADVAIR HFA already contains an inhaled, long-acting beta₂-agonist.

The recommended dosage should not be exceeded. ADVAIR HFA should not be used more often or at higher doses than recommended. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Large doses of inhaled or oral salmeterol (12 to 20 times the recommended dose) have been associated with clinically significant prolongation of the QTc interval, which has the potential for producing ventricular arrhythmias.

Paradoxical bronchospasm. As with other inhaled asthma medications, ADVAIR HFA can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with ADVAIR HFA, it should be treated immediately with an inhaled, short-acting bronchodilator; ADVAIR HFA should be discontinued immediately; and alternative therapy should be instituted.

Immediate hypersensitivity reactions. Immediate hypersensitivity reactions may occur after administration of ADVAIR HFA, 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 fluticasone propionate and salmeterol, components of ADVAIR HFA.

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

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

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.

Potential drug interactions with CYP 3A4 inhibitors. Both fluticasone propionate and salmeterol are substrates of CYP 3A4. **Fluticasone Propionate:** A drug interaction study in healthy subjects has shown that ritonavir (a strong cytochrome P450 3A4 inhibitor) can significantly increase systemic fluticasone propionate exposure (AUC), resulting in significantly reduced serum cortisol concentrations (see CLINICAL PHARMACOLOGY: Pharmacokinetics: *Fluticasone Propionate: Drug Interactions* and PRECAUTIONS: Drug Interactions: *Inhibitors of Cytochrome P450*). During postmarketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing syndrome and adrenal suppression. Therefore, coadministration of fluticasone propionate and ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.

Salmeterol: Because of the potential for drug interactions and the potential for increased risk of cardiovascular adverse events, the concomitant use of ADVAIR HFA with strong CYP 3A4 inhibitors (e.g., ketoconazole, ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) is not recommended (see CLINICAL PHARMACOLOGY: Pharmacokinetics: *Salmeterol Xinafoate: Drug Interactions*).

PRECAUTIONS

General: Cardiovascular Effects: Cardiovascular and central nervous system effects seen with all sympathomimetic drugs (e.g., increased blood pressure, heart rate, excitement) can occur after use of salmeterol, a component of ADVAIR HFA, and may require discontinuation of ADVAIR HFA. ADVAIR HFA, like all medications containing sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive disorders or thyrotoxicosis; and in patients who are unusually responsive to sympathomimetic amines.

As has been described with other beta-adrenergic agonist bronchodilators, clinically significant changes in ECGs have been seen infrequently in individual patients in controlled clinical studies with ADVAIR HFA and salmeterol. Clinically significant changes in systolic and/or diastolic blood pressure and pulse rate have been seen infrequently in individual patients in controlled clinical studies with salmeterol, a component of ADVAIR HFA.

Metabolic and Other Effects: Long-term use of orally inhaled corticosteroids may affect normal bone metabolism, resulting in a loss of bone mineral density. In patients with major risk factors for decreased bone mineral content, such as tobacco use, advanced age, sedentary lifestyle, poor nutrition, family history of osteoporosis, or chronic use of drugs that

can reduce bone mass (e.g., anticonvulsants and corticosteroids), ADVAIR HFA may pose an additional risk.

Doses of the related beta₂-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis. Beta-adrenergic agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation.

Clinically significant changes in blood glucose and/or serum potassium were seen infrequently during clinical studies with ADVAIR HFA at recommended doses.

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

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

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

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

A reduction of growth velocity in children and adolescents may occur as a result of poorly controlled asthma or from the therapeutic use of corticosteroids, including inhaled corticosteroids (see PRECAUTIONS: Pediatric Use). The effects of long-term treatment of children and adolescents with inhaled corticosteroids, including fluticasone propionate, on final adult height are not known. Patients should be maintained on the lowest strength of ADVAIR HFA that effectively controls their asthma.

The long-term effects of ADVAIR HFA in human subjects are not fully known. In particular, the effects resulting from chronic use of fluticasone propionate on developmental or immunologic processes in the mouth, pharynx, trachea, and lung are unknown. Some patients received inhaled fluticasone propionate on a continuous basis in a clinical study for up to 4 years. In clinical studies with patients treated for 2 years with inhaled fluticasone propionate, no apparent differences in the type or severity of adverse reactions were observed after long- versus short-term treatment.

Glaucoma, increased intraocular pressure, and cataracts have been reported in patients following the long-term administration of inhaled corticosteroids, including fluticasone propionate, a component of ADVAIR HFA.

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

In clinical studies with ADVAIR HFA, the development of localized infections of the pharynx with *Candida albicans* has occurred. When such an infection develops, it should be treated with appropriate local or systemic (i.e., oral antifungal) therapy while remaining on treatment with ADVAIR HFA, but at times therapy with ADVAIR HFA may need to be interrupted.

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

Eosinophilic Conditions: In rare cases, patients on inhaled fluticasone propionate, a component of ADVAIR HFA, may present with systemic eosinophilic conditions, with some patients presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of fluticasone propionate. Cases of serious eosinophilic conditions have also been reported with other inhaled corticosteroids in this clinical setting. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal relationship between fluticasone propionate and these underlying conditions has not been established (see ADVERSE REACTIONS: Observed During Clinical Practice: *Eosinophilic Conditions*).

Information for Patients: Patients should be instructed to read the accompanying Medication Guide with each new prescription and refill. The complete text of the Medication Guide is reprinted at the end of this document.

Patients being treated with ADVAIR HFA should receive the following information and instructions. This information is intended to aid them in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. It is important that patients understand how to use ADVAIR HFA in relation to other asthma medications they are taking.

- Patients should be informed that salmeterol, one of the active ingredients in ADVAIR HFA, may increase the risk of asthma-related death.** They should also be informed that data are not adequate to determine whether the concurrent use of inhaled corticosteroids, such as fluticasone propionate, the other component of ADVAIR HFA, or other asthma-controller therapy modifies this risk.
- ADVAIR HFA is not meant to relieve acute asthma symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting beta₂-agonist such as albuterol (the physician should provide the patient with such medication and instruct the patient in how it should be used).
- The physician should be notified immediately if any of the following signs of seriously worsening asthma occur:
 - decreasing effectiveness of inhaled, short-acting beta₂-agonists;
 - need for more inhalations than usual of inhaled, short-acting beta₂-agonists;
 - significant decrease in lung function as outlined by the physician.
- Patients should not stop therapy with ADVAIR HFA without physician/provider guidance since symptoms may recur after discontinuation.
- Patients should be cautioned regarding common adverse effects associated with beta₂-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.
- Long-term use of inhaled corticosteroids, including fluticasone propionate, a component of ADVAIR HFA, may increase the risk of some eye problems (cataracts or glaucoma). Regular eye examinations should be considered.
- When patients are prescribed ADVAIR HFA, other medications for asthma should be used only as directed by the physician.
- Patients who are pregnant or nursing should contact the physician about the use of ADVAIR HFA.
- Patients should use ADVAIR HFA at regular intervals as directed. Results of clinical trials indicated significant improvement may occur within the first 30 minutes of taking the first dose; however, the full benefit may not be achieved until treatment has been administered for 1 week or longer. The patient should not use more than the prescribed dosage but should contact the physician if symptoms do not improve or if the condition worsens.
- The bronchodilation from a single dose of ADVAIR HFA may last up to 12 hours or longer. The recommended dosage (2 inhalations twice daily, morning and evening) should not be exceeded. Patients who are receiving ADVAIR HFA twice daily should not use salmeterol or other inhaled, long-acting beta₂-agonists (e.g., formoterol) for prevention of EIB or maintenance treatment of asthma.
- Patients should be warned to avoid exposure to chickenpox or measles and, if they are exposed, to consult the physician without delay.
- Prime the inhaler before using for the first time by releasing 4 test sprays into the air away from the face, shaking well for 5 seconds before each spray. In cases where the inhaler has not been used for more than 4 weeks or when it has been dropped, prime the inhaler again by shaking well before each spray and releasing 2 test sprays into the air away from the face.
- After inhalation, rinse the mouth with water and spit out. Do not swallow.
- Clean the inhaler at least once a week after the evening dose. Keeping the canister and plastic actuator clean is important to prevent medicine buildup. (See Instructions for Using ADVAIR HFA in the Medication Guide accompanying the product.)
- Use ADVAIR HFA only with the actuator supplied with the product. Discard the inhaler after 120 sprays have been used.
- Patients should never immerse the canister into water to determine the amount remaining in the canister ("float test").
- For the proper use of ADVAIR HFA and to attain maximum improvement, the patient should read and carefully follow the Instructions for Using ADVAIR HFA in the Medication Guide accompanying the product.

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

Short-Acting Beta₂-Agonists: In three 12-week US clinical trials, the mean daily need for additional beta₂-agonist use in 277 patients receiving ADVAIR HFA was approximately 1.2 inhalations/day and ranged from 0 to 9 inhalations/day. Two percent (2%) of patients receiving ADVAIR HFA in these trials averaged 6 or more inhalations per day over the course of the

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12-week trials. No increase in frequency of cardiovascular events was observed among patients who averaged 6 or more inhalations per day.

Methylxanthines: The concurrent use of intravenously or orally administered methylxanthines (e.g., aminophylline, theophylline) by patients receiving ADVAIR HFA has not been completely evaluated. In five 12-week clinical trials (3 US and 2 non-US), 45 patients receiving ADVAIR HFA 45/21, 115/21, or 230/21 twice daily concurrently with a theophylline product had adverse event rates similar to those in 577 patients receiving ADVAIR HFA without theophylline.

Fluticasone Propionate Nasal Spray: In patients receiving ADVAIR HFA in three 12-week US clinical trials, no difference in the profile of adverse events or HPA axis effects was noted between patients receiving FLONASE® (fluticasone propionate) Nasal Spray, 50 mcg concurrently (n = 89) and those who were not (n = 192).

Monoamine Oxidase Inhibitors and Tricyclic Antidepressants: ADVAIR HFA should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of salmeterol, a component of ADVAIR HFA, on the vascular system may be potentiated by these agents.

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

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

Inhibitors of Cytochrome P450: Fluticasone propionate and salmeterol are substrates of cytochrome P450 3A4.

Fluticasone propionate: A drug interaction study with fluticasone propionate aqueous nasal spray in healthy subjects has shown that ritonavir (a strong cytochrome P450 3A4 inhibitor) can significantly increase plasma fluticasone propionate exposure, resulting in significantly reduced serum cortisol concentrations (see CLINICAL PHARMACOLOGY: Pharmacokinetics: *Fluticasone Propionate: Drug Interactions*). During postmarketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing's syndrome and adrenal suppression. Therefore, coadministration of fluticasone propionate and ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.

In a placebo-controlled, crossover study in 8 healthy adult volunteers, coadministration of a single dose of orally inhaled fluticasone propionate (1,000 mcg) with multiple doses of ketoconazole (200 mg) to steady state resulted in increased systemic fluticasone propionate exposure, a reduction in plasma cortisol AUC, and no effect on urinary excretion of cortisol.

Salmeterol: In a drug interaction study in 20 healthy subjects, coadministration of inhaled salmeterol (50 mcg twice daily) and oral ketoconazole (400 mg once daily) for 7 days resulted in greater systemic exposure to salmeterol (AUC increased 16-fold and C_{max} increased 1.4-fold). Three (3) subjects were withdrawn due to beta₂-agonist side effects (2 with prolonged QTc and 1 with palpitations and sinus tachycardia). Although there was no statistical effect on the mean QTc, coadministration of salmeterol and ketoconazole was associated with more frequent increases in QTc duration compared with salmeterol and placebo administration. Due to the potential increased risk of cardiovascular adverse events, the concomitant use of salmeterol with strong CYP3A4 inhibitors (e.g., ketoconazole, ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) is not recommended (see CLINICAL PHARMACOLOGY: Pharmacokinetics: *Salmeterol Xinafoate: Drug Interactions*).

Carcinogenesis, Mutagenesis, Impairment of Fertility: Fluticasone Propionate: Fluticasone propionate demonstrated no tumorigenic potential in mice at oral doses up to 1,000 mcg/kg (approximately 4 times the maximum recommended human daily inhalation dose on a mcg/m² basis) for 78 weeks or in rats at inhalation doses up to 57 mcg/kg (less than the maximum recommended human daily inhalation dose on a mcg/m² basis) for 104 weeks.

Fluticasone propionate did not induce gene mutation in prokaryotic or eukaryotic cells in vitro. No significant clastogenic effect was seen in cultured human peripheral lymphocytes in vitro or in the mouse micronucleus test.

No evidence of impairment of fertility was observed in reproductive studies conducted in male and female rats at subcutaneous doses up to 50 mcg/kg (less than the maximum recommended human daily inhalation dose on a mcg/m² basis). Prostate weight was significantly reduced at a subcutaneous dose of 50 mcg/kg.

Salmeterol: In an 18-month oral carcinogenicity study in CD-mice, salmeterol at oral doses of 1.4 mg/kg and above (approximately 10 times the maximum recommended human daily inhalation dose based on comparison of the AUCs) caused a dose-related increase in the incidence of smooth muscle hyperplasia, cystic glandular hyperplasia, leiomyomas of the uterus, and ovarian cysts. The incidence of leiomyosarcomas was not statistically significant. No tumors were seen at 0.2 mg/kg (approximately 2 times the maximum recommended human daily inhalation dose in adults based on comparison of the AUCs).

In a 24-month oral and inhalation carcinogenicity study in Sprague Dawley rats, salmeterol caused a dose-related increase in the incidence of mesovarian leiomyomas and ovarian cysts at doses of 0.68 mg/kg and above (approximately 65 times the maximum recommended human daily inhalation dose on a mcg/m² basis). No tumors were seen at 0.21 mg/kg (approximately 20 times the maximum recommended human daily inhalation dose on a mcg/m² basis). These findings in rodents are similar to those reported previously for other beta-adrenergic agonist drugs. The relevance of these findings to human use is unknown.

Salmeterol produced no detectable or reproducible increases in microbial and mammalian gene mutation in vitro. No clastogenic activity occurred in vitro in human lymphocytes or in vivo in a rat micronucleus test. No effects on fertility were identified in male and female rats treated with salmeterol at oral doses up to 2 mg/kg (approximately 190 times the maximum recommended human daily inhalation dose on a mcg/m² basis).

Pregnancy: Teratogenic Effects: ADVAIR HFA Inhalation Aerosol: Pregnancy Category C. From the reproduction toxicity studies in mice and rats, no evidence of enhanced toxicity was seen using combinations of fluticasone propionate and salmeterol compared to toxicity data from the components administered separately. In mice combining 150 mcg/kg subcutaneously of fluticasone propionate (less than the maximum recommended human daily inhalation dose on a mcg/m² basis) with 10 mg/kg orally of salmeterol (approximately 480 times the maximum recommended human daily inhalation dose on a mcg/m² basis) were teratogenic. Cleft palate, fetal death, increased implantation loss and delayed ossification was seen. These observations are characteristic of glucocorticoids. No developmental toxicity was observed at combination doses up to 40 mcg/kg subcutaneously of fluticasone propionate (less than the maximum recommended human daily inhalation dose on a mcg/m² basis) and up to 1.4 mg/kg orally of salmeterol (approximately 70 times the maximum recommended human daily inhalation dose on a 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 human daily inhalation dose on a mcg/m² basis) and up to 1 mg/kg of salmeterol (approximately 95 times the maximum recommended human daily inhalation dose on a mcg/m² basis). Combining 100 mcg/kg subcutaneously of fluticasone propionate (equivalent to the maximum recommended human daily inhalation dose on a mcg/m² basis) with 10 mg/kg orally of salmeterol (approximately 970 times the maximum recommended human daily inhalation dose on a 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 HFA in pregnant women. ADVAIR HFA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Fluticasone Propionate: Pregnancy Category C. Subcutaneous studies in the mouse and rat at 45 and 100 mcg/kg, respectively (less than and equivalent to, respectively, the maximum recommended human daily inhalation dose on a mcg/m² basis), revealed fetal toxicity characteristic of potent corticosteroid compounds, including embryonic growth retardation, omphalocele, cleft palate, and retarded cranial ossification. No teratogenicity was seen in the rat at inhalation doses up to 68.7 mcg/kg (less than the maximum recommended human daily inhalation dose on a mcg/m² basis).

In the rabbit, fetal weight reduction and cleft palate were observed at a subcutaneous dose of 4 mcg/kg (less than the maximum recommended human daily inhalation dose on a mcg/m² basis). However, no teratogenic effects were reported at oral doses up to 300 mcg/kg (approximately 5 times the maximum recommended human daily inhalation dose on a mcg/m² basis) of fluticasone propionate. No fluticasone propionate was detected in the plasma in this study, consistent with the established low bioavailability following oral administration (see CLINICAL PHARMACOLOGY: Pharmacokinetics: *Fluticasone Propionate: Absorption*).

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

There are no adequate and well-controlled studies in pregnant women. ADVAIR HFA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Experience with oral corticosteroids since their introduction in pharmacologic, as opposed to physiologic, doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans. In addition, because there is a natural increase in corticosteroid production during pregnancy, most women will require a lower exogenous corticosteroid dose and many will not need corticosteroid treatment during pregnancy.

Salmeterol: Pregnancy Category C. No teratogenic effects occurred in the rat at oral doses up to 2 mg/kg (approximately 190 times the maximum recommended human daily inhalation dose on a mcg/m² basis). In pregnant Dutch rabbits administered oral doses of 1 mg/kg and above (approximately 25 times the maximum recommended human daily inhala-

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tion dose based on the comparison of the AUCs), salmeterol exhibited fetal toxic effects characteristically resulting from beta-adrenoceptor stimulation. These included precocious eyelid openings, cleft palate, sternal fusion, limb and paw flexures, and delayed ossification of the frontal cranial bones. No significant effects occurred at an oral dose of 0.6 mg/kg (approximately 10 times the maximum recommended human daily inhalation dose based on comparison of the AUCs).

New Zealand White rabbits were less sensitive since only delayed ossification of the frontal cranial bones was seen at an oral dose of 10 mg/kg (approximately 1,900 times the maximum recommended human daily inhalation dose on a mcg/m² basis). Extensive use of other beta-agonists has provided no evidence that these class effects in animals are relevant to their use in humans.

Salmeterol xinafoate crossed the placenta following oral administration of 10 mg/kg to mice and rats (approximately 480 and 970 times, respectively, the maximum recommended human daily inhalation dose on a mcg/m² basis).

There are no adequate and well-controlled studies with salmeterol in pregnant women. Salmeterol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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

Nursing Mothers: Plasma levels of salmeterol, a component of ADVAIR HFA, after inhaled therapeutic doses are very low. In rats, salmeterol xinafoate is excreted in the milk. There are no data from controlled trials on the use of salmeterol by nursing mothers. It is not known whether fluticasone propionate, a component of ADVAIR HFA, is excreted in human breast milk. However, other corticosteroids have been detected in human milk. Subcutaneous administration to lactating rats of 10 mcg/kg tritiated fluticasone propionate (less than the maximum recommended human daily inhalation dose on a mcg/m² basis) resulted in measurable radioactivity in milk.

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

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

Pediatric Use: Thirty-eight (38) patients 12 to 17 years of age were treated with ADVAIR HFA in US pivotal clinical trials. Patients in this age-group demonstrated efficacy results similar to those observed in patients 18 years of age and older. There were no obvious differences in the type or frequency of adverse events reported in this age-group compared with patients 18 years of age and older.

The safety and effectiveness of ADVAIR HFA in children under 12 years have not been established.

Controlled clinical studies have shown that inhaled corticosteroids may cause a reduction in growth in pediatric patients. In these studies, the mean reduction in growth velocity was approximately 1 cm/year (range, 0.3 to 1.8 cm/year) and appears to depend upon dose and duration of exposure. This effect was observed in the absence of laboratory evidence of HPA axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The long-term effects of this reduction in growth velocity associated with orally inhaled corticosteroids, including the impact on final adult height, are unknown. The potential for "catch-up" growth following discontinuation of treatment with orally inhaled corticosteroids has not been adequately studied. The effects on growth velocity of treatment with orally inhaled corticosteroids for over 1 year, including the impact on final adult height, are unknown. The growth of children and adolescents receiving orally inhaled corticosteroids, including ADVAIR HFA, should be monitored. If a child or adolescent on any corticosteroid appears to have growth suppression, the possibility that he/she is particularly sensitive to this effect of corticosteroids should be considered. The potential growth effects of prolonged treatment should be weighed against the clinical benefits obtained and the risks associated with alternative therapies. To minimize the systemic effects of orally inhaled corticosteroids, including ADVAIR HFA, each patient should be titrated to the lowest strength that effectively controls his/her asthma (see DOSAGE AND ADMINISTRATION).

Geriatric Use: Of the total number of patients in clinical studies treated with ADVAIR HFA, 41 were 65 years of age or older and 21 were 75 years of age or older. No overall differences in safety were observed between these patients and younger patients, and other reported clinical experience, including studies of the individual components, has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. As with other products containing beta₂-agonists, special caution should be observed when using ADVAIR HFA in geriatric patients who have concomitant cardiovascular disease that could be adversely affected by beta₂-agonists. Based on available data for ADVAIR HFA or its active components, no adjustment of dosage of ADVAIR HFA in geriatric patients is warranted.

ADVERSE REACTIONS

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

The incidence of common adverse events in Table 4 is based upon 2 placebo-controlled, 12-week, US clinical studies (Studies 1 and 3) and 1 active-controlled, 12-week, US clinical study (Study 2). A total of 1,008 adolescent and adult patients with asthma (556 females and 452 males) previously treated with albuterol alone, salmeterol, or inhaled corticosteroids were treated twice daily with 2 inhalations of ADVAIR HFA 45/21 or ADVAIR HFA 115/21, fluticasone propionate CFC inhalation aerosol (44- or 110-mcg doses), salmeterol CFC inhalation aerosol 21 mcg, or placebo HFA inhalation aerosol.

Table 4. Overall Adverse Events With ≥3% Incidence in US Controlled Clinical Trials With ADVAIR HFA Inhalation Aerosol in Patients With Asthma

Adverse Events	ADVAIR HFA		Fluticasone Propionate CFC Inhalation Aerosol		Salmeterol CFC Inhalation Aerosol	Placebo HFA Inhalation Aerosol
	45/21 (n = 187) %	115/21 (n = 94) %	44 mcg (n = 186) %	110 mcg (n = 91) %	21 mcg (n = 274) %	(n = 176) %
Ear, nose, & throat						
Upper respiratory tract infection	16	24	13	15	17	13
Throat irritation	9	7	12	13	9	7
Upper respiratory inflammation	4	4	3	7	5	3
Hoarseness/dysphonia	3	1	2	0	1	0
Lower respiratory						
Viral respiratory infections	3	5	4	5	3	4
Neurology						
Headaches	21	15	24	16	20	11
Dizziness	4	1	1	0	<1	0
Gastrointestinal						
Nausea & vomiting	5	3	4	2	2	3
Viral gastrointestinal infections	4	2	2	0	1	2
Gastrointestinal signs & symptoms	3	2	2	1	1	1
Non-site specific						
Pain	3	1	2	1	2	2
Musculoskeletal						
Musculoskeletal pain	5	7	8	2	4	4
Muscle pain	4	1	1	1	3	<1
Drug interaction, overdose, & trauma						
Muscle injuries	3	0	2	1	3	2
Reproduction						
Menstruation symptoms	5	3	1	0	<1	<1
Psychiatry						
Intoxication & hangover	3	0	0	0	0	0
Average duration of exposure (days)	81.3	78.6	79.9	74.6	71.4	56.3

Table 4 includes all events (whether considered drug-related or nondrug-related by the investigator) that occurred at a rate of 3% or greater in any of the groups receiving ADVAIR HFA and were more common than in the placebo group. In considering these data, differences in average duration of exposure should be taken into account. These adverse reactions were mostly mild to moderate in severity.

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

Cardiovascular: Tachycardia, arrhythmias, myocardial infarction.
Drug Interaction, Overdose, and Trauma: Postoperative complications, wounds and lacerations, soft tissue injuries, poisoning and toxicity, pressure-induced disorder.

Ear, Nose, and Throat: Ear, nose, and throat infection; ear signs and symptoms; rhinorrhea/postnasal drip; epistaxis; nasal congestion/blockage; laryngitis; unspecified oropharyngeal plaques; dryness of nose.

Endocrine and Metabolic: Weight gain.

Eye: Allergic eye disorders, eye edema and swelling.

Gastrointestinal: Gastrointestinal discomfort and pain, dental discomfort and pain, candidiasis mouth/throat, hyposalivation, gastrointestinal infections, disorders of hard tissue of teeth, hemorrhoids, gastrointestinal gaseous symptoms, abdominal discomfort and pain, constipation, oral abnormalities.

Musculoskeletal: Arthralgia and articular rheumatism, muscle cramps and spasms, musculoskeletal inflammation, bone and skeletal pain.

Neurology: Sleep disorders, migraines.

Non-Site Specific: Allergies and allergic reactions, viral infections, bacterial infections, candidiasis unspecified site, congestion, inflammation.

Reproduction: Bacterial reproductive infections.

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

Skin: Eczema, dermatitis and dermatosis.

Urology: Urinary infections.

Rare cases of immediate and delayed hypersensitivity reactions, including rash and other rare events of angioedema and bronchospasm, have been reported.

The incidence of common adverse events reported in Study 4, a 12-week, non-US clinical study of 509 patients previously treated with inhaled corticosteroids who were treated twice daily with 2 inhalations of ADVAIR HFA 230/21, fluticasone propionate CFC inhalation aerosol 220 mcg, or 1 inhalation of ADVAIR DISKUS 500/50 was similar to the incidences reported in Table 4.

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

In extensive US and worldwide postmarketing experience with salmeterol, a component of ADVAIR HFA, serious exacerbations of asthma, including some that have been fatal, have been reported. In most cases, these have occurred in patients with severe asthma and/or in some patients in whom asthma has been acutely deteriorating (see WARNINGS), but they have also occurred in a few patients with less severe asthma. It was not possible from these reports to determine whether salmeterol contributed to these events.

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

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

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

Eye: Cataracts, glaucoma.

Gastrointestinal: Dyspepsia, xerostomia.

Hepatobiliary Tract and Pancreas: Abnormal liver function tests.

Musculoskeletal: Back pain, myositis.

Neurology: Paresthesia, restlessness.

Non-Site Specific: Fever, immediate and delayed hypersensitivity reaction, pallor.

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

Respiratory: Asthma; asthma exacerbation; chest congestion; chest tightness; cough; dyspnea; immediate bronchospasm; influenza; paradoxical bronchospasm; tracheitis; wheezing; pneumonia; reports of upper respiratory symptoms of laryngeal spasm, irritation, or swelling; stridor; choking.

Skin: Contact dermatitis, contusions, ecchymoses, photodermatitis, pruritus.

Urogenital: Dysmenorrhea, irregular menstrual cycle, pelvic inflammatory disease, vaginal candidiasis, vaginitis, vulvovaginitis.

Eosinophilic Conditions: In rare cases, patients on inhaled fluticasone propionate, a component of ADVAIR HFA, may present with systemic eosinophilic conditions, with some patients presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of fluticasone propionate. Cases of serious eosinophilic conditions have also been reported with other inhaled corticosteroids in this clinical setting. While ADVAIR HFA should not be used for transferring patients from systemic corticosteroid therapy, physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal relationship between fluticasone propionate and these underlying conditions has not been established (see PRECAUTIONS: General: *Eosinophilic Conditions*).

OVERDOSAGE

ADVAIR HFA Inhalation Aerosol: No deaths occurred in rats given a single-dose combination of salmeterol 3.6 mg/kg and fluticasone propionate 1.9 mg/kg given as the inhalation powder (approximately 290 and 15 times, respectively, the maximum recommended human daily inhalation dose on a mg/m² basis).

Fluticasone Propionate: Chronic overdosage with fluticasone propionate may result in signs/symptoms of hypercorticism (see PRECAUTIONS: General: *Metabolic and Other Effects*). Inhalation by healthy volunteers of a single dose of 4,000 mcg of fluticasone propionate inhalation powder or single doses of 1,760 or 3,520 mcg of fluticasone propionate CFC inhalation aerosol were well tolerated. Fluticasone propionate given by inhalation aerosol at 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 (>4,400 times the maximum recommended human daily inhalation dose on a mg/m² basis). In rats the subcutaneous median lethal dose was >1,000 mg/kg (>8,800 times the maximum recommended human daily inhalation dose on a mg/m² basis).

Salmeterol: The expected signs and symptoms with overdosage of salmeterol are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and symptoms listed under ADVERSE REACTIONS, e.g., seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, and insomnia. Overdosage with salmeterol may be expected to result in exaggeration of the pharmacologic adverse effects associated with beta-adrenoceptor agonists, including tachycardia and/or arrhythmia, tremor, headache, and muscle cramps. Overdosage with salmeterol can lead to clinically significant prolongation of the QTc interval, which can produce ventricular arrhythmias. Other signs of overdosage may include hypokalemia and hyperglycemia.

As with all sympathomimetic medications, cardiac arrest and even death may be associated with abuse of salmeterol.

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

No deaths were seen in rats given salmeterol at an inhalation dose of 2.9 mg/kg (approximately 280 times the maximum recommended human daily inhalation dose on a mg/m² basis) and in dogs at an inhalation dose of 0.7 mg/kg (approximately 230 times the maximum recommended human daily inhalation dose on a mg/m² basis). By the oral route, no deaths occurred in mice at 150 mg/kg (approximately 7,200 times the maximum recommended human daily inhalation dose on a mg/m² basis) and in rats at 1,000 mg/kg (approximately 97,000 times the maximum recommended human daily inhalation dose on a mg/m² basis).

DOSAGE AND ADMINISTRATION

ADVAIR HFA should be administered by the orally inhaled route only in patients 12 years of age and older. ADVAIR HFA should not be used for transferring patients from systemic corticosteroid therapy. ADVAIR HFA has not been studied in patients under 12 years of age or in patients with COPD.

Long-acting beta₂-adrenergic agonists, such as salmeterol, one of the active ingredients in ADVAIR HFA, may increase the risk of asthma-related death (see WARNINGS). Therefore, when treating patients with asthma, physicians should only

prescribe ADVAIR HFA for patients not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severely clearly warrants initiation of treatment with 2 maintenance therapies. ADVAIR HFA is not indicated in patients whose asthma can be successfully managed by inhaled corticosteroids along with occasional use of inhaled, short-acting beta₂-agonists.

ADVAIR HFA is available in 3 strengths, ADVAIR HFA 45/21 Inhalation Aerosol, ADVAIR HFA 115/21 Inhalation Aerosol, and ADVAIR HFA 230/21 Inhalation Aerosol, containing 45, 115, and 230 mcg of fluticasone propionate, respectively, and 21 mcg of salmeterol per inhalation.

ADVAIR HFA should be administered as 2 inhalations twice daily every day. More frequent administration (more than twice daily) or a higher number of inhalations (more than 2 inhalations twice daily) of the prescribed strength of ADVAIR HFA is not recommended as some patients are more likely to experience adverse effects with higher doses of salmeterol. The safety and efficacy of ADVAIR HFA when administered in excess of recommended doses have not been established.

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

Patients who are receiving ADVAIR HFA twice daily should not use additional salmeterol or other inhaled, long-acting beta₂-agonists (e.g., formoterol) for prevention of EIB or for any other reason.

For patients 12 years of age and older, the dosage is 2 inhalations twice daily (morning and evening, approximately 12 hours apart).

The recommended starting dosages for ADVAIR HFA are based upon patients' current asthma therapy.

• For patients not adequately controlled on an inhaled corticosteroid, Table 5 provides the recommended starting dosage.

• For patients not currently on inhaled corticosteroids, whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies, the recommended starting dosage is 2 inhalations of ADVAIR HFA 45/21 or ADVAIR HFA 115/21 twice daily (see INDICATIONS AND USAGE).

The maximum recommended dosage is 2 inhalations of ADVAIR HFA 230/21 twice daily.

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

Table 5. Recommended Dosages of ADVAIR HFA Inhalation Aerosol for Patients Not Adequately Controlled on Inhaled Corticosteroids

Current Daily Dose of Inhaled Corticosteroid		Recommended Strength of ADVAIR HFA (2 inhalations twice daily)
Beclomethasone dipropionate HFA inhalation aerosol	≤160 mcg	45/21
	320 mcg	115/21
	640 mcg	230/21
Budesonide inhalation powder	≤400 mcg	45/21
	800-1,200 mcg	115/21
	1,600 mcg*	230/21
Flunisolide CFC inhalation aerosol	≤1,000 mcg	45/21
	1,250-2,000 mcg	115/21
Flunisolide HFA inhalation aerosol	≤320 mcg	45/21
	640 mcg	115/21
Fluticasone propionate HFA inhalation aerosol	≤176 mcg	45/21
	440 mcg	115/21
	660-880 mcg*	230/21
Fluticasone propionate inhalation powder	≤200 mcg	45/21
	500 mcg	115/21
	1,000 mcg*	230/21
Mometasone furoate inhalation powder	220 mcg	45/21
	440 mcg	115/21
	880 mcg	230/21
Triamcinolone acetonide inhalation aerosol	≤1,000 mcg	45/21
	1,100-1,600 mcg	115/21

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

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

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

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

ADVAIR HFA should be primed before using for the first time by releasing 4 test sprays into the air away from the face, shaking well for 5 seconds before each spray. In cases where the inhaler has not been used for more than 4 weeks or when it has been dropped, prime the inhaler again by shaking well before each spray and releasing 2 test sprays into the air, away from the face.

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

HOW SUPPLIED

Each strength of ADVAIR HFA Inhalation Aerosol is supplied in a 12-g pressurized aluminum canister containing 120 metered inhalations in a box of 1.* Each canister is supplied with a purple actuator with a light purple strapcap and is sealed in a plastic-coated, moisture-protective foil pouch with a desiccant that should be discarded when the pouch is opened. Each canister is packaged with a Medication Guide leaflet.

*NDC 0173-0715-00 ADVAIR HFA 45/21 Inhalation Aerosol

*NDC 0173-0716-00 ADVAIR HFA 115/21 Inhalation Aerosol

*NDC 0173-0717-00 ADVAIR HFA 230/21 Inhalation Aerosol

The purple actuator supplied with ADVAIR HFA Inhalation Aerosol should not be used with any other product canisters, and actuators from other products should not be used with an ADVAIR HFA Inhalation Aerosol canister.

The correct amount of medication in each inhalation cannot be assured after 120 inhalations, even though the canister is not completely empty and will continue to operate. The inhaler should be discarded when 120 actuations have been used. Never immerse the canister into water to determine the amount remaining in the canister ("float test").

Keep out of reach of children. Avoid spraying in eyes.

Contents Under Pressure: Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 120°F may cause bursting. Never throw container into fire or incinerator.

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). Store the inhaler with the mouthpiece down. For best results, the inhaler should be at room temperature before use. SHAKE WELL FOR 5 SECONDS BEFORE USING.

ADVAIR HFA Inhalation Aerosol does not contain chlorofluorocarbons (CFCs) as the propellant.



GlaxoSmithKline

Research Triangle Park, NC 27709

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Please see the Medication Guide for ADVAIR HFA on the following pages.

MEDICATION GUIDE

ADVAIR® HFA [ad'vair] 45/21 Inhalation Aerosol
(fluticasone propionate 45 mcg and salmeterol 21 mcg)

ADVAIR® HFA 115/21 Inhalation Aerosol
(fluticasone propionate 115 mcg and salmeterol 21 mcg)

ADVAIR® HFA 230/21 Inhalation Aerosol
(fluticasone propionate 230 mcg and salmeterol 21 mcg)

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

What is the most important information I should know about ADVAIR HFA?

- ADVAIR HFA contains 2 medicines:
 - fluticasone propionate (the same medicine found in FLOVENT®)**, an inhaled corticosteroid medicine. Inhaled corticosteroids help to decrease inflammation in the lungs. Inflammation in the lungs can lead to asthma symptoms.
 - salmeterol (the same medicine found in SEREVENT®)**, a long-acting beta₂-agonist medicine or LABA. LABA medicines are used in patients with asthma. LABA medicines help the muscles around the airways in your lungs stay relaxed to prevent symptoms, such as wheezing and shortness of breath. These symptoms can happen when the muscles around the airways tighten. This makes it hard to breathe. In severe cases, wheezing can stop your breathing and cause death if not treated right away.
- In patients with asthma, LABA medicines, such as salmeterol (one of the medicines in ADVAIR HFA), may increase the chance of death from asthma problems. In a large asthma study, more patients who used salmeterol died from asthma problems compared with patients who did not use salmeterol. It is not known whether fluticasone propionate, the other medicine in ADVAIR HFA, changes your chance of death from asthma problems seen with salmeterol. Talk with your healthcare provider about this risk and the benefits of treating your asthma with ADVAIR HFA.
- ADVAIR HFA does not relieve sudden symptoms. Always have a short-acting beta₂-agonist medicine with you to treat sudden symptoms. If you do not have an inhaled, short-acting bronchodilator, contact your healthcare provider to have one prescribed for you.
- Do not stop using ADVAIR HFA unless told to do so by your healthcare provider because your symptoms might get worse.
- ADVAIR HFA should be used only if your healthcare provider decides that another asthma-controller medicine alone does not control your asthma or that you need 2 asthma-controller medicines.
- Call your healthcare provider if breathing problems worsen over time while using ADVAIR HFA. You may need different treatment.
- Get emergency medical care if:
 - breathing problems worsen quickly, and
 - you use your short-acting beta₂-agonist medicine, but it does not relieve your breathing problems.

What is ADVAIR HFA?

ADVAIR HFA combines an inhaled corticosteroid medicine, fluticasone propionate (the same medicine found in FLOVENT) and a long-acting beta₂-agonist medicine, salmeterol (the same medicine found in SEREVENT). ADVAIR HFA is used for asthma as follows:

ADVAIR HFA is used long term, twice a day to control symptoms of asthma, and prevent symptoms such as wheezing in adolescents and adults 12 years of age and older.

ADVAIR HFA contains salmeterol (the same medicine found in SEREVENT). Because LABA medicines, such as salmeterol, may increase the chance of death from asthma problems, ADVAIR HFA is not for adults and children with asthma who:

- are well controlled with another asthma-controller medicine, such as a low to medium dose of an inhaled corticosteroid medicine
- only need short-acting beta₂-agonist medicines once in awhile

What should I tell my healthcare provider before using ADVAIR HFA?

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

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

Tell your healthcare provider about all the medicines you take including prescription and non-prescription medicines, vitamins, and herbal supplements. ADVAIR HFA and certain other medicines may interact with each other. This may cause serious side effects. Especially, tell your healthcare provider if you take ritonavir. The anti-HIV medicines NORVIR® (ritonavir capsules) Soft Gelatin, NORVIR (ritonavir oral solution), and KALETRA® (lopinavir/ritonavir) Tablets contain ritonavir.

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

How do I use ADVAIR HFA?

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

- Use ADVAIR HFA exactly as prescribed. Do not use ADVAIR HFA more often than prescribed. ADVAIR HFA comes in 3 strengths. Your healthcare provider will prescribe the one that is best for your condition.
- The usual dosage of ADVAIR HFA is 2 inhalations twice a day (morning and evening). The 2 doses should be about 12 hours apart. Rinse your mouth with water after using ADVAIR HFA.
- If you miss a dose of ADVAIR HFA, just skip that dose. Take your next dose at your usual time. Do not take 2 doses at one time.
- While you are using ADVAIR HFA twice a day, do not use other medicines that contain a long-acting beta₂-agonist or LABA for any reason. Other LABA-containing medicines include ADVAIR DISKUS® (fluticasone propionate and salmeterol inhalation powder), SEREVENT® DISKUS® (salmeterol xinafoate inhalation powder), FORADIL® AEROLIZER® (formoterol fumarate inhalation powder), SYMBICORT® (budesonide and formoterol fumarate dihydrate) Inhalation Aerosol, PERFOROMIST™ (formoterol fumarate) Inhalation Solution, and BROVANA™ (arformoterol tartrate) Inhalation Solution.
- Do not change or stop any of your medicines used to control or treat your breathing problems. Your healthcare provider will adjust your medicines as needed.
- Make sure you always have a short-acting beta₂-agonist medicine with you. Use your short-acting beta₂-agonist medicine if you have breathing problems between doses of ADVAIR HFA.
- Call your healthcare provider or get medical care right away if:
 - your breathing problems worsen with ADVAIR HFA
 - you need to use your short-acting beta₂-agonist medicine more often than usual
 - your short-acting beta₂-agonist medicine does not work as well for you at relieving symptoms
 - you need to use 4 or more inhalations of your short-acting beta₂-agonist medicine for 2 or more days in a row
 - you use 1 whole canister of your short-acting beta₂-agonist medicine in 8 weeks' time
 - your peak flow meter results decrease. Your healthcare provider will tell you the numbers that are right for you.
 - you have asthma and your symptoms do not improve after using ADVAIR HFA regularly for 1 week

What are the possible side effects with ADVAIR HFA?

- ADVAIR HFA contains salmeterol (the same medicine found in SEREVENT). In patients with asthma, LABA medicines, such as salmeterol, may increase the chance of death from asthma problems. See "What is the most important information I should know about ADVAIR HFA?"

Other possible side effects with ADVAIR HFA include:

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

- chest pain
- headache
- tremor
- nervousness
- immune system effects and a higher chance for infections
- lower bone mineral density. This may be a problem for people who already have a higher chance for low bone density (osteoporosis).
- eye problems including glaucoma and cataracts. You should have regular eye exams while using ADVAIR HFA.
- slowed growth in children. A child's growth should be checked often.
- throat irritation

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

These are not all the side effects with ADVAIR HFA. Ask your healthcare provider or pharmacist for more information. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How do I store ADVAIR HFA?

- Store ADVAIR HFA at room temperature with the mouthpiece down.
- Do not puncture the canister. Do not use or store ADVAIR HFA near heat or an open flame. Never throw it into a fire or incinerator.
- Keep ADVAIR HFA and all medicines out of the reach of children.

General Information about ADVAIR HFA

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

This Medication Guide summarizes the most important information about ADVAIR HFA. If you would like more information, talk with your healthcare provider or pharmacist. You can ask your healthcare provider or pharmacist for information about ADVAIR HFA that was written for healthcare professionals. You can also contact the company that makes ADVAIR HFA (toll free) at 1-888-825-5249 or at www.advaair.com.

Instructions for Using Your ADVAIR HFA

Follow the instructions below for using your ADVAIR HFA.

Take your ADVAIR HFA inhaler out of the moisture-protective foil pouch just before you use it for the first time. Safely throw away the foil pouch and the drying packet that comes inside the pouch.

The inhaler should be at room temperature before you use it.

The purple actuator that comes with ADVAIR HFA should not be used with any other product canisters. Actuators that come with other products should not be used with an ADVAIR HFA canister.

Prime the inhaler before using it for the first time. To prime the inhaler, shake it well for 5 seconds. Then spray it 1 time into the air away from your face. Shake and spray the inhaler like this 3 more times to finish priming it. **Avoid spraying in eyes.**

If you have not used your inhaler in more than 4 weeks or if you have dropped it, shake it well for 5 seconds and spray it 2 times into the air away from your face.

Shake the inhaler well for 5 seconds just before each use.

- Take the cap off the mouthpiece (see Figure 1). The strap on the cap will stay attached to the actuator.

Look for foreign objects inside the inhaler before each use, especially if the strap is no longer attached to the actuator or if the cap is not being used to cover the mouthpiece.

Make sure the canister is fully and firmly inserted into the actuator.

Shake the inhaler well for 5 seconds right before each use.

- Breathe out fully through your mouth**, pushing as much air out of your lungs as you can.

Put the mouthpiece all the way into your mouth. Hold the inhaler with the mouthpiece down (see Figure 1). Close your lips around it.

- It is important to get the medicine in the spray into your lungs where it works. To do this, you need to **inhale the spray at the same time you take in a slow, deep breath.**

So, just after starting to take in a slow, deep breath through your mouth, press down firmly on the top of the metal canister (see Figure 2) and keep breathing in through your mouth.

Take your finger off the canister after the spray comes out of the canister. Take the mouthpiece out of your mouth after you have finished breathing in.

- Hold your breath as long as you can**, up to 10 seconds. Then breathe normally.

- Wait about 30 seconds and shake** the inhaler again. Repeat steps 2 through 4.

- Put the cap back on the mouthpiece after each time you use the inhaler.**

- After you finish taking this medicine, rinse your mouth with water. Spit out the water. Do not swallow it.

- Never put the canister in water to find out how much medicine is left in the canister ("float test").

- You should keep track of the number of inhalations used from your inhaler. **Then throw away the inhaler after you have used 120 inhalations.** Even though the canister might not be empty and will keep spraying, you might not get the right amount of medicine in each inhalation. Before you get to 120 inhalations, ask your doctor if you need to refill your prescription.

Do not use after the expiration date, which is shown as "EXP" on the product label and box.

Cleaning your ADVAIR HFA Inhalation Aerosol:

Clean the inhaler at least once a week after your evening dose. Keeping the canister and plastic actuator clean is important to prevent medicine buildup.

Step 1. Take the cap off the mouthpiece. The strap on the cap will stay attached to the actuator. Do not take the canister out of the plastic actuator.

Step 2. Use a dry cotton swab to clean the small circular opening where the medicine sprays out of the canister. Carefully twist the swab in a circular motion to take off any medicine (see Figure 3). Then wipe the inside of the mouthpiece with a clean tissue dampened with water. Let the actuator air-dry overnight.

Step 3. Put the mouthpiece cover back on after the actuator has dried.

Rx only



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March 2008 ADH:1MG

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

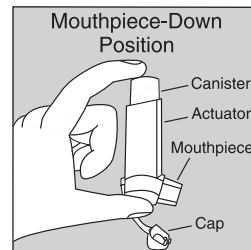


Figure 1

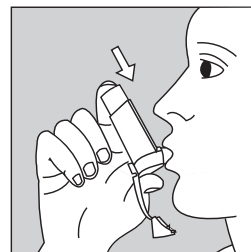


Figure 2

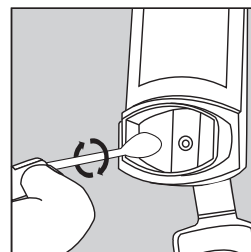


Figure 3