Best Pharmaceuticals for Children Act (BPCA)
1-Year Post-Pediatric Exclusivity Adverse Event Reporting: Salmeterol

Pediatric Advisory Committee Meeting
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GlaxoSmithKline

Briefing Document

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1. EXECUTIVE SUMMARY

1.1. INTRODUCTION

Section 17 of the Best Pharmaceuticals for Children Act mandates that the US Food and Drug Administration (FDA) convene the Pediatric Advisory Committee to review safety data for the 1-year period following granting of pediatric exclusivity. On 21 December 2005, GlaxoSmithKline (GSK) filed a supplemental NDA for SEREVENT (salmeterol xinafoate) Inhalation Aerosol in response to the Written Request for Pediatric Studies and exclusivity was granted on 09 March 2006. Salmeterol is the active component of SEREVENT® DISKUS® (salmeterol xinafoate inhalation powder) and one of the components of ADVAIR DISKUS® (fluticasone propionate and salmeterol) and ADVAIR® HFA; therefore, data on ADVAIR have been included to further assess the safety of salmeterol.

The purpose of this briefing package is to provide the Pediatric Advisory Committee members and consultants with information pertinent to the evaluation of the safety of the long-acting β_2-agonist salmeterol xinafoate in pediatric patients. This document will review key data from the GSK post-marketing surveillance studies, a pooled analysis of clinical trials, recently completed studies, worldwide exposure to salmeterol-containing products, worldwide spontaneous adverse event reports, a review of literature, relevant pharmacoepidemiology and health outcomes studies examining safety outcomes, and a summary of current labeling. The primary focus of this document will be to review the safety data available regarding the use of salmeterol-containing products in pediatric patients with asthma, compared with the safety data available for the adult asthma population.

Based on a comprehensive review of the safety of salmeterol-containing products, GSK believes that salmeterol continues to exhibit a favorable safety profile in pediatric subjects and the safety profile is similar to that seen in adults. SEREVENT and ADVAIR are appropriately labeled to reflect the safety profile of these products. Salmeterol when used as described in the approved labeling offers an important therapeutic option for patients and clinicians and has been shown to improve the level of care in children with asthma.

1.2. BACKGROUND

Asthma is a common disorder although the etiology remains unknown. In the US, 7%, or 20.5 million patients (including 6.2 million children <18 years) have current asthma [CDC, 2007; ALA, 2006]. The onset of asthma generally occurs during childhood and symptom and disease severity vary over a patient's lifetime. 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, and in 2004, the Centers for Disease Control (CDC) reported 190,000 hospitalizations due to asthma in children under the age of 15 [ALA, 2006].

The pathophysiology of asthma is characterized by airway inflammation and smooth muscle dysfunction or hyperresponsiveness. Airway inflammation is typically treated with anti-inflammatory agents and smooth muscle dysfunction with bronchodilators. ICS are the most effective medication class to treat airway inflammation and evidenced-based asthma treatment guidelines recommend use of ICS in all patients with persistent asthma. However, in many patients, ICS alone is not sufficient to control the symptoms of asthma. In this instance, national and international guidelines recommend adding a long-acting β_2-agonist (LABA) to ICS as part of a stepwise treatment approach to gain control of asthma [NIH, 2007; GINA, 2002].

The goal of asthma pharmacotherapy is to control daily symptoms and reduce exacerbations while producing minimal or no adverse effects. The risk of experiencing an adverse effect from existing asthma medications is generally low, but present for all asthma medications. This report characterizes the safety profile of salmeterol and salmeterol-containing products in children.

1.3. SALMETEROL

Salmeterol is an inhaled long-acting β_2-agonist. Salmeterol has a 12-hour duration of action and represents a clinical advance from short-acting β_2-agonists, such as albuterol, which have a 4- to 6-hour duration of action. Studies with salmeterol have demonstrated improved lung function, a decrease in both daytime and nighttime symptoms, reduced rescue medication use and improved health related quality of life.

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

The use of salmeterol for the treatment of asthma in pediatric patients ≥4 years of age was approved on 25 September 1998 and 21 April 2004, for SEREVENT DISKUS and ADVAIR DISKUS, respectively. In addition, SEREVENT DISKUS was approved for use for prevention of exercise induced bronchospasm in patients ≥4 years on 25 September 1998. Adverse event data for patients down to age 4 are included in the labels for SEREVENT and ADVAIR DISKUS.

Additionally, SEREVENT DISKUS and ADVAIR DISKUS were approved on 22 March 2002 and 17 November 2003, respectively, for the treatment of chronic obstructive pulmonary disease (COPD).

As of December 2005, the worldwide exposure to salmeterol alone was estimated to be 20.6 million patient years for treatment of asthma and COPD. Additionally, worldwide

exposure to salmeterol administered with FP in a single device (ADVAIR) was estimated to be 22.1 million patient years. Therefore, in total there has been an estimated 42.7 million patient years of exposure to salmeterol-containing products.

1.4. PEDIATRIC EXCLUSIVITY

The Agency issued a Written Request for Pediatric Studies requesting submission of pediatric information for SEREVENT (salmeterol xinafoate) Inhalation Aerosol pursuant to Section 505A of the Federal Food, Drug and Cosmetic Act (the "Act'). Therefore, on 21 December 2005, GSK submitted a supplemental NDA containing the full reports of the pediatric studies conducted pursuant to the Written Request. This application consisted of four pediatric studies with salmeterol: two dose-ranging safety studies (one in children between the ages of 2 years and 4 years and one in children 6 months and ≤2 years) and two efficacy and safety studies (one in children between the ages of 2 years and 4 years and one in children 6 months and ≤2 years). Additionally, an *in vitro* study characterizing the dose delivery from different US approved spacers was performed and a nonclinical study in juvenile dogs was performed as required before administering salmeterol to very young children (6 months to ≤2 years).

In our application, GSK proposed changes to the labeling to describe the results of the pediatric exclusivity studies and report the safety results from the trials. In summary, for the two parallel group studies, the types of adverse events occurring more frequently in patients receiving SEREVENT Inhalation Aerosol compared with those receiving placebo were generally similar to those observed in patients 12 years of age and older with the exception of a higher incidence of fever, rhinorrhea/post-nasal drip, rhinitis, diarrhea, mood disorders and irritability, and common disorders of childhood, including otitis and pharyngotonsillitis. In general, the incidence of adverse events was higher in children aged 6 to 23 months compared with children aged 24 to 47 months, largely due to a higher incidence of fever and diarrhea. Evaluation of clinical laboratory tests, ECGs, vital signs, and symptoms of adrenergic stimulation revealed similar findings across groups receiving SEREVENT Inhalation Aerosol or placebo. In the two dose-ranging studies, 24 hour Holter monitoring also revealed similar findings across all treatments.

Subsequent to our pediatric exclusivity supplemental application, exclusivity was granted by FDA on 9 March 2006.

On 13 June 2006, the Agency issued an approvable letter for our pediatric exclusivity supplemental NDA citing that GSK had not provided adequate data to characterize the *in vitro* performance of SEREVENT Inhalation Aerosol with valved holding chambers in children <4 years of age, thereby limiting the interpretation of the data from the clinical studies. In 2002, GSK ceased manufacturing the CFC-containing product in accordance with the Montreal Protocol as part of the Company's transition to CFC-free respiratory formulations. By June 2006, when the action letter was received, all stocks of the product had been depleted and we were unable to comply with the request of the Agency to generate additional *in vitro* data. Therefore the application remains approvable. The changes to the labeling proposed in the supplement have not been incorporated into any approved salmeterol-containing product labels. While the pediatric exclusivity studies

included patients less than 4 years of age, the approved and marketed salmeterol products are approved only for use in the treatment of asthma in patients 4 years of age and older.

1.5. LABELING REVISIONS

Since the approval of salmeterol-containing products in the US, the product labels have been revised to reflect emerging information.

The original package insert for SEREVENT included language advising patients that SEREVENT should not be used as a rescue inhaler for sudden asthma symptoms. After GSK received reports of misuse with salmeterol in the early marketing period for SEREVENT, the labeling for SEREVENT was revised to emphasize and update warnings on use of SEREVENT as a rescue inhaler and in patients with deteriorating asthma. In addition, on 16 January 1995, a "Dear Doctor letter" was issued by GSK informing prescribers of this labeling revision.

In 2003, the labeling for both SEREVENT and ADVAIR were updated to incorporate the results of a large, prospective clinical trial, the Salmeterol Multicenter Asthma Research Trial (SMART), which found small, but statistically significant increases in the respiratory- and asthma-related combined endpoints and asthma-related death in the salmeterol group compared with placebo. The label changes at this time included the addition of a boxed warning to both labels, and new language in the WARNINGS sections providing information regarding the study.

The safety of long-acting bronchodilators, including salmeterol-containing products, was extensively reviewed and discussed at the July 2005 Pulmonary-Allergy Drugs Advisory Committee. The Committee discussed the specific findings of severe asthma outcomes observed in SMART, and in the Phase III clinical studies conducted by Novartis with formoterol to support registration of formoterol in the US. The Committee was provided with a briefing document that reviewed salmeterol, including data from pooled clinical trials, spontaneously reported adverse events, and safety outcomes from observational studies. The outcome of the Committee meeting and discussions with the Agency were revisions of the labeling for all LABA-containing products, including SEREVENT DISKUS and ADVAIR. The changes included revisions to the boxed warning already included in the SEREVENT and ADVAIR labeling, the addition of a Medication Guide for both products, and modification to the indications.

This briefing document will examine data from similar sources provided to the Committee in July 2005 but will focus on the pediatric experience and is summarized below.

1.6. SUMMARY OF PEDIATRIC SAFETY RESULTS

1.6.1. SMART

SMART was a large observational, randomized, controlled, 28-week, surveillance trial in >26,000 patients ≥12 years of age, initiated in 1996 and terminated in 2003. SMART

showed an 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). The prescribing information for salmeterol-containing products provides detailed information about the possibility of these rare events.

In 12-18 year-olds, primary and secondary respiratory- and asthma-related events were low (≤2 events in any treatment) and similar in subjects who received salmeterol compared with subjects who received placebo.

More all-cause hospitalizations occurred in subjects 12-18 years of age treated with salmeterol (n=35 [2%]) compared with placebo subjects (n=16 [<1%]); this difference was statistically significant. All-cause hospitalizations were reported more frequently compared with the ≥19 year-old group. A *post-hoc*, non-adjudicated examination of each report for asthma-related hospitalizations found 13 events in the salmeterol group compared with 9 in the placebo group; this difference was not statistically significant. No trend in any particular type of event was observed for the non-respiratory-related hospitalizations in the salmeterol-treated subjects (e.g., depression, injury/trauma, appendicitis) (Table 7).

In 12-18 year olds, there were more primary and secondary events in African-Americans compared with non-African-Americans; however, these events were infrequent. This finding is consistent with findings observed in the adult population (subjects ≥19 years of age).

The results of SMART are described in the Prescribing Information for SEREVENT DISKUS and ADVAIR (DISKUS and HFA).

1.6.2. Pooled Randomized Controlled Trials

To further inform on the safety profile of salmeterol, GSK combined data from all US chronic dosing trials (n=72) which included any salmeterol-containing treatment arm with labeled doses. This analysis of over 22,000 patients included more than 4,500 patients under the age of 18 and compared Serious Adverse Events (SAEs) between the age groups. In a subset (n=54) of these studies where data on exacerbations were specifically collected, asthma exacerbations and asthma-related hospitalizations were evaluated.

In pediatric subjects 0-18 years of age, salmeterol-containing products were not associated with increased incidence of SAEs in the cardiovascular, respiratory, or metabolic categories compared with placebo or ICS treatment arms. There were no deaths or cardiovascular SAEs reported in this age group.

The incidence of exacerbations between pediatric subjects 0-18 years of age and adults was not increased in studies of salmeterol, or salmeterol administered with an ICS, compared with placebo or ICS alone, respectively.

Overall, the incidence of asthma-related hospitalizations was infrequent in children compared with adults. In studies of salmeterol, asthma-related hospitalizations occurred

more frequently compared with placebo. The incidence of asthma-related hospitalization was identical with salmeterol plus ICS compared with ICS alone. These findings were observed in the younger (0-18 years) and older (≥19 year) age groups.

1.6.3. Recently Completed Studies

In SMART, African Americans experienced a greater incidence of events compared with Caucasians. Therefore, in order to better understand the safety findings from SMART, GSK initiated a study in African Americans (SFA103153) to assess the rate of asthma exacerbations. A separate pharmacogenetic study (SFA100062) was conducted to examine whether genetic variation in β_2-adrenergic receptor gene modifies the response to salmeterol in patients with asthma.

The SFA103153 study was conducted in over 400 African American subjects ≥12 years of age to evaluate asthma exacerbations in subjects receiving ADVAIR 100/50 or FLOVENT® DISKUS® (fluticasone propionate inhalation powder) 100mcg twice daily for 1 year. The rate of exacerbations was lower in African-American subjects receiving ADVAIR compared with FLOVENT (p=ns). Overall, asthma-related hospitalizations were reported for 2 and 3 subjects receiving ADVAIR and FLOVENT, respectively. In subjects 12-18 years of age, no asthma-related hospitalizations occurred in ADVAIR compared with one in FLOVENT. The incidence of adverse events was similar between the treatments in both age groups.

The SFA100062 clinical study was conducted in nearly 550 subjects ≥12 years of age to prospectively evaluate the influence of genotypic variation at the B16 position on lung function and other asthma-related outcomes in subjects receiving salmeterol alone or salmeterol plus ICS (ADVAIR). This study showed similar lung function and other clinical responses for Arg16Gly genotypes in patients receiving SEREVENT or ADVAIR. In addition, adverse events were similar by genotype within treatments.

1.6.4. Spontaneously Reported Adverse Events

Global safety surveillance of medications is conducted through analysis of spontaneously reported adverse events.

A review of GSK's internal database for events within the one year post-exclusivity, revealed 14 spontaneous cases received for SEREVENT and 348 spontaneous cases received for ADVAIR for pediatric patients 0 to 16 years of age. In general, the total number of spontaneous reports for both products has not increased relative to exposure.

In addition, an analysis for salmeterol-containing products was performed on the publicly-available FDA Adverse Event Reporting System (AERS) database for any adverse events in children that were reported more frequently than expected and more frequently than in adults. The data do not highlight any new safety concerns for SEREVENT or ADVAIR.

1.6.5. Literature Review

A literature search was conducted for references specific to salmeterol or salmeterol-containing products and safety in subjects <18 years of age. The search was inclusive of references available through September 2007.

A review of the pediatric literature did not identify new safety information which changes the overall safety profile of salmeterol-containing products.

1.6.6. Observational Studies

Epidemiological techniques have examined the associations between asthma-related hospitalizations and asthma-related death and exposure to salmeterol-containing products. The results of these analyses show no significant increase in asthma-related hospitalization or asthma-related death following increasing exposure of salmeterol-containing products in children or adults.

In addition, administrative data linking health care utilization and pharmacy claims provide a powerful tool to examine associations between outcomes and medication use. These data allow for the examination of health care utilization in a "real world" setting. The risks for serious events such as asthma-related ED visit or asthma-related hospitalization have been assessed in 3 separate studies of children, representing over 350,000 children with asthma. Studies conducted in North America suggest that the use of salmeterol in combination with an inhaled corticosteroid (ADVAIR) was not associated with an increase in the risk of asthma-related ED visit or asthma-related hospitalization when used in clinical practice. This finding was corroborated in the pooled analysis of asthma-related exacerbations and asthma-related hospitalizations from randomized clinical studies described above.

1.6.7. Overall Conclusion

Based on a comprehensive review of the safety of salmeterol-containing products, GSK believes that salmeterol continues to exhibit a favorable safety profile in pediatric subjects and the safety profile is similar to that seen in adults. SEREVENT and ADVAIR are appropriately labeled to reflect the safety profile of these products. Salmeterol when used as described in the approved labeling offers an important therapeutic option for patients and clinicians and has been shown to improve the level of care in children with asthma.

2. POST-MARKETING SURVEILLANCE STUDIES

Following the initial launch of SEREVENT in the UK (1990) and the subsequent launch in the US (1994), GSK conducted two post-marketing surveillance studies to further characterize the use of salmeterol for the treatment of asthma, the SEREVENT Nationwide Surveillance (SNS) study and SMART. This section summarizes the information from these studies.

2.1. SEREVENT NATIONWIDE SURVEILLANCE (SNS) STUDY

The SNS study, conducted in the UK, was initiated in late 1990 and completed in December 1991. It was a randomized controlled trial that studied over 25,000 subjects (≥12 years of age) treated with salmeterol (16,787) or albuterol (8,393) for 16 weeks; 1,320 of the subjects were <18 years of age (899 [5%] salmeterol and 421 [5%] albuterol). The SNS study showed that the overall incidence of serious events from all causes was similar between salmeterol- and albuterol-treated subjects. The incidence of asthma-related death in the total population was numerically, though not statistically, greater in patients taking salmeterol compared with the albuterol group. One subject <18 years of age died while receiving salmeterol treatment. No additional analyses of the data (including by age group) are available from this study. The results from this study have been incorporated into the SEREVENT and ADVAIR labels since US approval, and are reported in the literature [Castle, 1993].

2.2. SALMETEROL MULTI-CENTER ASTHMA RESEARCH TRIAL (SMART)

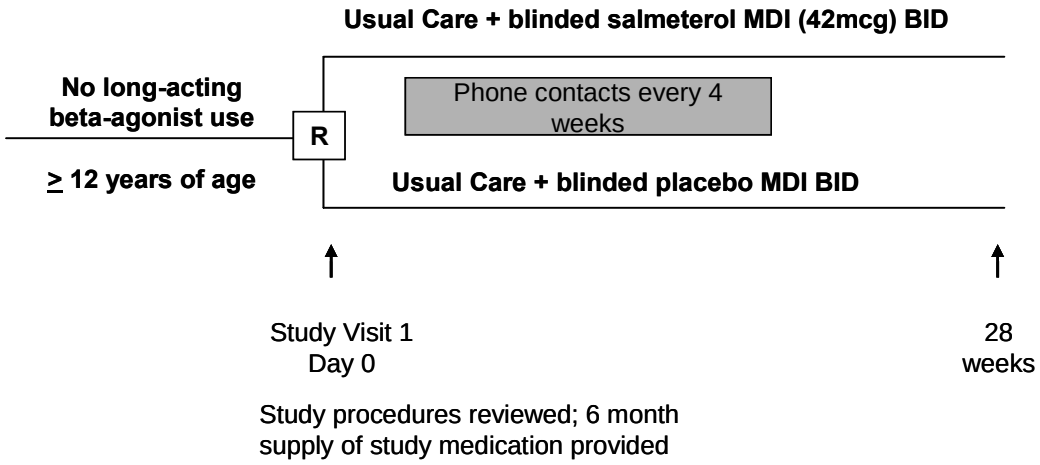
During the time when SEREVENT was launched in the US (1994), there was ongoing debate concerning the regular use of β_2-agonists. In November 1994, in consultation with the FDA, GSK agreed to design and conduct a large, prospective clinical trial to obtain safety surveillance information.

2.2.1. Study Design

SMART (Protocol SLGA5011) was a multi-center, randomized, double-blind, parallel-group, placebo-controlled, surveillance study conducted from June 1996 through July 2003 at 6,163 investigative sites in the US. This study was designed to compare respiratory- and asthma-related event outcomes in subjects receiving usual asthma pharmacotherapy (plus placebo) with event outcomes in subjects receiving usual pharmacotherapy plus salmeterol CFC MDI 42mcg twice-daily over 28-weeks of treatment. [Note: The dose of 42mcg (2 actuations of 21mcg) is the dose delivered from the actuator. After Figure 1, the dose will be referred to as 50mcg (2 actuations of 25mcg), the dose delivered from the valve.] A total of 26,355 male and non-pregnant female subjects ≥12 years of age, with a clinical diagnosis of asthma who had no previous use of inhaled long-acting β_2-agonists were evaluated in this study. Concurrent use of prescription asthma medication(s) other than long-acting β_2-agonists (salmeterol or salmeterol-containing product [i.e., ADVAIR DISKUS] and formoterol) was permitted.

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

Figure 1 SMART Study Design



During the study, data regarding SAEs were collected. However, per agreement with the FDA, non-serious adverse events were not collected.

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

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

Results for the total population (subjects ≥12 years of age) showed that there was no statistically significant difference in the primary outcome (combined respiratory-related death or life-threatening experiences) in patients receiving salmeterol versus placebo. However, there were small, but statistically significant increases in the secondary endpoint of combined asthma-related death or life-threatening experiences and in respiratory- and asthma-related death alone in the salmeterol group compared with the placebo group. In addition, SMART suggested that the risk of asthma-related death or life-threatening experiences may be greater in African-Americans.

This briefing document provides a summary comparison of results by treatment group and age group (i.e., subjects 12-18 years of age and subjects ≥19 years of age) for the primary endpoint and the key secondary endpoints 1-6 above over the 28-week treatment period.

2.2.2. Results

Table 1 summarizes the subject accountability between the 12-18 and ≥19 year-old age groups in the overall population.

Table 1 Summary of Subject Accountability by Age (12-18 and ≥19 Years) (SMART)

	Salmeterol CFC 50mcg BID (N= 13,176[a])		Placebo (N=13,179[b])	
	12-18 Years	**≥19 Years**	**12-18 Years**	**≥19 Years**
Randomized, n	1,653	11,515	1,622	11,555
Completed, n (%)	1,289 (78)	8,358 (73)	1,230 (76)	8,242 (71)
Prematurely Discontinued, n (%)	284 (17)	2,675 (23)	320 (20)	2,823 (24)
Consent Withdrawn	143 (9)	1,561 (14)	163 (10)	1,749 (15)
Lost to Follow-Up	91 (6)	735 (6)	98 (6)	729 (6)
Sponsor Stopped Study	39 (2)	185 (2)	40 (2)	168 (1)
Serious Adverse Event	7 (<1)	136 (1)	6 (<1)	128 (1)
Other	4 (<1)	58 (<1)	13 (<1)	49 (<1)
Unknown (Alive)[c]	68 (4)	407 (4)	61 (4)	414 (4)
Unknown[d]	12 (<1)	75 (<1)	11 (<1)	76 (<1)

a. Total includes 8 subjects whose age was not reported/outside the protocol-defined age (≥12 years of age)
b. Total includes 2 subjects whose age was not reported/outside the protocol-defined age (≥12 years of age)
c. includes those subjects lost to follow-up, but for whom verification of their status (alive) was subsequently obtained from a relative or investigator
d. unknown category who had case report form (CRF) data, but who did not register for follow-up telephone interviews; no additional information is available for these subjects after Visit 1

Across both treatment groups and between the age groups across both groups, a comparable percentage of subjects were prematurely discontinued from the study.

Table 2 summarizes the demographic characteristics between the 12-18 year-old and ≥19 year-old age groups in the overall population.

Table 2 Demographic Characteristics by Age (12-18 and ≥19 Years) (SMART)

	Salmeterol CFC 50mcg BID (N= 13,176[a])		Placebo (N=13,179[b])	
	12-18 Years	**≥19 Years**	**12-18 Years**	**≥19 Years**
n (%)	1,653 (13)	11,515 (87)	1,622 (12)	11,555 (88)
Age, mean (years)	14.7	42.7	14.8	42.6
Sex, n (%)				
Female	765 (47)	7,565 (66)	791 (49)	7,546 (66)
Male	870 (53)	3,830 (34)	816 (51)	3,869 (34)
Not Reported	18	120	15	140
Ethnic Origin[c], n (%)				
Caucasian	1044 (64)	8,231 (72)	1050 (65)	8,310 (73)
African-American	380 (23)	1,986 (17)	334 (21)	1,985 (17)
Hispanic	160 (10)	835 (7)	172 (11)	827 (7)
Other	39 (2)	191 (2)	36 (2)	188 (2)
Asian	18 (1)	155 (1)	19 (1)	130 (1)
Not Reported	12	117	11	115

a. Total includes 8 subjects whose age was not reported/outside the protocol-defined age (≥12 years of age)
b. Total includes 2 subjects whose age was not reported/outside the protocol-defined age (≥12 years of age)
c. Study conducted prior to FDA's "Guidance for Industry: Collection of Race and Ethnicity Data in Clinical Trials" in (issued September 2005); therefore, the Ethnic Origin categories above vary from the FDA's current reporting recommendations

The mean age within the two age groups was comparable between both treatment groups. Across both treatment groups, there were more males in the 12-18 year-old age group compared with more females in the ≥19 year-old age group.

Table 3 summarizes the key baseline characteristics between the 12-18 and ≥19 year-old age groups in the overall population.

Table 3 Baseline Characteristics by Age (12-18 and ≥19 Years) (SMART)

	Salmeterol CFC 50mcg BID (N= 13,176[a])		Placebo (N=13,179[b])	
	12-18 Years	**≥19 Years**	**12-18 Years**	**≥19 Years**
n (%)	1,653 (13)	11,515 (87)	1,622 (12)	11,555 (88)
Age at diagnosis, mean (yrs)	7.0	25.4	7.1	25.2
ED visit for asthma last 12 months, n (%)				
None	1,222 (74)	8,518 (74)	1242 (77)	8,466 (73)
≥1 visit	429 (26)	2,966 (26)	379 (23)	3,085 (27)
Hospitalization for asthma last 12 months, n (%)				
None	1,558 (94)	10,557 (92)	1,525 (94)	10,559 (91)
≥1 hospitalization	93 (6)	957 (8)	96 (6)	992 (9)
Frequency of nocturnal symptoms that interfere with sleep n (%)				
None	785 (49)	4,175 (37)	770 (49)	4,309 (38)
1-3 nights per week	639 (40)	4,866 (43)	633 (40)	4,852 (43)
≥4 nights per week	167 (10)	2,162 (19)	175 (11)	2,072 (18)
% Predicted Peak Expiratory Flow, mean	89.5	83.2	89.1	83.0

a. Total includes 8 subjects whose age was not reported/outside the protocol-defined age (≥12 years of age)
b. Total includes 2 subjects whose age was not reported/outside the protocol-defined age (≥12 years of age)

Pre-study asthma characteristics were similar between the same age group across both treatments. The cohorts, independent of age, had a history of frequent ED visit for asthma (approximately 25% of all subjects in the previous 12 months) and 6-9% of subjects by age group had been hospitalized for asthma in the previous year. Daily morbidity was high as 51-62% of subjects reported disturbed sleep due to asthma symptoms.

Table 4 summarizes the overall incidence of primary (combined respiratory-related death or life threatening experience) and secondary endpoints between the 12-18 year-old and ≥19 year-old age groups in the overall population.

Table 4 Overall Incidence of Primary and Secondary Safety Endpoints by Age (SMART)

	12-18 Year-Olds (N= 3,275)		≥19 Year-Olds (N=23,070)	
	Salmeterol CFC 50mcg BID	Placebo	Salmeterol CFC 50mcg BID	Placebo
n (%)	1,653 (50)	1,622 (50)	11,515 (50)	11,555 (50)
Primary Endpoint, n (%)				
Combined respiratory-related death or life-threatening experience[a]	2 (<1)	2 (<1)	48 (<1)	34 (<1)
Secondary Endpoints, n (%)				
Respiratory-related death	1 (<1)	0	23 (<1)	11 (<1)
Combined asthma-related death or life-threatening experience[a]	2 (<1)	2 (<1)	35 (<1)	20 (<1)
Asthma-related death	1 (<1)	0	12 (<1)	3 (<1)
Combined all-cause death or life-threatening experience	2 (<1)	2 (<1)	68 (<1)	57 (<1)
All-cause death	1 (<1)	0	41 (<1)	32 (<1)
All-cause hospitalization	35 (2)	16 (<1)	434 (4)	404 (3)

a. Life threatening experience (intubation and mechanical ventilation)

Of the 3,275 subjects enrolled in 12-18 year-old age group, 51 (2%) of the subjects were hospitalized during the 28-week treatment period. In this age group, only 2 subjects in each treatment group experienced a primary outcome event; only 1 of these events was a fatality (salmeterol group). Secondary outcome events in this younger age group were similar and the incidence did not exceed 2 events for either treatment, with the exception of all-cause hospitalization, experienced by significantly more subjects in the salmeterol group compared with the placebo group (Table 5).

Table 5 provides a summary of the relative risk of respiratory-related (including asthma) and asthma-related hospitalizations by treatment within the 12-18 year-old age group over the entire treatment period (28 weeks). Table 6 and Table 7 provide a listing of the respiratory-related and non-respiratory-related hospitalizations, respectively, in the 12-18 year-old age group. The events reported in these three tables were compiled *post hoc* by GSK following a manual review of the investigator-approved FDA MedWatch forms.

Table 5 Summary of Cumulative Relative of Risk of Respiratory-Related Hospitalizations Over the Treatment Period (28 Weeks) – Subjects 12-18 Years of Age (SMART)

12-18 Year-Olds (n=3,275)			
Category	**Salmeterol CFC 50mcg BID (n=1,653)**	**Placebo (n=1,622)**	**RR[a] (95% CI)**
Subjects with All-Cause Hospitalization	35 (2)	16 (<1)	2.0668 (1.1489, 3.7181)
Subjects with Respiratory-Related (Including Asthma) Hospitalization	18[b] (1)	9[c](<1)	1.8974 (0.8551, 4.2102)
Subjects with Asthma-Related Hospitalization	13 (<1)	9 (<1)	1.3689 (0.5869, 3.1930)
Subjects with Other Respiratory- Related Hospitalization	5[d] (<1)	0	N/A
Subjects with Non-Respiratory-Related Hospitalization	17 (1)	7 (<1)	2.2908 (0.9528, 5.5078)

a. RR (relative risk: quotient of event rate for salmeterol group divided by event rate for placebo) and CI (confidence interval) correspond to end of time period interval
b. Respiratory-related events reported include: asthma, pneumonia, viral infection of the lung, and acute pharyngitis
c. Respiratory-related events reported include asthma; no other respiratory-related events were reported in this group
d. Other respiratory-related events include only pneumonia, viral infection of the lung, and acute pharyngitis

Of the 1,653 salmeterol-treated subjects in this age group, 18 (1%) were hospitalized due to a respiratory-related SAE, 13 (<1%) of which were asthma-related. Of the 1,622 subjects in the placebo group, 9 (<1%) were hospitalized due to a respiratory-related SAE, all of which were asthma-related and the comparison of asthma-related hospitalizations was not statistically significant between treatments (Table 5 and Table 6).

There was no trend in any particular type of event within or across treatment groups for subjects 12-18 years of age who were hospitalized due to a non-respiratory-related event (Table 7).

Across both treatment and age groups, the incidence of primary and secondary events was low (<1% for any outcome), although numerically more events were experienced by salmeterol-treated subjects compared with placebo subjects. The finding of an increased risk of asthma-related death with salmeterol treatment noted in Table 4 above was observed in the total population and this finding was incorporated into the product labeling for all salmeterol-containing products in 2003.

Table 6 Listing of All-Cause Hospitalizations – Subjects 12-18 Years of Age: Respiratory-Related Events (SMART)

Treatment	Subject No.	Gender	Age (Yrs)	Ethnic Origin	Baseline ICS Use (Y/N)	No. Days on Treatment at Time of Onset	Event or Problem as Reported on MedWatch Form
Salmeterol CFC 50mcg BID	23829	Male	12	Caucasian	Y	13	Asthma
	38889	Female	17	Caucasian	Y	23	Asthma
	20399	Female	13	Caucasian	Y	24	Asthma
	24115	Female	15	Caucasian	N	28	Asthma
	23775	Female	14	Caucasian	N	61	Asthma
	12616	Male	16	Caucasian	N	73	Asthma
	41523	Female	14	Caucasian	Y	124	Asthma
	13949	Female	15	African-American	N	20	Asthma
	57102	Male	12	African-American	N	69	Asthma
	22337	Male	13	African-American	Y	97	Asthma
	22432	Male	12	African-American	Y	107	Asthma
	7812	Female	12	African-American	Y	176	Asthma
	11777	Male	14	Asian	Y	60	Asthma
	13066	Female	13	African-American	N	9	Pneumonia
	60886	Male	14	African-American	N	103	Pneumonia
	16494	Female	16	Caucasian	Y	56	Pneumonia
	18845	Male	13	Caucasian	N	26	Viral infection of lungs
	19492	Female	18	Hispanic	Y	193	Acute pharyngitis
Placebo	18868	Male	13	Caucasian	Y	4	Asthma
	22252	Male	13	Caucasian	N	19	Asthma
	43050	Male	12	Caucasian	Y	41	Asthma
	41413	Male	12	Caucasian	Y	120	Asthma
	49668	Male	12	Caucasian	Y	160	Asthma
	44663	Male	12	Caucasian	N	177	Asthma
	10004	Female	17	African-American	Y	23	Asthma
	50995	Female	15	African-American	Y	91	Asthma
	50176	Female	14	African-American	N	177	Asthma

ICS = inhaled corticosteroid

Table 7 Listing of All-Cause Hospitalizations – Subjects 12-18 Years of Age: Non-Respiratory-Related Events (SMART)

Treatment	Subject No.	Gender	Age (Yrs)	Ethnic Origin	Baseline ICS Use (Y/N)	Event or Problem as Reported on MedWatch Form
Salmeterol CFC 50mcg BID	7733	Female	18	Caucasian	N	Depression
	12719	Female	14	Caucasian	N	Depression
	53614	Female	17	Caucasian	N	Depression Suicidal ideation
	11875	Female	16	Caucasian	Y	Cellulitis of leg
	41840	Female	13	Caucasian	Y	Overdose of aspirin
	19509	Female	16	Caucasian	N	Hydrocephaly
	43221	Female	15	Caucasian	Y	Severe tic Dyslexia
	47857	Female	12	Caucasian	Y	Appendicitis
	63626	Female	18	Caucasian	Y	Miscarriage
	7670	Male	12	Caucasian	N	Dehydration
	26534	Male	16	Caucasian	Y	Broken leg
	24168	Male	15	Caucasian	Y	Loss of consciousness
	10583	Female	16	African-American	N	Auto accident
	24288	Female	15	African-American	Y	Ovarian cyst Severe vomiting
	57018	Female	16	African-American	Y	Pyelonephritis
	25160	Male	17	African-American	Y	Nasopharyngeal cancer
	20619	Male	13	Hispanic	N	Vomiting Diarrhea
Placebo	3196	Female	14	Caucasian	Y	Depression
	15967	Female	16	Caucasian	N	Kidney infection
	42833	Female	18	Caucasian	N	Lacerated liver
	16945	Male	13	Caucasian	N	Ruptured spleen
	45553	Female	13	African-American	N	Sickle cell crisis
	46959	Male	13	Hispanic	Y	Head injury Fracture Abrasions
	47411	Female	15	Hispanic	Y	Weakness Headache Sinus polyp

ICS = inhaled corticosteroid

Table 8 summarizes the overall incidence of primary (combined respiratory-related death or life-threatening experience) and secondary endpoints between the 12-18 and ≥19 year-old age groups within the African-American and non-African-American sub-groups. The categories of "combined respiratory-related death or life threatening experience," "combined asthma-related death or life threatening experience," and "combined all-cause death or life threatening experience" include subjects who are also reported in the

"respiratory-related death," "asthma-related death" and "all-cause death" categories, respectively. Also, for completeness of reporting, subjects whose ethnicity was not reported (see Table 2) are included in the non-African-American group.

Table 8 Overall Incidence of Primary and Secondary Safety Endpoints – Subjects 12-18 and ≥19 Years of Age – African-American and Non-African-American (including Caucasian) Subjects (SMART)

	12-18 Years (n=3,275)				≥19 Years (n=23,070)			
	Salmeterol CFC 50mcg BID (n=1,653)		Placebo (n=1,622)		Salmeterol CFC 50mcg BID (n=11,515)		Placebo (n=11,555)	
	AA	*Non-AA*	*AA*	*Non-AA*	*AA*	*Non-AA*	*AA*	*Non-AA*
n (%)	380 (23)	1,273 (77)	334 (21)	1,288 (79)	1,986 (17)	9,529 (83)	1,985 (17)	9,570 (83)
Primary Endpoint, n (%)								
Combined respiratory-related death or life-threatening experience[a]	2 (<1)	0	0	2 (<1)	18 (<1)	30 (<1)	5 (<1)	29 (<1)
Secondary Endpoints, n (%)								
Respiratory-related death	1 (<1)	0	0	0	7 (<1)	16 (<1)	2 (<1)	9 (<1)
Combined asthma-related death or life-threatening experience	2 (<1)	0	0	2 (<1)	17 (<1)	18 (<1)	4 (<1)	16 (<1)
Asthma-related death	1 (<1)	0	0	0	6 (<1)	6 (<1)	1 (<1)	2 (<1)
Combined all-cause death or life-threatening experience	2 (<1)	0	0	2 (<1)	22 (1)	46 (<1)	11 (<1)	46 (<1)
All-cause death	1 (<1)	0	0	0	11 (<1)	30 (<1)	7 (<1)	25 (<1)
All-cause hospitalization	11 (3)	24 (2)	4 (1)	12 (<1)	91 (5)	343 (4)	73 (4)	331 (3)

AA= African-American

a. Life threatening experience (intubation and mechanical ventilation)

Within the 12-18 year-old group, excluding all-cause hospitalization, primary and secondary events were infrequent in subjects treated with salmeterol; no events were reported in non-African-Americans, compared with 1-2 events reported for these outcomes for African-Americans treated with salmeterol. The converse was observed in the placebo group. A total of 11 African-American subjects treated with salmeterol were hospitalized, 5 of whom were hospitalized due to asthma (Table 6). In addition, one subject treated with salmeterol died due to asthma but was not hospitalized prior to this outcome. A total of 12 non-African-American subjects who received placebo were hospitalized, 6 due to asthma (Table 6). None of these subjects died due to a respiratory- or asthma-related event.

In subjects ≥19 years of age, there were a numerically greater number of both primary and secondary events for African-American subjects treated with salmeterol compared with African-American subjects who received placebo. This increased risk of asthma-related events was incorporated into the labeling for all salmeterol-containing products in 2003. In addition, since 2003, the label for salmeterol-containing products has noted the data from SMART suggest that African-Americans may be at increased risk for a severe respiratory-related event. There were similar findings in non-African-American subjects, although the relative risk for salmeterol subjects was reduced compared with African-American subjects and a similar number of events were reported for some outcomes.

Though not presented in this report, the overall incidence of primary (combined respiratory-related death or life threatening experience) and secondary endpoints by treatment was similar between the 12-18 and ≥19 year-old age groups by gender (i.e., male and female) and baseline ICS use (i.e., use and no use) and disease severity (defined as percent predicted Peak Expiratory Flow (PEF) (i.e., ≤60% and >60%).

2.2.3. Summary

- In 12-18 year-olds, primary and secondary respiratory- and asthma-related events were low (≤2 in any treatment) and similar in subjects who received salmeterol 50mcg BID for 28 weeks compared with subjects who received placebo
- Statistically significantly more all-cause hospitalizations occurred in subjects 12-18 years of age treated with salmeterol (n=35 [2%]) compared with placebo subjects (n=16 [<1%]). All-cause hospitalizations were reported more frequently compared with the ≥19 year-old group
    - An examination of each hospitalization report found that 13 events in the salmeterol group were asthma-related compared with 9 in placebo, which was not statistically significant
    - No trend in any particular type of event was observed for the non-respiratory-related hospitalizations in the salmeterol-treated subjects
- In 12-18 year olds, there were more primary and secondary events in African-Americans compared with non-African-Americans; however, these events were infrequent.

3. SALMETEROL SAFETY FROM US ASTHMA CLINICAL TRIALS

The large GSK asthma clinical trials database was examined for studies with a salmeterol-containing treatment arm and which included pediatric subjects ≤18 years of age, in order to further explore the safety of salmeterol in pediatric patients. Additionally, this data exploration was undertaken to detect any potential safety signals not already included in current labeling. Data from relevant studies were pooled and are described below.

Additionally, two recently completed clinical studies and a retrospective analysis of pooled pharmacogenetic data from 10 completed studies were conducted in order to better understand the safety findings from SMART. Results are also described in this section.

3.1. POOLED ANALYSIS OF COMPLETED US RANDOMIZED CONTROLLED TRIALS

GSK has extensively studied the regular use of both the inhalation aerosol and powder formulations of salmeterol-containing products for the treatment of asthma. The primary focus of this section is to present the safety (Serious Adverse Events [SAEs], deaths, exacerbations and asthma-related hospitalizations) and efficacy (lung function) data from a pooled analysis. This retrospective analysis includes 72 completed US randomized controlled studies in the pediatric and adult populations. The pediatric analysis includes data from 4,665 subjects 0-18 years of age. Results are grouped by age (0 to <2, 2-<5, 6-11, 12-18, 0-18, and ≥19 years).

Studies were selected for inclusion if they contained a salmeterol 50mcg BID or ADVAIR 100/50, 250/50, or 500/50 BID randomized treatment arm. The following treatment groups were evaluated:

- Salmeterol 50mcg BID compared with placebo
- Salmeterol 50mcg BID plus ICS compared with ICS alone.

In the salmeterol group, subjects may or may not have been using background concurrent ICS therapy. The salmeterol plus ICS group represents subjects randomized to salmeterol and an ICS, and includes studies where salmeterol was administered with fluticasone propionate, either combined within a single inhaler or administered concurrently from separate inhalers.

Seven studies included albuterol treatment arms. These treatment arms were combined with placebo treatment arms, since subjects in all treatment groups received albuterol to be used as rescue. Together these groups will be referred to as placebo in this section.

This analysis combines data from studies of different design, duration of exposure, age groups, and treatment groups. Studies that contained either a randomized treatment arm of salmeterol 50mcg BID or salmeterol 50mcg BID plus ICS were included. From these

selected studies, additional randomized treatment arms of placebo or ICS were included in the pooled analysis for comparison purposes. Due to the small size of the pediatric subgroups and the limited number of events within each study, selected studies were not required to contain randomized treatment arms of both salmeterol and placebo, or both salmeterol plus ICS and ICS, within the same study. Interpretation of the results of this analysis is limited, particularly given the small sample size and any imbalances within the selected studies in the treatment arms of interest.

3.1.1. Serious Adverse Events from US Asthma Clinical Trials (excluding SMART) – Pediatrics

SAEs were reported as events that resulted in death, were life-threatening, required hospitalization or prolongation of hospitalization, or resulted in disability or incapacity. For this *post hoc* analysis of SAEs, all MedDRA coding terms that fell within the general categories of respiratory, cardiovascular and metabolic related were included. The incidence of SAEs in the metabolism and nutrition System Organ Class (SOC) were low (≤0.05% across groups) and are not reported. This section will focus on deaths and events associated with the cardiovascular and respiratory systems.

This assessment of SAEs from 72 studies includes 22,071 subjects, of which 4,665 subjects were 0-18 years of age. Treatment duration ranged from one to 52 weeks and included efficacy endpoints for lung function (e.g., PEF). Safety endpoints included collection of adverse events and exacerbations.

3.1.1.1. Deaths

There were no deaths in subjects ≤18 years old. There were 5 deaths in subjects ≥19 years of age, none of which was considered related to study drug by the investigator. Table 9 summarizes each event.

Table 9 Listing of Deaths (Pooled Analysis)

Treatment	Age in years	Gender	Ethnicity	AE verbatim Text	Related to Study Drug? Yes/No
ICS					
	31	F	White/Caucasian	Pulmonary Embolism	No
	42	M	White/Caucasian	Deep Vein Thrombosis Cardiac Arrest Seizure	No
Salmeterol					
	30	M	Other	Severe Asthma Exacerbation	No
	41	F	Hispanic	Respiratory Arrest	No
Salmeterol + ICS					
	77	F	White/Caucasian	Cerebral Infarct	No

3.1.1.2. Cardiovascular and Respiratory Events

SAEs from the cardiovascular and respiratory SOC are presented in Table 10.

Table 10 Serious Adverse Events in the Cardiovascular and Respiratory Body Systems (Pooled Analysis)

System Organ Class	Salmeterol (N=5571)	Placebo (N=4611)	Salmeterol plus ICS (N=6267)	ICS (N=5622)
Cardiovascular, n (%)	9 (<1)	7 (<1)	19 (<1)	16 (<1)
Respiratory, n (%)	73 (1)	28 (<1)	14 (<1)	26 (<1)

The overall incidence of cardiovascular SAEs was low (≤1%). The incidence of cardiovascular SAEs in each age by treatment group is summarized in Table 11.

Table 11 Cardiovascular Serious Adverse Events by Age (Pooled Analysis)

N events/N subjects (%) Age (years)	Salmeterol (N=5571)	Placebo (N=4611)	Salmeterol plus ICS (N=6267)	ICS (N=5622)
0 to <2	0/51	0/49	0/0	0/0
2 to 5	0/156	0/246	0/32	0/100
6 to 11	0/187	0/517	0/194	0/423
12 to 18	0/690	0/637	0/720	0/663
0 to18	0/1084	0/1449	0/946	0/1186
≥19	9/4486 (<1)	7/3162 (<1)	19/5320 (<1)	16/4434 (<1)

There were no cardiovascular SAEs in the 0-18 year old population. The incidence of cardiovascular SAEs observed in the ≥19 year old population was low (<1%) and evenly distributed between the treatment comparisons of interest.

The occurrence of SAEs within the Respiratory, Thoracic and Mediastinal disorders SOC was low (≤1%-see Table 10). Individual respiratory-related SAEs that occurred in ≥5 subjects in any group are reported in Table 12.

Table 12 Respiratory Serious Adverse Events Reported by 5 or More Subjects (Pooled Analysis)

SAE	Salmeterol (N=5571)	Placebo (N=4611)	Salmeterol plus ICS (N=6267)	ICS (N=5621)
Asthma, n (%)	46 (<1)	13 (<1)	9 (<1)	12 (<1)
Status asthmaticus, n (%)	14 (<1)	8 (<1)	0	0

Asthma and status asthmaticus comprised the majority of the SAEs in this body system category as shown in Table 12. Of the other SAEs reported, bronchitis and sinusitis were

observed in 4 or fewer subjects in each treatment. The other SAEs in this SOC were observed in <4 (0.07%) subjects in each treatment.

Comparison of the Respiratory body system SAEs among various age groups is shown in Table 13.

Table 13 Respiratory Serious Adverse Events by Age (Pooled Analysis)

n events/N subjects (%) Age (years)	Salmeterol (n=5571)	Placebo (n=4611)	Salmeterol plus ICS (n=6267)	ICS (n=5622)
0 to <2	1/51 (2)	0/49	0/0	0/0
2 to 5	2/156 (1)	4/246 (2)	0/32	1/100 (1)
6 to 11	6/187 (3)	5/517 (<1)	0/194	1/423 (<1)
12 to18	10/690 (1)	2/637 (<1)	1/720 (<1)	2/663 (<1)
0 to18	19/1084 (2)	11/1449 (<1)	1/946 (<1)	4/1186 (<1)
≥19	54/4486 (1)	17/3162 (<1)	13/5320 (<1)	22/4434 (<1)

The incidence of respiratory related SAEs was relatively similar in the salmeterol group compared with the placebo group in subjects 0 to18 years, and was similar to the incidence in subjects ≥19 years. When salmeterol was used with an ICS, the incidence of respiratory-related SAEs was equal to, or lower, compared with ICS alone.

3.1.2. Exacerbations and Hospitalizations Due to Asthma

To further characterize the safety of salmeterol-containing products, GSK analyzed outcomes from all US studies in which exacerbations were protocol-defined and specific details about each exacerbation, including site of treatment (e.g., hospital, ED visit, etc.) were captured (n=54 studies). The most common definition of an exacerbation in these studies was an event that required medication beyond study drug or albuterol. Other definitions included a combination of the following: ED visit and/or hospitalization, unscheduled physician visit, treatment with inhaled, oral or parenteral corticosteroids, or >12 puffs albuterol in 24 hours.

Results from this analysis are compared for age groups (0-<2, 2-5, 6-11, 12-18, 0-18, and ≥19 years) as well as for African American and Caucasian subgroups and are presented below.

Table 14 describes the baseline characteristics of all subjects in the trials by age group receiving salmeterol alone, placebo, salmeterol plus ICS, or ICS therapy alone.

Table 14 Baseline Characteristics of Subjects Randomized to Salmeterol or Placebo (Pooled Analysis)

	Salmeterol (N=4216)	Placebo (N=3621)	Salmeterol+ICS (N=5183)	ICS (N=4121)
AGE 0-<2 years (n)	31	28	-	-
Age years, mean (SD)	1.3 (0.5)	1.2 (0.4)	-	-
Sex, M/F (%)	68/32	71/29	-	-
AGE 2-5 years (n)	24	113	32	35
Age years, mean (SD)	4.5 (0.5)	4.7 (0.5)	4.7 (0.5)	4.5 (0.5)
Sex, M/F (%)	67/33	62/38	59/41	69/31
AGE 6-11 years (n)	187	517	194	184
Age years, mean (SD)	9.0 (1.6)	8.8 (1.7)	8.9 (1.6)	8.9 (1.7)
Sex, M/F (%)	65/35	58/42	66/34	61/39
AGE 12-18 years (n)	530	487	615	516
Age years, mean (SD)	15.0 (1.9)	14.6 (1.9)	14.9 (1.9)	14.6 (1.9)
Sex, M/F (%)	80/20	85/15	57/43	55/45
% predicted FEV_1 (mean)	72.1	71.4	78.6	79.6
AGE 0-18 years (n)	772	1145	841	735
Age years, mean (SD)	12.6 (4.2)	10.6 (4.1)	13.2 (3.5)	12.7 (3.6)
Sex, M/F (%)	76/24	70/30	59/41	57/43
% predicted FEV_1 (mean)	70.8	72.1	79.2	79.9
AGE ≥19 years (n)	3444	2475	4342	3386
Age years, mean (SD)	38.8 (13.1)	36.8 (12.8)	39.2 (12.7)	39.7 (12.7)
Sex, M/F (%)	43/57	47/53	38/62	38/62
% predicted FEV_1 (mean)	68.5	68.1	72.6	71.1

Note: % predicted FEV_1 not done in all subjects <12 years old; the Age group of 0 to <2years old did not contain a salmeterol plus ICS or ICS study treatment.

Demographic characteristics across the age groups were generally similar.

A summary of all exacerbations for subjects who received salmeterol or placebo is presented in Table 15. This table includes subgroup analysis for age groups (0-<2, 2-5, 6-11, 12-18, 0-18, and ≥19 years) and Caucasians and African-Americans.

Table 15 Exacerbations and Asthma-Related Hospitalizations by Age and Race in Subjects Randomized to Salmeterol or Placebo (Pooled Analysis)

	All Subjects[a]		African-American Subjects		Caucasian Subjects	
	Salmeterol (N=4216)	Placebo (N=3621)	Salmeterol (N=322)	Placebo (N=284)	Salmeterol (N=3517)	Placebo (N=3002)
AGE 0-<2 years (n)	31	28	0	0	18	20
Subjects with an Exacerbation, n (%)	3 (10)	1 (4)	0	0	3 (17)	1 (5)
# of Exacerbations	3	1	0	0	3	1
Hospitalizations[a] n (%)	0	0	0	0	0	0
AGE 2-5 years (n)	24	113	4	11	14	74
Subjects with an Exacerbation	10 (42)	34 (30)	2 (50)	3 (27)	4 (29)	23 (31)
# of Exacerbations	15	48	3	6	6	28
Hospitalizations[a], n (%)	1 (7)	2 (4)	0	0	1 (17)	2 (7)
AGE 6-11 years (n)	187	517	25	75	142	337
Subjects with an Exacerbation, n (%)	53(28)	107 (21)	10 (40)	16 (21)	38 (27)	72 (21)
# of Exacerbations	78	151	16	22	54	104
Hospitalizations[a], n (%)	5 (6)	3 (2)	1 (6)	1 (5)	2 (4)	1 (1)
AGE 12-18 years (n)	530	487	58	37	415	420
Subjects with an Exacerbation, n (%)	99 (19)	122 (25)	7(12)	10 (27)	79 (19)	103 (25)
# of Exacerbations	138	184	8	13	109	161
Hospitalizations[a], n (%)	2 (1)	0	1(13)	0	1 (<1)	0
AGE 0-18 years (n)	772	1145	87	123	589	851
Subjects with an Exacerbation, n (%)	165 (21)	264 (23)	19 (22)	29 (24)	124 (21)	199 (23)
# of Exacerbations	234	384	27	41	172	294
Hospitalizations[a], n (%)	8 (3)	5 (1)	2 (7)	1 (2)	4 (2)	3 (1)
AGE ≥19 years (n)	3444	2475	235	161	2928	2151
Subjects with an Exacerbation, n (%)	498 (15)	611 (25)	28 12)	34 (21)	439 (15)	533 (25)
# of Exacerbations	643	964	32	55	572	843
Hospitalizations[a], n (%)	31 (5)	13 (1)	3 (9)	1 (2)	25 (4)	10 (1)

a. Hospitalizations= percent calculated based on total number of exacerbations for the respective group

The incidence of asthma exacerbations in the total pediatric population (0-18 years) was lower in salmeterol subjects compared with placebo, although the difference between salmeterol and placebo was very small in the younger age group (0-18 years) compared with subjects ≥19 years. Within the pediatric subgroups, the incidence of asthma

exacerbations was higher with salmeterol compared with placebo in all age subgroups with the exception of subjects 12-18 years.

An asthma-related hospitalization may represent a more severe form of an asthma exacerbation. Asthma-related hospitalizations were infrequent, and in the subgroups for age occurred at a slightly higher incidence in subjects receiving salmeterol compared with placebo. The largest difference seen occurred in African-American adults, where 9% (n=3) and 2% (n=1) of salmeterol and placebo subjects, respectively, experienced an asthma-related hospitalization. Comparatively in African-American subjects 0-18 years of age, 7% (n=2) and 2% (n=1) of salmeterol and placebo subjects, respectively, reported an asthma-related hospitalization.

A summary of all exacerbations in subjects receiving salmeterol plus ICS therapy or ICS therapy alone is presented in Table 16. This table includes subgroup analysis for age groups (0 to <2, 2 to 5, 6 to 11, 12 to18, 0 to18, and ≥19 years) and Caucasians and African-Americans.

Table 16 Exacerbations and Asthma-Related Hospitalizations by Age and Race in Subjects Randomized to Salmeterol plus ICS or ICS Alone (Pooled Analysis)

	All Subjects		African American Subjects		Caucasian Subjects	
	Salmeterol plus ICS (N=5183)	ICS (N=4121)	Salmeterol plus ICS (N=747)	ICS (N=605)	Salmeterol plus ICS (N=3952)	ICS (N=3226)
AGE 0-<2 years (n)[a]	-	-	-	-	-	-
AGE 2-5 years (n)	32	35	8	6	19	24
Subjects with an Exacerbation, n (%)	1 (3)	5 (14)	1 (13)	0	0	5 (21)
# of Exacerbations	1	5	1	0	0	5
Hospitalizations[b], n (%)[b]	0	0	0	0	0	0
AGE 6-11 years (n)	194	184	54	51	114	108
Subjects with an Exacerbation, n (%)	5 (3)	6 (3)	2 (4)	1 (2)	3 (3)	3 (3)
# of Exacerbations	5	6	2	1	3	3
Hospitalizations[b], n (%)	0	0	0	0	0	0
AGE 12-18 years (n)	615	516	123	116	435	347
Subjects with an Exacerbation, n (%)	36 (6)	61 (12)	12 (10)	14 (12)	23 (5)	43 (12)
# of Exacerbations	47	76	19	19	26	51
Hospitalizations[b], n (%)	1 (2)	2 (3)	0	1 (5)	1 (4)	1 (2)
AGE 0-18 years (n)	841	735	185	173	568	479
Subjects with an Exacerbation, n (%)	42 (5)	72 (10)	15 (8)	15 (9)	26 (5)	51 (11)
# of Exacerbations	53	87	22	20	29	59
Hospitalizations[b], n (%)	1 (2)	2 (2)	0	1 (5)	1 (3)	1 (2)
AGE ≥19 years (n)	4342	3386	562	432	3384	2747
Subjects with an Exacerbation, n (%)	248 (6)	416 (12)	65 (12)	76 (18)	168 (5)	309 (11)
# of Exacerbations	306	516	89	113	201	363
Hospitalizations[b], n (%)	6 (2)	10 (2)	3 (3)	3 (3)	2 (1)	7 (2)

a. The 0 to <2year-old group did not contain salmeterol plus ICS or ICS study treatment

b. Hospitalizations= percent calculated based on number of exacerbations for the respective group.

The percentage of subjects experiencing an exacerbation or asthma-related hospitalization in all age groups was lower in the salmeterol plus ICS therapy compared with ICS therapy alone, except for a few of the age subgroups where the percentages were equal. The percentage of subjects experiencing an exacerbation or asthma-related hospitalization in the 0-18 year old population and ≥19 years was comparable. These findings were generally consistent within the ethnic subgroups.

3.1.3. Efficacy Outcomes

GSK has extensively studied the regular use of both the inhalation aerosol and powder formulations of salmeterol for the treatment of asthma. Efficacy results of the 54 studies which also evaluated subjects experiencing an exacerbation and hospitalizations due to exacerbations, including 3,494 subjects 0-18 years of age, are summarized in this section.

Lung Function

Treatment with salmeterol is known to result in clinically significant increases in lung function within the first hour of treatment with maintenance of bronchodilator effect for up to 12 hours and greater in the adults and children. Change from baseline (BL) at endpoint in AM PEF evaluated in subjects 2-5, 6-11, 12-18, 0-18, and ≥19 years of age is summarized in Table 17. Lung function changes were the primary endpoint for studies in pediatrics which contained a primary efficacy endpoint.

Table 17 Morning Peak Expiratory Flow (AM PEF) (Pooled Analysis)

	Salmeterol (n=4216)	**Placebo (n=3621)**	**Salmeterol +ICS (n=5183)**	**ICS (n=4121)**
AGE 2-5 years, n/N	24/24	112/113	30/32	33/35
Change from BL AM PEF at endpoint (L/min) mean (SD)	28.5 (24.8)	15.6 (26.0)	20.0 (21.1)	5.8 (39.8)
AGE 6-11 years, n/N	183/187	515/517	184/194	175/184
Change from BL AM PEF at endpoint (L/min) mean (SD)	22.7 (36.2)	15.2 (36.7)	19.9 (38.1)	13.9 (40.9)
AGE 12-18 years, n/N	515/530	480/487	595/615	484/516
Change from BL AM PEF at endpoint (L/min) mean (SD)	25.8 (48.4)	13.5 (46.2)	33.6 (60.9)	24.6 (65.6)
AGE 0-18 years, n/N	722/772	1108/1146	809/841	692/735
Change from BL AM PEF at endpoint (L/min) mean (SD)	25.1 (45.0)	14.5 (40.2)	30.0 (55.8)	21.0 (59.5)
AGE ≥19 years, n/N	3375/3444	2414/2475	4258/4342	3310/3386
Change from BL AM PEF at endpoint (L/min) mean (SD)	29.0 (56.3)	4.7 (49.6)	42.7 (64.5)	21.8 (60.7)

Overall, there was a greater change from baseline at endpoint in AM PEF in the salmeterol-treated group when compared to placebo group and in the salmeterol plus ICS group when compared to the ICS group. The findings within the race and age subgroups were consistent with the overall population.

3.1.4. Overall Summary – Randomized Controlled Trials

This analysis combines data from studies of different design, duration of exposure, age groups, and treatment groups. Due to the small size of the pediatric subgroups, the number of events, and any imbalances between treatment arms of interest within the selected studies, caution should be used in interpreting results.

SAEs and Deaths

- No cardiovascular SAEs or deaths were observed in subjects 0-18 years of age. The incidence of respiratory related SAEs was low for all treatments and age groups (≤1%).

Exacerbations and Asthma-Related Hospitalizations

- The incidence of asthma exacerbations in the total pediatric population (0-18 years) was lower in salmeterol subjects compared with placebo subjects. The difference between salmeterol and placebo was very small in the total pediatric population compared with subjects ≥19 years.
    - The incidence of asthma-related hospitalizations in the pediatric population was higher in salmeterol subjects compared with placebo. The incidence of asthma-related hospitalizations was infrequent in children compared with adults.
- The incidence of asthma exacerbations in the total pediatric population (0-18 years) was lower in salmeterol plus ICS subjects compared with ICS subjects. This observation was also noted in subjects ≥19 years.
    - The incidence of asthma-related hospitalizations in the total pediatric population was identical in salmeterol plus ICS subjects compared with ICS subjects. There was no difference between pediatrics and adults.
- Trends in exacerbations and asthma-related hospitalizations for African-American subjects in pediatrics and adults were similar to the results described above.

Efficacy

- Across all age groups, salmeterol improved lung function (PEF), whether alone or in combination with an ICS.

Data from this pooled analysis demonstrates that salmeterol provides clinically meaningful benefit to patients and has a positive safety profile. The extensive clinical data on salmeterol is embodied in current evidence based asthma treatment guidelines which supports the use of long-acting β_2-agonists with ICS, in both pediatric and adult patients, as a recommended treatment option for patients with persistent asthma not controlled on ICS alone.

3.2. RECENTLY COMPLETED STUDIES

In order to better understand the safety findings from SMART, GSK initiated two pharmacogenetic studies to examine whether genetic variation in β2-adrenergic receptor gene modifies the response to salmeterol. The first study was a retrospective analysis of pooled data from 10 completed studies.

The second study was initiated to examine the role of salmeterol added to ICS in controlling asthma exacerbations in a potential high risk population, African-Americans (SFA103153). In addition, a prospective study (SAS100062) was conducted in nearly 550 subjects ≥12 years of age to evaluate the influence of genotypic variation at the B16 position on lung function and other asthma-related outcomes in subjects receiving salmeterol alone or salmeterol plus ICS (ADVAIR). Brief summaries of these two clinical studies are provided below. Results are also summarized for subjects 12-18 years of age.

3.2.1. Retrospective Pharmacogenetic Analysis (10-Study Combined Analysis)

GSK pooled data from 10 completed studies to examine the effects of polymorphisms in the β_2-adrenergic receptor gene (*ADRB2*) on the response to salmeterol, fluticasone propionate and fluticasone propionate/salmeterol (FSC) in subjects ≥12 years old. Polymorphisms in *ADRB* have been associated with an altered response to β_2-agonists [Liggett, 2000; Leineweber, 2004]. The position 16 polymorphism in which subjects have either arginine (Arg) or glycine (Gly) has been most studied [Taylor, 2000; Israel, 2000].

3.2.1.1. Analysis Design

Ten clinical protocols were combined for the retrospective analysis. These studies (FAP30007, FAP30008, FAS40023, SAS30001, SAS30003, SAS30004, SAS30017, SAS40015, SAS40020 and SAS40021). All were similar in design with a run-in period of at least 1 week and treatment duration of 12 weeks. Combined pharmacogenetics results from two of the trials (SAS40020 and SAS40021) are published [Bleeker, 2006]. Subjects had an FEV_1 at baseline between 40-85% predicted and demonstrated ≥12% reversibility to 2 puffs of albuterol.

3.2.1.2. Results

There were 886 subjects with DNA and consent for pharmacogenetic analyses. Eight-hundred-twenty-nine (829) subjects were self-reported as Caucasian and 57 as African-American. Analysis was restricted to Caucasians due to sample size. Within the Caucasian age group 12-18 years, there were only 8 subjects in the salmeterol treatment group and 14 subjects in the FSC group. Due to low numbers of subjects, there were no statistical comparisons between genotypes in this age range for the efficacy parameters.

There were 4 treatment arms; placebo (n=106), salmeterol (n=93), fluticasone propionate (n=324) and FSC (n=306). All doses of fluticasone propionate (100, 250, and 500mcg) were analyzed as a single group with dose utilized in the models as a covariate.

Seven polymorphisms were analyzed in the *ADRB2* gene; -2633 C/T (RS1432622), -654 A/G (RS12654778), -47 Cys19Arg (RS1042711), 46 Arg16Gly (RS1042713), 79 Gln27Glu (RS1042714), 491 Thr164Ile (RS1800888) and 523 Arg175Gly (RS1042718). In this analysis there were no significant differences observed in AM PEF between the Arg16Gly genotype for any of the treatment arms. In the salmeterol treatment group, none of the additional *ADRB2* polymorphisms were associated with any of the response phenotypes. In the FSC group one marker, Gln27Glu was associated with short-acting β_2-agonist (SABA) use (p=0.048) and symptom score (p=0.03) but not AM PEF or FEV_1.

Overall, in the 829 subjects, there were 12 asthma exacerbations occurring in the FSC group, 2 in the fluticasone propionate group and none in the salmeterol group (Table 18).

Table 18 Asthma Exacerbations in the Combined Pharmacogenetics Studies

Genotype	Subject ID	Age	Sex	Ethnicity	Severity	Number of Exacerbations
Arg/Arg	682587	43	F	Hispanic	mild	8
	682588	54	M	Caucasian	mild	1
	682650	41	F	Caucasian	mild	1
	682678	40	F	African-American	mild	4
	682332	51	F	Caucasian	mild	1
Arg/Gly	682566	40	F	African-American	mild	1
	682571	42	M	Other	mild	5
	682629	18	M	Other	mild	2
	682710	36	F	Other	mild	1
	682766	50	M	Other	mild	1
	682400	21	F	Caucasian	mild	1
Gly/Gly	682599	47	F	Caucasian	mild	1

Only one subject with an exacerbation was <18 years old (Arg/Gly genotype). There does not appear to be any association between genotype, age, gender or ethnicity and the frequency of exacerbations. Exacerbations were judged as mild by the investigator.

3.2.2. African-American Exacerbation Study (SFA103153)

3.2.2.1. Study Design

In SMART, a greater incidence of severe asthma-related events was reported with salmeterol compared with usual care (placebo). The incidence of these events was also greater in African-Americans compared with non-African-Americans. SFA103153 was a randomized, double-blind, parallel group trial in African-Americans designed to show a lower rate of asthma-related exacerbations in ADVAIR recipients compared with FP recipients. Subjects were 12-65 years of age with persistent asthma, and were

symptomatic while taking baseline ICS (FP 100mcg BID or equivalent). Subjects continued their baseline ICS for two weeks, followed by open-label fluticasone propionate 250mcg BID (FP 250mcg) for four weeks. Subjects next entered a 52-week double-blind treatment period and were assigned FSC 100/50mcg BID or fluticasone propionate 100mcg BID (FP 100mcg). Subjects who completed double-blind treatment entered a four week open-label FP 250mcg BID run-out period.

The primary efficacy endpoint for this study was the asthma exacerbation rate per subject per year. The secondary endpoints included AM and PM peak expiratory flow, asthma symptoms, and use of rescue albuterol.

3.2.2.2. Results

A total of 475 subjects ≥12 years of age were randomly assigned to treatment: 238 received ADVAIR and 236 FP. Results for the total population did not satisfy the primary objective (asthma-related exacerbation rate per subject per year) since the exacerbation rate was lower but not statistically significant in ADVAIR compared with FP (p=0.169). The rate of asthma-related exacerbations predicted from African-American subjects in previous studies was 0.4 and 0.8 for ADVAIR and FP, respectively. The asthma-related exacerbation rate observed in this study was 0.44 for ADVAIR and 0.53 for FP.

In a *post hoc* analysis for this report, the data were grouped and analyzed by age; 111 subjects were 12-18 years of age and 364 subjects were ≥19 years of age. In the 12-18 age group, the majority of subjects (59%) were male and in the ≥19 age group the majority of subjects (68%) were female.

The subject disposition and asthma exacerbations by age groups are summarized in Table 19.

Table 19 Subject Disposition and Asthma Exacerbations (ITT Population) (SFA103153)

	12–18 years		≥19 years	
	FSC 100/50 N=60 n (%)	FP 100 N=51 n (%)	FSC 100/50 N=179 n (%)	FP 100 N=185 n (%)
Disposition				
Completed the study	43 (72)	34 (67)	126 (70)	117 (63)
Prematurely withdrawn	17 (28)	17 (33)	53 (30)	68 (37)
Adverse event	0	0	5 (3)	6 (3)
Exacerbation	0	2 (4)	6 (3)	7 (4)
Asthma Exacerbations (Double-blind treatment)				
Mean Rate [SE]	0.412 [0.150]	0.506 [0.209]	0.462 [0.113]	0.536 [0.102]
# subjects with an exacerbation	11 (18)	11 (22)	36 (20)	43 (23)
# of exacerbations	18	15	51	70
# subjects hospitalized due to an asthma exacerbation	0	1	2	2

In the 12-18 age group, a greater number of subjects who received FSC 100/50mcg completed the study compared to those who received FP 100mcg. This was consistent with the ≥19 age group.

Primary Efficacy Measure: Asthma Exacerbation Rate

In the 12-18 age group the asthma exacerbation rate was lower in subjects who received FSC 100/50mcg compared with those who received FP 100mcg, and lower than either treatment group in the ≥19 year age group. In addition, no subject in the 12-18 year age group who received FSC 100/50mcg was hospitalized due to an asthma exacerbation where one subject who received FP 100mcg was hospitalized for an exacerbation. In the ≥19 age group, two subjects in each treatment group were hospitalized due to an asthma exacerbation. All the asthma exacerbations reported during the study resolved.

Secondary Efficacy Measures

The secondary efficacy measures in this study included FEV_1, AM and PM PEF, asthma symptom scores, and supplemental albuterol use. In the 12-18 age group, subjects who received FSC 100/50mcg demonstrated greater improvements from baseline in all secondary efficacy measures, with the exception of percent of albuterol-free days and 24-hour asthma symptom score. In the ≥19 age group subjects who received FSC 100/50mcg demonstrated greater improvements in all the secondary measures compared with the FP 100mcg treatment group.

Safety

The types of adverse events reported were generally similar between age groups for each treatment and consistent with the events listed in the approved product label for each product. The incidence of adverse events was lowest in subjects 12-18 years of age who received FSC 100/50mcg.

Serious Adverse Events

In the 12-18 age group, no subject who received FSC 100/50mcg experienced a serious adverse event compared with the FP 100mcg group where two subjects experienced SAEs (infective arthritis and ligament rupture in one subject and an asthma exacerbation in one subject).

In the ≥19 age group SAEs were reported for six subjects and nine subjects in the FSC 100/50mcg and FP 100mcg treatment groups, respectively.

3.2.2.3. Summary

Results in the *post hoc* analysis by age groups were similar to the results in the total population. The exacerbation rate was lower for both pediatric and adult subjects treated with FSC compared with FP. In addition, no subject in the FSC treatment group was hospitalized due to an asthma exacerbation. Also in the 12-18 age group, FSC 100/50mcg was well tolerated with a lower incidence of adverse events than

subjects treated with FP 100mcg. The type and incidence of adverse events reported for the 12-18 age group were generally similar to those reported in the ≥19 age group.

3.2.3. Pharmacogenetic Prospective Study (SFA100062)

The SFA100062 clinical study was conducted in subjects ≥12 years of age to prospectively evaluate the influence of genotypic variation at the B16 position on lung function and other asthma-related outcomes in subjects receiving salmeterol alone or salmeterol plus ICS. This study was recently completed, and a summary of the study design and results from subjects 12 to 18 years of age and subjects ≥19 years of age, are presented below.

SFA100062 was a randomized, double-blind, parallel group, controlled study. Eligible subjects with persistent asthma taking short-acting β2-agonists and FEV_1 70-100% of predicted normal were enrolled. Following a screening period, subjects entered two 8-week open-label run-in periods (8 weeks of as-needed albuterol followed by 8 weeks of as-needed ipratropium bromide), then 544 subjects ≥12 years of age were stratified by genotype (Arg/Arg, Arg/Gly, or Gly/Gly) and race/ethnicity. Subjects were then randomized to receive twice daily fluticasone propionate 100mcg plus salmeterol 50mcg administered in combination (FSC 100/50mcg), or salmeterol 50mcg via DISKUS for 16 weeks.

The primary endpoint of this study was AM PEF. Safety endpoints included adverse events and asthma exacerbations.

Results of the primary efficacy parameter for the overall population during the double-blind treatment period showed that the Arg/Arg, Gly/Gly, and Arg/Gly genotypes were not statistically different in the FSC 100/50mcg or salmeterol 50mcg treatment groups.

A *post-hoc* analysis was performed by age. One hundred three (103) subjects 12-18 years of age (19% of total) were enrolled. Treatment groups and genotypes within treatments were balanced with respect to age. A larger proportion of salmeterol subjects were withdrawn prematurely independent of age sub-group or genotype compared with FSC 100/50mcg. Subjects 12-18 years of age and ≥19 years of age demonstrated improvements in efficacy parameters over the double-blind treatment period, in all genotypes, within both treatment groups.

Adverse events were similar by age and genotype within treatments. During the double-blind treatment period, no SAEs were reported in either treatment group in subjects 12-18 years of age.

There were no exacerbations in the 12-18 year old group receiving FSC 100/50mcg and only one exacerbation in the older FSC 100/50mcg subgroup. In the salmeterol group, exacerbations occurred in 6 subjects (11%) 12-18 years of age compared with 4 subjects (2%) ≥19 years of age. No subject was hospitalized due to an exacerbation in either treatment group.

There was one fatality in this study, a 31-year-old male Hispanic subject (Arg/Gly) in Peru. Forty-three days after the start of salmeterol, the subject developed a severe asthma exacerbation. He did not seek medical attention, continued on study drug and rescue medication, and self medicated with prednisone. He died 3 days later. The investigator did not consider the fatality related to study drug.

In summary, data from subjects 12-18 years of age in the SFA100062 study demonstrated generally similar safety and efficacy outcomes compared with subjects ≥19 years of age. Outcomes did not differ by genotype and no unexpected results were noted.

3.3. SUMMARY OF US ASTHMA CLINICAL TRIALS

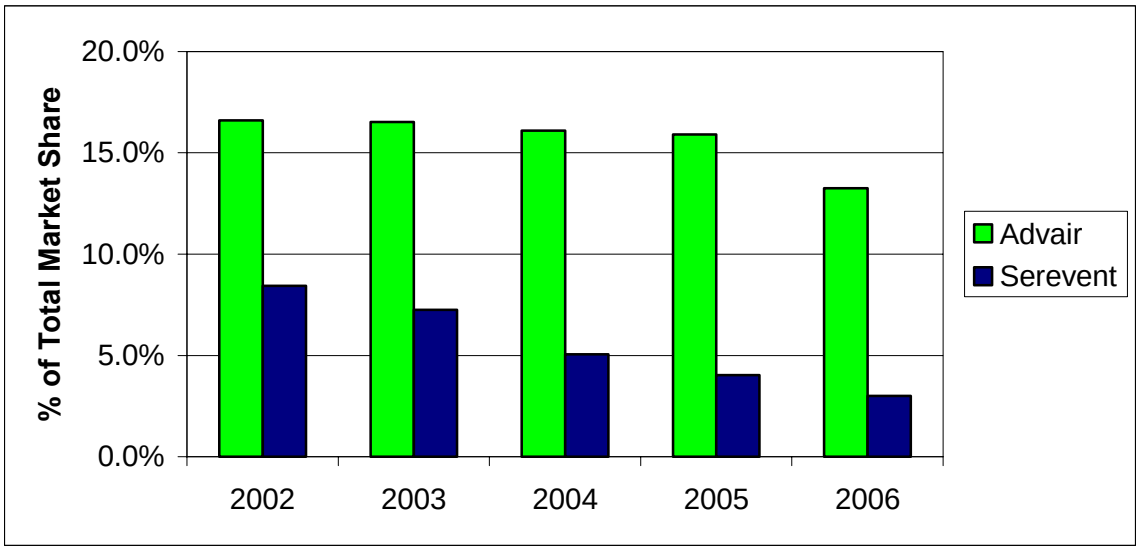
- Pooled data from 72 clinical trials including 4,665 subjects 0-18 years of age evaluating cardiovascular and respiratory-related SAEs demonstrated a low incidence of respiratory-related SAEs. No cardiovascular events or deaths were observed in subjects 0-18 years of age.
- Pooled data in 3,494 subjects 0-18 years of age from 54 clinical trials collecting specific data on asthma-related exacerbations showed that the incidence of exacerbations in the total pediatric population (0-18 years) was lower in salmeterol subjects compared with placebo, and salmeterol plus ICS subjects compared with ICS subjects. The difference between salmeterol and placebo was very small in the total pediatric population (0-18 years) compared with older subjects (≥19 years).
- The incidence of asthma-related hospitalizations in this pooled subset of 54 studies was higher in salmeterol compared with placebo, although the number of events was low. The incidence of asthma-related hospitalization was identical in salmeterol plus ICS compared with ICS alone. These findings were observed in the younger (0-18 years) and older (≥19 years) age groups.
- Retrospective and prospective pharmacogenetics studies showed that responses to salmeterol or salmeterol plus ICS were similar in subjects with genetic polymorphisms of the β_2-receptor.
- A one-year study in African-Americans, a population shown to experience greater asthma morbidity and mortality compared with other population groups, experienced a similar rate of asthma exacerbations and asthma-related hospitalizations with salmeterol plus ICS compared with ICS alone.

4. POST-MARKETING EXPOSURE – PEDIATRICS

Salmeterol has been marketed in the US since 1994 under the trade name SEREVENT and as a component of ADVAIR since 2001. Person-years of exposure to salmeterol-containing products was estimated based on the number of units sold annually in the US and outside the US. Yearly total prescription unit data are available for SEREVENT and ADVAIR since their respective introductions into the market. However, data grouped by age ≤18 and ≥19 are only available since 2002. Therefore, exposure by pediatric and adult population segments is estimated for all years prior to 2002 using the proportion of dispensings from 2002 [Verispan, 2007].

In 2006, 13.3% of total ADVAIR dispensings and 3% of total SEREVENT dispensings in US retail pharmacies were for children (Figure 2).

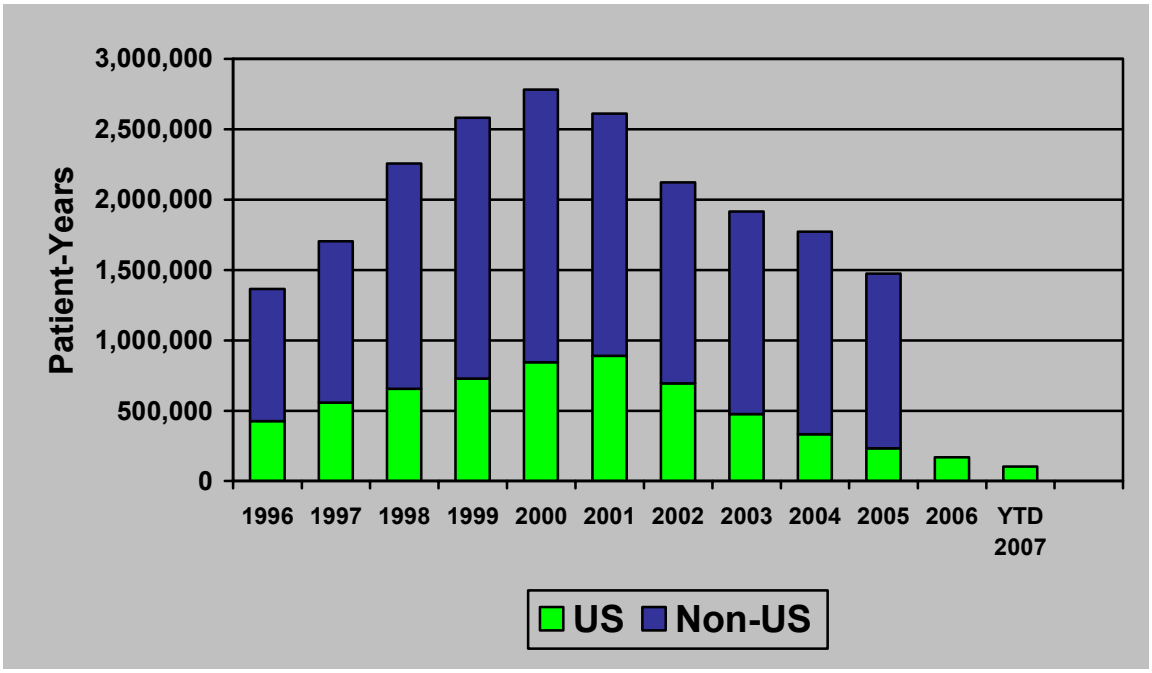
Figure 2 Proportion (%) of Salmeterol-Containing Dispensings for Pediatric Patients (Children 0-18 Years of Age) in US Retail Pharmacies



4.1. POST-MARKETING EXPOSURE TO SALMETEROL ALONE

Figure 3 shows that SEREVENT use has decreased since reaching its peak in 2000, which coincides with the increased use of ADVAIR from 2001 to the present. From 1996 through September 2007, the exposure to SEREVENT is estimated at approximately 6 million person-years in the US (Figure 3). Worldwide, exposure was 20.6 million person-years (5.8 million in the US, 14.7 million non-US) from 1996 to 2005.

Figure 3 Worldwide Total SEREVENT Annual Person-Years of Exposure (All Patients)



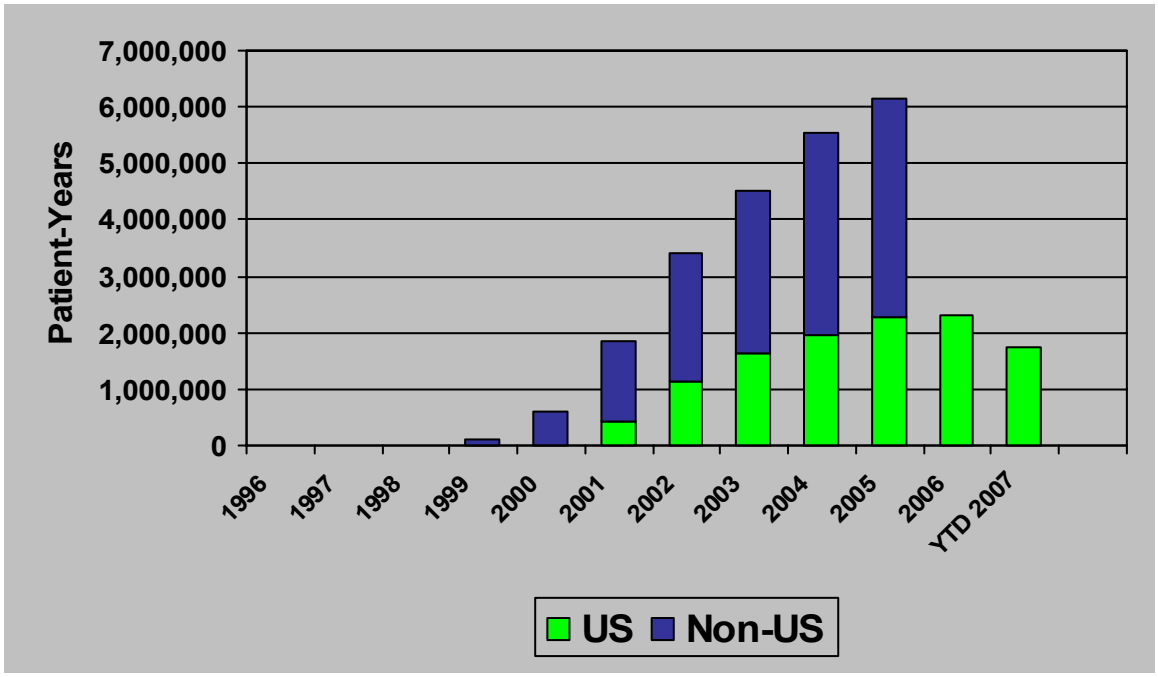
*Non-US data unavailable for 2006-2007.

Exposure to SEREVENT in pediatric patients is estimated to be <10% of the SEREVENT exposure in the total population. This estimate was derived by assuming that the proportion of pediatric dispensings from 1996 to 2001 were similar to 2002 (8.4%), and applying US retail pharmacy estimates to US and non-US data, SEREVENT pediatric exposure through 2005 is estimated to be 3.9 million person years worldwide (approximately 1.1 million person-years in the US and 2.8 million outside the US).

4.2. POST-MARKETING EXPOSURE TO SALMETEROL ADMINISTERED WITH FP IN A SINGLE DEVICE

ADVAIR use has increased significantly since its launch (1999 UK, 2001 US). From 1998 through September 2007, the exposure to ADVAIR is estimated to be approximately 18.8 million person-years in the US (Figure 4). Worldwide, person-years of exposure were 22.1 million person-years (7.1 million in the US, 14.7 million non-US) from 1996 to 2005.

Figure 4 Total ADVAIR Annual Person-Years of Exposure (All Patients)



*Non-US data unavailable for 2006-2007

Exposure to ADVAIR in pediatric patients is estimated to be <15% of the exposure in the total population. Applying the proportion of pediatric dispensings in the US retail pharmacy to US and non-US data and assuming 2002 proportion of pediatric market share applies to 1999 through 2001, ADVAIR pediatric exposure through 2005 is estimated to be 4.2 million person-years worldwide (approximately 1.7 million person-years in the US and 2.5 million in the non-US).

4.3. SUMMARY OF POST-MARKETING EXPOSURE TO SALMETEROL – PEDIATRICS

The use of salmeterol-containing products has increased with the approval of ADVAIR. From 1996 through September 2005, the exposure to salmeterol-containing products is estimated to be approximately 42.7 million person-years worldwide (20.6 million person-years of SEREVENT, 22.2 million person-years of ADVAIR). Using estimates of pediatric market share based on the US and applying the market share from 2002 to prior years, pediatric exposure to salmeterol-containing products through 2005 is approximately 8.1 million person years (2.8 million person-years in the US and 5.3 million person-years in non-US markets).

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

5.1. SPONTANEOUS REPORTS

Data from spontaneous reporting can be used to generate hypotheses concerning potential safety signals. Several caveats should, however, be borne in mind when reviewing spontaneous data. Spontaneous data are reported voluntarily from an unknown population size with lack of accurate information on the denominator (actual number of patients on the drug) and the numerator (the actual number of events). Reporting patterns are influenced by stage of the product life cycle in the market, characteristics of the patient population treated, publicity around the drug or the drug class and familiarity of healthcare professionals in using the product, as well as regional medical practices. Furthermore, spontaneous adverse event reports are received from all sources including reports from patients without medical verification and often lack sufficient information pertinent to the medical evaluation of the case. Due to these inherent limitations of spontaneous reporting it is not possible to draw firm conclusions from these data alone, spontaneous reports should therefore not be viewed in isolation but interpreted in the context of data from randomized control trials and observational studies.

5.1.1. Methods

GSK's internal adverse event safety database was searched to retrieve all worldwide spontaneous reports for SEREVENT and ADVAIR from the time of first approval to 31 December 2006 and also for the one year period following granting of salmeterol pediatric exclusivity (1 April 06 to 31 March 07). The data received from the time of first approval to 31 December 2006 was broken down by the standard age conventions in AERS into 0-16 years and ≥17 years age groups along with an unknown age category for cases where age was not reported. The data for the one year period was broken down into additional age groups as follows, 0-<2 years, 2-5 years, 6-11 years, 12-16 years, ≥17 years and unknown age.

Data are presented as total number of spontaneous reports, total number of serious reports, total number of reports with a fatal outcome and number of reports classified as serious due to hospitalization. *Fatal outcome* cases on the GSK internal adverse event safety database are defined as cases where either the case outcome is reported as fatal, the outcome of an event within the case is reported as fatal, the case seriousness criteria includes patient died or an event in the case is included as a Preferred Term (PT) within the GSK fatality MedDRA Query. *Hospitalization* reports were defined as reports where the seriousness criteria included hospitalization. If reports met the criteria for both *hospitalization* and *fatal outcome*, they were classified in the fatal category only.

It should be noted that fatal cases from New Zealand have been excluded from this analysis. A total of 250 salmeterol cases with a fatal outcome, were reported from New Zealand, the vast majority (96%) of which originated from the Intensive Medicine Monitoring Programme (IMMP). The IMMP was a government subsidized program, in

which patients need to meet certain criteria for eligibility for treatment with salmeterol, including poorly controlled or uncontrolled disease state for at least 3 months and ongoing treatment with 1500mcg beclomethasone or 750mcg FP. Analysis of these reports revealed a distinctive reporting pattern due to the nature of patients permitted to receive salmeterol in the IMMP. Reports were influenced by patients with severe asthma and older patients (82% involved patients aged 60 years or above) with significant multi-morbidities. Where age was specified, two of the cases occurred in the 0-16 age group. The fatal cases from New Zealand have been excluded from this analysis since these are solicited reports and not spontaneous.

5.1.2. Worldwide Spontaneous Reports from Time of First Approval

5.1.2.1. SEREVENT

Table 20 and Table 21 summarize the worldwide spontaneous reports received for salmeterol since first approval in 1990 up to the end of 2006.

Table 20 SEREVENT - Count of Worldwide Spontaneous Reports, Serious Reports, Fatal Outcome Reports and Serious due to Hospitalization Reports up to 31 Dec 2006

Age	Total spontaneous Reports	Serious reports	Fatal outcome reports	Serious due to hospitalization reports
0-16 years	681	141	47	48
17+ years	7041	1315	298	553
All Reports[a]	10180	1679	406	689

a. Includes reports where age was not reported

Table 21 SEREVENT - Reporting trend of worldwide spontaneous reports by age up to 31 Dec 2006

Year	Number of Cases (All ages)	Number of Pediatric Cases (0 -16 years)
1990	3	0
1991	454	13
1992	540	16
1993	461	49
1994	934	81
1995	708	67
1996	482	50
1997	481	57
1998	552	44
1999	515	43
2000	764	60
2001	835	64
2002	608	33
2003	1181	37
2004	763	27
2005	429	23
2006	470	17

Spontaneous Salmeterol Reports with a Fatal Outcome

As discussed in Section 5.2.3.2, the relative reporting frequencies for *fatal outcome* decreased in the period after 1996 relative to the period prior to 1996 in both adults and pediatrics. The number of pediatric cases in each SOC for the two time periods is shown in Table 22. The number of cases with a fatal outcome has decreased from 1996 onwards; this may be related to more appropriate use of salmeterol following labeling changes and broad communications warning against the use of salmeterol in significantly worsening or acutely deteriorating asthma.

Table 22 System Organ Class (SOC) of Primary Event for Salmeterol Fatal Pediatric Cases received from Time of First Approval

System Organ Class	Number up to 31 Dec 95	Number from 01 Jan 96 to 31 Dec 06
Respiratory, thoracic and mediastinal disorders	21	6
General disorders and administration site conditions	5	6
Congenital familial and genetic disorders	0	2
Cardiac disorders	1	1
Immune system disorders	0	1
Infections and infestations	0	1
Injury, poisoning and procedural complications	0	1
Pregnancy, puerperium and perinatal conditions	0	1
Vascular disorders	1	0
TOTAL	**28**	**19**

The 19 cases received from 01 January 1996 are discussed in detail below.

Respiratory, Thoracic and Mediastinal Disorders SOC

Of the 6 respiratory cases since 1996, 3 originated from the US, 1 from France and 2 from the UK. In 3 of the cases it was confirmed that inhaled corticosteroids were also being taken; this information was not available in the other 3.

The first case from the US concerns a 16 year old male receiving inhaled salmeterol for asthma who had an exacerbation during football and apparently treated his attack with a sample canister of salmeterol and died. No further information was available. The second case was reported by a lawyer and details a 9 year old male with a history of asthma and allergy who had been receiving salmeterol for 3 years. Concomitant medications included fluticasone propionate and albuterol. He had known cat allergies and experienced a rapid and severe asthma exacerbation after exposure to a cat at a friend's house and subsequently died. At autopsy, the cause of death was acute respiratory insufficiency directly related to acute asthma attack. The third case from the US was also reported by a lawyer and concerns a 10 year old male who had been receiving salmeterol and fluticasone propionate for approximately 18 months. He developed wheezing which was unresponsive to home bronchodilation and went into respiratory arrest and died. The cause of death was "respiratory arrest following severe asthma attack".

The one report from France concerns a 9 year old male treated with beclomethasone, salmeterol and albuterol. About 2 months after starting salmeterol, and 8 hours after last salmeterol dose, he played sport without his usual prior use of albuterol and developed bronchospasm which did not respond to albuterol and died within 30 minutes.

The two UK reports are very similar and are likely the same case. Both reports concern an 11 year old female who 2 weeks prior to death developed trouble breathing and was treated with unspecified pills and inhalers and later with salmeterol inhaler. The

following day she became more unwell with difficulty breathing and collapsed and died. The cause of death at post-mortem was attributed to asthma.

Other SOCs

The cases have been categorized according to the SOC of the primary event within the case. Cases not included in the Respiratory, Thoracic and Mediastinal Disorders SOC may contain respiratory events and may describe asthma-related fatal outcomes.

Review of the other 13 cases does not reveal any features or events suggestive of a particular concern with salmeterol use. Four are reports of abnormalities in a fetus or infant in association with maternal exposure to salmeterol: the first is a report of a pregnant female who received beclomethasone dipropionate and salmeterol for asthma. At 26 weeks gestation the fetus developed hydrops fetalis and died in utero. No malformation was noted but an abnormally heavy placenta (640g). The second report is of a fetus with Ebstein's tricuspid cardiopathy that died at 22 weeks gestation; the mother was receiving salmeterol, montelukast and beclomethasone for severe asthma for the first 5 weeks of the pregnancy. The third is a poorly documented report of a female receiving salmeterol, albuterol and ipratropium who gave birth to a baby with unspecified severe congenital abnormalities that subsequently died. The final report with maternal exposure is a report of an infant born with hypoplastic left heart syndrome who died from the condition at 6 days of age. The mother was a 33 year old woman who received salmeterol, budesonide, theophylline and fenoterol during all trimesters.

Of the remaining 9 cases, one is a report of death secondary to viral pneumonia and one a report of bronchospasm and respiratory arrest attributed to anaphylactic reaction to nuts. One case reported death following cardiac arrest in a 12 year old male with a history of several asthma exacerbations requiring corticosteroids who, 9 months after starting salmeterol had an asthma exacerbation and required mechanical ventilation; he deteriorated and experienced cardiac arrest and brain death secondary to anoxia. There is one poorly documented report of death, not otherwise specified, in a 16 year old male who may have been taking salmeterol and two consumer reports of a 13 year old male with a history of exercise induced asthma being found dead following salmeterol use. The date of death was the same for both cases which may indicate duplicate reports. Further information was very limited in both reports.

One report of death in occurred in a 34 month old female who was found dead 45 days after starting lamotrigine. She had a history of severe asthma and seizures and was also receiving carbamazepine, clonazepam, salmeterol, budesonide and loratadine.

The final 2 reports concern a case of death due to unknown cause in a 4 year old male with a history of severe asthma, psychomotor and neurological problems and super infections who developed abdominal pain and hypertonia, approximately 2 months after starting salmeterol, and died about 20 minutes later, and a 14 year old female with a 12 year history of bronchial asthma and unclear treatment compliance. She apparently refused corticosteroid treatment for worsening dyspnea and was initially treated with salmeterol, replaced with albuterol and fluticasone propionate 24 hours later. Within a few hours she developed cyanosis and died the same day. No autopsy was performed.

5.1.2.2. ADVAIR

Table 23 and Table 24 summarize the worldwide spontaneous received for ADVAIR since first approval in 1998 up to the end of 2006.

Table 23 ADVAIR - Count of Worldwide Spontaneous Reports, Serious Reports, Fatal Outcome Reports and Serious due to Hospitalization Reports up to 31 Dec 2006

	Total spontaneous Reports	Serious reports	Fatal outcome reports	Serious due to hospitalization reports
0-16 years	1658	345	24	87
17+ years	11808	1696	124	501
All Reports[a]	18534	2418	170	663

a. Includes reports where age was not reported

Table 24 ADVAIR - Reporting trend of worldwide spontaneous reports by age up to 31 Dec 2006

Year	Number of Cases (All ages)	Number of Pediatric Cases (0 -16 years)
1998	0	0
1999	119	6
2000	360	24
2001	1792	137
2002	3047	258
2003	3057	203
2004	3407	342
2005	3357	336
2006	3395	352

In general, across age groups, the annual number of spontaneous reports received for ADVAIR increases as annual exposure to ADVAIR increases.

Spontaneous ADVAIR Reports with a Fatal Outcome

A total of 24 pediatric cases associated with a fatal outcome have been received for ADVAIR up to 31 Dec 2006. The number of pediatric cases in each System Order Class (SOC) is shown below in Table 25.

Table 25 System Organ Class (SOC) of primary event for ADVAIR Fatal Pediatric Cases received cumulatively to 31 Dec 2006

System Organ Class	Number
Respiratory, thoracic and mediastinal disorders	11
General disorders and administration site conditions	5
Cardiac disorders	4
Endocrine disorders	1
Injury, poisoning and procedural complications	1
Nervous system disorders	1
Pregnancy, puerperium and perinatal conditions	1
TOTAL	**24**

Cases in 2006 (n=11)

Following the July 2005 advisory committee concerning the safety of LABA products, the labeling for salmeterol containing products, including ADVAIR DISKUS, was revised in March 2006. The publicity associated with labeling change resulted in an increase in the number of ADVAIR DISKUS reports of fatal outcome, with 11 of the 24 total fatal pediatric cases were reported in 2006. A summary of the 11 reports received by GSK during 2006 is provided below.

Ten of these cases originated from the US; 1 is of death, not otherwise specified, in the ED (12 year old female with a history of asthma who may have been taking salmeterol) and the other 9 report deaths from severe asthma exacerbations/status asthmaticus. Five of these 9 reports were received from lawyers; of these 5 latter cases, 2 concerned deaths in 2004 and 2 related to deaths from 2005. One Australian case received during 2006 initially reported a patient dying but upon physician follow-up was found to be non-fatal, although this remains in the total number of cases for 2006. Eight of the reports from 2006 had a primary event in the Respiratory, thoracic and mediastinal disorders SOC, two in the General disorders and administration site conditions SOC and one in the Injury, poisoning and procedural complications SOC.

This increase in the number of reports of fatal asthma exacerbations is likely related to heightened public awareness that long-acting β_2–adrenergic agents may be associated with an increased risk of asthma related death following revised labeling for ADVAIR in early 2006 and publicity around the use of long-acting β_2-agonists. In total, three pediatric cases associated with a fatal outcome have been received in 2007 up to 31 August.

Other Cases (n=13)

Of the remaining 13 cases, 8 originated from the US, 2 from the UK and 1 each from Switzerland, Russia and Croatia.

Respiratory, Thoracic and Mediastinal Disorders SOC (n=3)

The first of these cases described an asthma attack leading to death in a 13 year old boy with a history of multiple hospital admissions for asthma exacerbations. The second concerned a 14 year old boy with who died following an asthma attack and progression to a full cardiac arrest. He had a history of full respiratory arrest and mechanical ventilation prior to commencing ADVAIR. The third case from the US was also reported by a lawyer and concerns a 10 year old male who had been receiving salmeterol and fluticasone propionate for approximately 18 months. He developed wheezing which was unresponsive to home bronchodilation and went into respiratory arrest and died. The cause of death was "respiratory arrest following severe asthma attack". SEREVENT was a co-suspect drug in this case. This case was also discussed in Section 5.1.2.1.

Other SOCs (n=10)

The cases have been categorized according to the SOC of the primary event within the case. Cases not included in the Respiratory, Thoracic and Mediastinal Disorders SOC may contain respiratory events and may describe asthma-related fatal outcomes.

There were two reports of fatal outcome in infants born to women who had received ADVAIR. The first is a consumer report of a stillbirth in a 39 year old woman who had taken ADVAIR "on and off for a couple of years". The second is a report of a 20 year old female who received ADVAIR during the first 2 weeks of pregnancy. Intranasal beclomethasone was started at 20 weeks and inhaled salmeterol, beclomethasone and albuterol at 28 weeks. Following a normal delivery the infant was born in cardio-respiratory arrest and remained flaccid despite resuscitation, and had severe metabolic acidosis. The next day the baby was unresponsive and noted to have fixed dilated pupils and treatment was withdrawn.

A 14 year old male died due to acute bronchial asthma and cardiopulmonary arrest. He had poor compliance with ADVAIR and a history of multiple hospitalizations for respiratory distress. A further case reported the death of a 14 year old female with a 12 year history of bronchial asthma and unclear treatment compliance. She apparently refused corticosteroid treatment for worsening dyspnea and was initially treated with salmeterol, replaced with salmeterol and fluticasone propionate 24 hours later. Within a few hours she developed cyanosis and died the same day. No autopsy was performed (this is the same case described in Section 5.1.2.1). An 11 year girl from Croatia died during an asthma attack, the cause of death was reported as unknown and it is unknown whether an autopsy was performed.

Of the other 5 reports, 2 were of cardiac arrest: one in a 15 year old male, with a history of poor visit and medication compliance, who collapsed while playing sport and one in a 13 year old male; follow-up from the Medical Examiner's office in this case indicated death due to bronchial asthma. There were also two reports of death not otherwise specified and the final case was a UK report of death attributed to drug-induced adrenal suppression in a 5 year old female.

5.1.3. Worldwide Spontaneous Reports over One Year Period Following Granting of Salmeterol Pediatric Exclusivity

5.1.3.1. SEREVENT

Table 26 summarizes the spontaneous reports received for salmeterol over the one year period following granting of salmeterol pediatric exclusivity (01 April 06 to 31 March 07). These are broken down into 0-<2 years, 2-5 years, 6-11 years, 12-16 years, ≥17 years and unknown age categories.

Table 26 Salmeterol- Count of Worldwide Spontaneous Reports, Serious Reports, Fatal Outcome Reports and Serious due to Hospitalization Reports – 01 April 2006 to 31 March 2007

	Total spontaneous Reports	Serious reports	Fatal outcome reports	Serious due to hospitalization reports
0 - <2 years	1	0	0	0
2 - 5 years	2	0	0	0
6 -11 years	4	2	1	0
12 - 16 years	7	1	1	0
17+ years	258	68	7	12
All Reports[a]	466	92	11	18

a. Includes reports where age was not reported

Overall, 14 spontaneous cases in subjects 0-16 years of age were received for salmeterol in this time period. Two of these cases were fatal and have been discussed in Section 5.1.2.1.

5.1.3.2. ADVAIR

Table 27 summarizes the spontaneous reports received for ADVAIR over the one year period following approval of salmeterol pediatric exclusivity (01 April 06 to 31 March 07). These are broken down into 0-<2 years, 2-5 years, 6-11 years, 12-16 years, ≥17 years and unknown age categories.

Table 27 ADVAIR - Count of Worldwide Spontaneous Reports, Serious Reports, Fatal Outcome Reports and Serious due to Hospitalization Reports – 01 April 2006 to 31 March 2007

	Total spontaneous Reports	Serious reports	Fatal outcome reports	Serious due to hospitalization reports
0 - <2 years	42	15	1	4
2 - 5 years	66	11	0	2
6 -11 years	149	39	3	9
12 - 16 years	91	28	7	3
17+ years	2259	512	36	122
All Reports[a]	3633	747	55	160

a. Includes reports where age was not reported

Overall, 11 fatal cases in subjects 0-16 years of age were received for ADVAIR in this time period. Ten of these cases occurred in 2006 and have been discussed in Section 5.1.2.2. The remaining case occurred in 2007 and described death not otherwise specified in a little boy/child, exact age was not reported.

5.1.4. Summary of Spontaneous Reports for Salmeterol-Containing Products – Pediatrics

Safety data from spontaneous reports for SEREVENT and ADVAIR are routinely monitored and evaluated, and are reported to FDA.

The number of pediatric reports associated with a fatal outcome with salmeterol decreased from 1996, following labeling changes and broad communications to prescribers emphasizing appropriate use. As expected, the number of spontaneous reports with ADVAIR has increased with increasing use of the product. The number of pediatric asthma reports associated with a fatal outcome seen in 2006 may be related to public attention surrounding labeling changes.

5.2. DISPROPORTIONALITY ANALYSES OF SPONTANEOUS ADVERSE EVENT REPORTS

Historically, spontaneous adverse event reports have been evaluated using qualitative techniques such as individual case reviews and medical judgement. In March 2005, the Agency published a *Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment* [US HHS, 2005] which describes the use of statistical or mathematical tools, or so-called "data mining," to provide additional information about the existence of an excess of adverse events reported for a product. As such, Disproportionality Analysis (DPA) is a quantitative signal detection tool that provides information on the reporting frequencies of adverse events, relative to background reporting. The aim of this analysis is to identify higher-than-expected reporting of adverse events in pediatric patients relative to adults.

5.2.1. Methods

Disproportionality analysis was conducted using the public-release version of Adverse Event Reporting System (AERS) and the empiric Bayes data mining algorithm, Multi-item Gamma Poisson Shrinker (MGPS), [DuMouchel 1999; DuMouchel and Pregibon 2001].

AERS, the U.S. Food and Drug Administration'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 2007, the public-release version of AERS contained over 3 million reports involving approximately 2000 drugs. The public release version of AERS does not contain adverse event (AE) report narratives. Verbatim text of event terms included in the AERS database is indicated by the use of *italics* in this section. A single case report generally contains more than one adverse event term (e.g., shortness of breath, pneumonia, and cough may all be contained within a single case report), and all individual adverse event terms are analyzed independently when conducting a DPA.

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≥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].

The specifications in Table 28 were used for this analysis:

Table 28 Specifications used for Disproportionality Analysis

Database	AERS (1968-1Q2007)
Data mining algorithm	MGPS
Drug(s) of interest[a]	ADVAIR, SEREVENT
Events of interest Preferred Terms based on the Medical Dictionary for Regulatory Activities (MedDRA) v.10	• The database was screened for AEs which were reported more frequently in children than for adults • In addition, the following events of interest were analyzed: *acute respiratory failure; respiratory arrest; respiratory failure; sudden death; fatal outcome; hospitalization*
Age Groups Analyzed	Pediatrics: 0-16 years of age Adults: ≥17 years of age
Stratification Variables[b]	Age, gender, year of report

a. where either drug was designated as suspect by the reporter
b. Stratification minimizes the detection of apparent drug-event associations that may be due to independent relationships between a drug and a stratum variable and an event and the same stratum variable. (An example is the reporting association between a drug used commonly in the elderly and an event commonly reported in the elderly.)

Relative reporting rates for all drug-event pairs were calculated for the following age subsets: pediatric (0-16 years) and adult (≥17 years), based on standardized settings within WebVDME.

The following conservative criteria were applied to detect events reported more frequently for children than for adults.

- EB05 (pediatric) > EB95 (adult), i.e., the confidence interval around EBGM (pediatric) lies entirely above the confidence interval around EBGM (adult), and
- EB05 (pediatric) ≥1

Additionally, the following events of interest were selected based on the results of SMART: *acute respiratory failure, respiratory arrest, respiratory failure, sudden death, fatal outcome,* and *hospitalization*. The latter two events were created as custom terms for the analysis. "Fatal outcome" reports were defined as reports where 1) seriousness criterion was designated as death or 2) Medical Dictionary for Regulatory Activities (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.

5.2.2. Limitations of Disproportionality Analyses

- Disproportionality analysis 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.
- Comparisons of adult and pediatric age groups should be interpreted cautiously, since the expected values for each age group (i.e., the background or denominator in the relative reporting ratio calculation) are derived from different distributions of drugs and events. For example, chest pain is relatively uncommon in non-asthmatic children, whereas in non-asthmatic adults taking medicines this is a more common event. Thus, the pediatric event rate of chest pain would be expected to be relatively larger than the adult event rate.

5.2.3. Results

5.2.3.1. Number of Reports

The reports in AERS for SEREVENT and ADVAIR include a number of reports (approximately one-third) for which age is either missing or unknown; these reports were not considered in the analysis. A separate analysis of fatal outcome for all patients, including those with unknown age, was also performed, which confirmed low reporting frequencies for SEREVENT and ADVAIR (EB05<2, data not shown). What follows is a review of the events reported in subjects for whom age was specified.

5.2.3.2. SEREVENT

DPA Results in Children

Relative reporting frequencies for all events were similar in children and adults, with the exception of *cardiac arrest*, *syncope*, and *malaise* (Figure 5). (Note: cardiac arrest is generally the terminal event in the progression of a fatal asthma exacerbation.) Although differences between children and adults were seen for *cardiac arrest* and *syncope* before 1996, these differences were no longer present after 1996 (EB05<2) (Figure 6). Differences in *malaise* remained post-1996; however, these differences were extremely small, with EB05=1.16, which is less than the generally recognized threshold for a safety signal (EB05≥2).

Events of Interest

- Relative reporting frequencies were low in children for *hospitalization*, *respiratory arrest*, *sudden death*, *acute respiratory failure*, or *respiratory failure* (Figure 7). EB05 values for these events were <1.28.
- The relative reporting frequency for *fatal outcome* in children was higher than expected (EB05=2.7) and slightly higher than in adults (EB05=1.5).

On 16 January 1995, a 'Dear Doctor letter' was issued by GSK informing physicians of revisions to the prescribing information for salmeterol. The communications warned against the use of salmeterol in significantly worsening or acutely deteriorating asthma and in the treatment of acute asthma symptoms.

In view of the labeling revisions and associated communications, we computed the relative reporting frequency for *fatal outcome* for the time period before and after 1996. Relative reporting frequencies for *fatal outcome* decreased in the period after 1996 relative to the period prior to 1996 in both adults and children (Figure 6). The difference in relative reporting frequency between children and adults was small in the post-1996 period, with confidence intervals nearly overlapping between children (EB05=1.8) and adults (EB95=1.5) (Figure 6).

5.2.3.3. ADVAIR

DPA Results in Children

Relative reporting frequencies for all events were similar for children and adults, with the exceptions of *chest pain*, *hypersensitivity*, *weight increased*, and *myalgia*, which were reported more frequently for children than adults. For children, the relative reporting frequencies (EBGM values) for these events were slightly increased, with the highest EB05 of 1.8, for the event of *weight increased* (Figure 5). One possible explanation for increases in weight may be due to the effects of ICS seen in ADVAIR. Furthermore, all four events showed modest signals of disproportionality, with no EB05 value reaching the generally recognized threshold of 2.0. Hypersensitivity, weight gain, and myalgia are included in the Adverse Reactions section of the labeling for ADVAIR products. In addition, chest tightness, chest congestion, and chest symptoms are included in the Adverse Reactions section of the labeling for ADVAIR products, and chest pain is included in the Medication Guide and Patient Information sections of the labeling.

Events of Interest

- All events of interest (*acute respiratory failure, respiratory arrest, respiratory failure, sudden death, fatal outcome,* and *hospitalization)* were reported infrequently in children. EBGM values were <1 and EB05 values <0.38 (Figure 7).
- For all events of interest, relative reporting frequencies for children were similar to those for adults.

Figure 5 **Cumulative EBGM (EB05 – EB95) Values in Children and Adults for Events in AERS Where Relative Reporting Frequency in Children is Greater than in Adults**

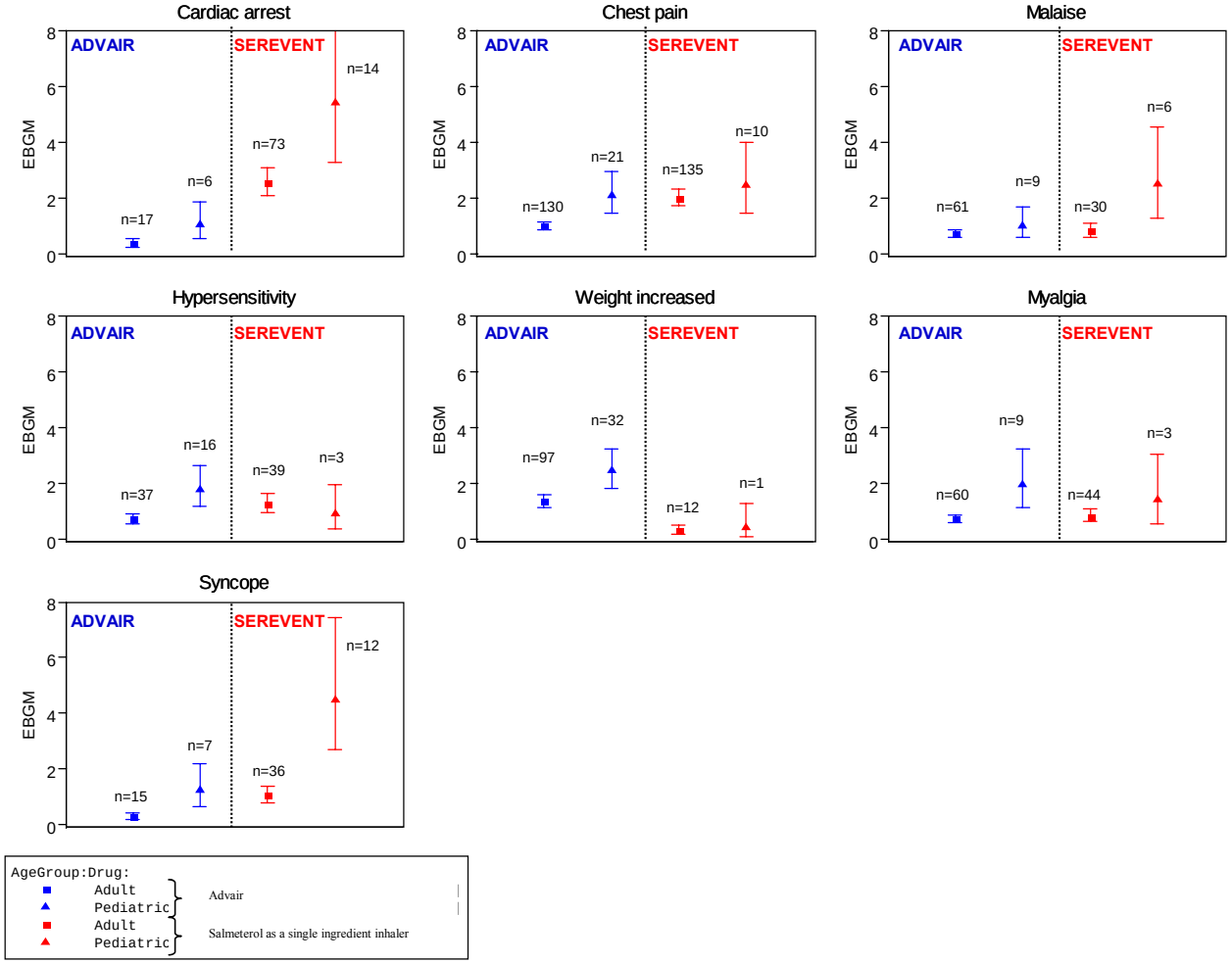


Figure 6 **Adverse Events with Salmeterol (single ingredient inhaler): Early Marketing Period (to 1996) versus Past Decade of Use**

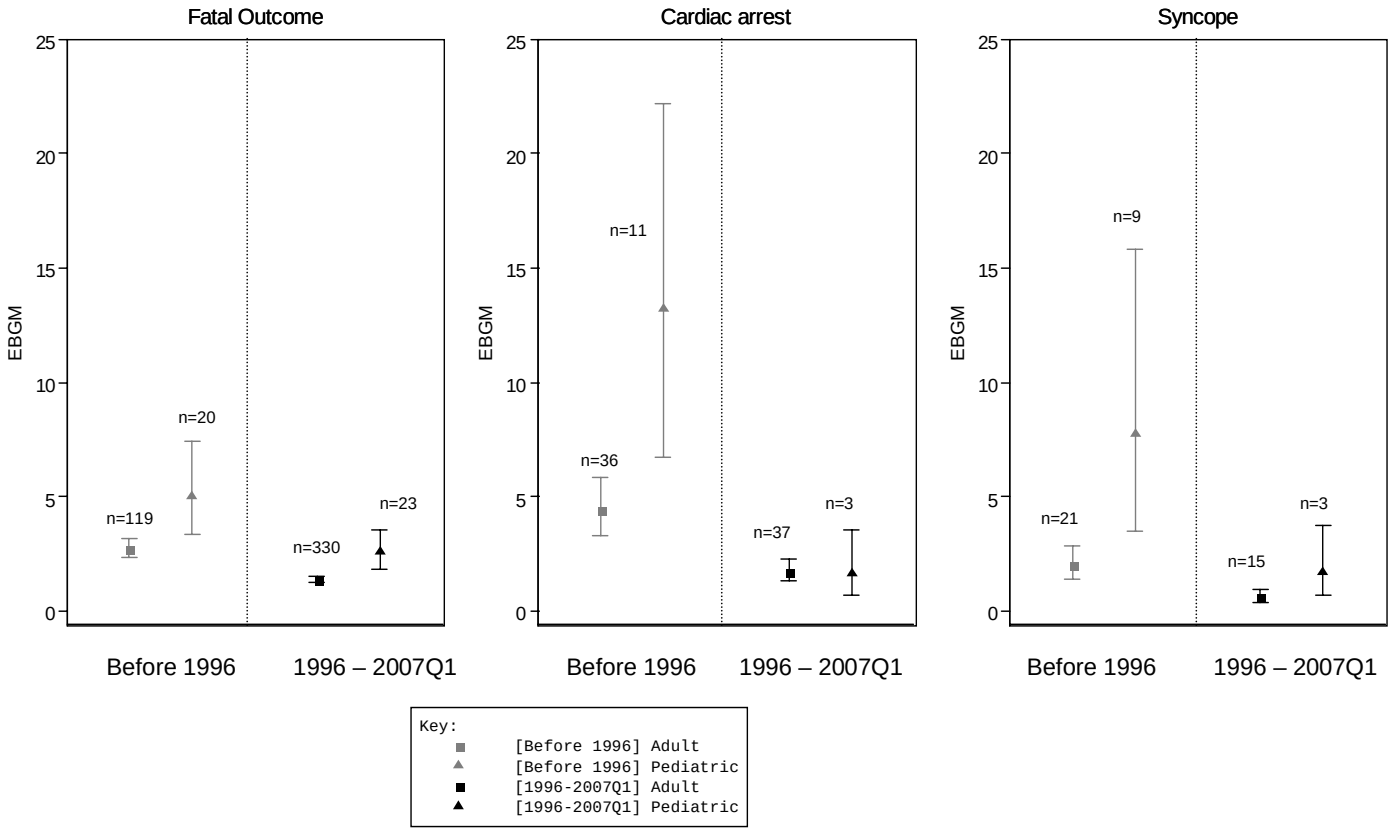
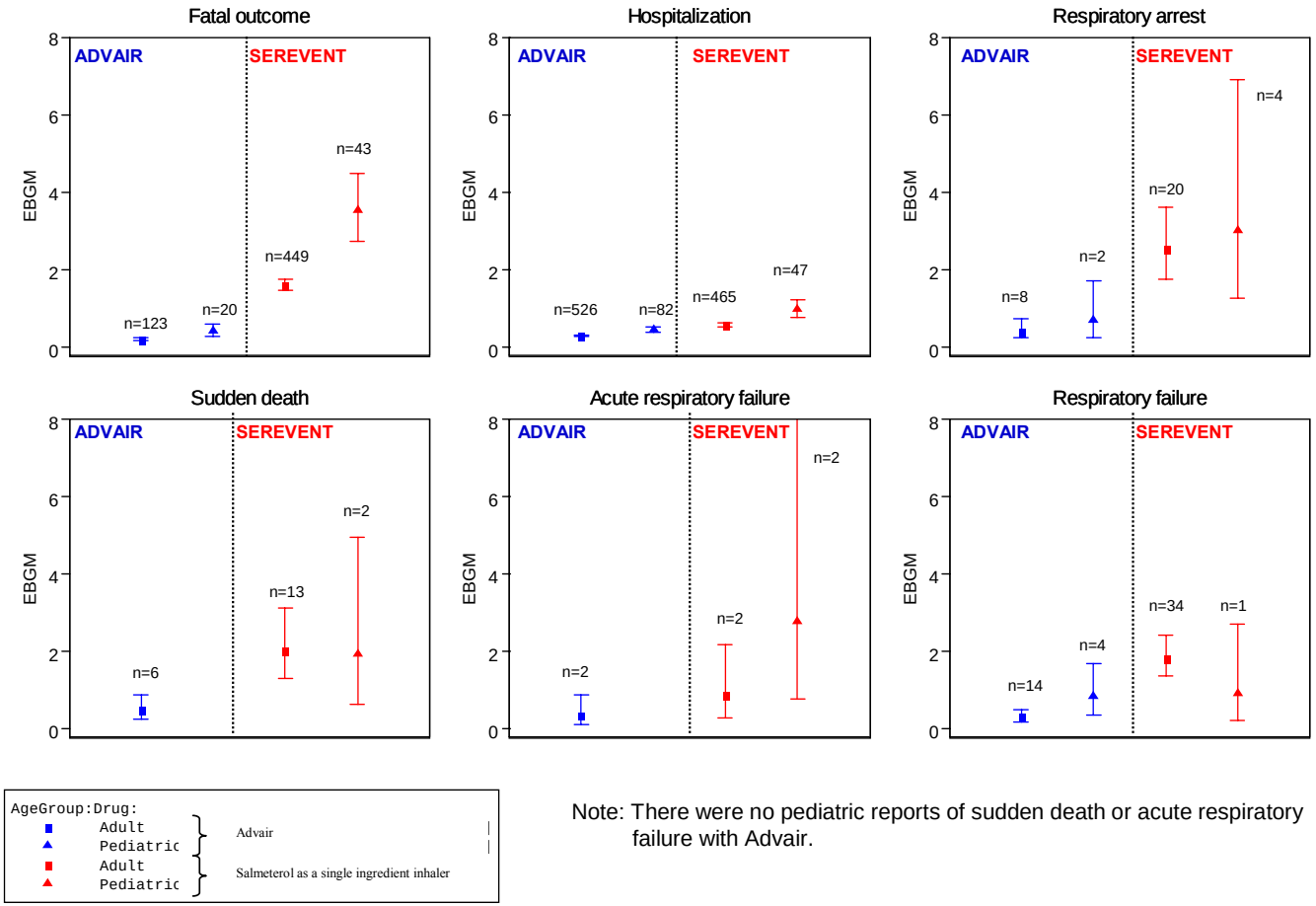


Figure 7 Cumulative EBGM (EB05 – EB95) Values in Children and Adults for Events of Interest in AERS



Note: There were no pediatric reports of sudden death or acute respiratory failure with Advair.

5.2.4. Summary of Disproportionality Analyses

Disproportionality analyses were performed to evaluate relative reporting frequencies of adverse events for SEREVENT and ADVAIR in children and adults. These analyses showed:

SEREVENT:

- A review of all adverse events demonstrated that the relative reporting frequencies for salmeterol were similar in children and adults, with the exception of a higher relative reporting frequency of *syncope*, *cardiac arrest*, and *malaise* in children. (Note: cardiac arrest is generally the terminal event in the progression of a fatal asthma exacerbation.) In the early marketing period for salmeterol (pre-1996), small differences in relative reporting frequencies for these events were seen between children and adults. From 1996 to 2007, differences for *syncope* and *cardiac arrest* were no longer present.
- For SEREVENT, a cumulative analysis showed low reporting frequencies in children for the serious adverse events of interest *hospitalization, respiratory arrest, sudden death, acute respiratory failure,* and *respiratory failure*. A slightly higher than expected frequency for *fatal outcome* was seen in children, which was also higher than that in adults. However, a separate analysis of AERS post-1996 (1996 to 2007Q1) showed low reporting frequencies of *fatal outcome* in both children and adults (EB05 values of 1.8 in children and 1.3 in adults), with minimal differences between the two age groups. This reduction in relative reporting of fatal outcomes may be related to broad communication following labeling changes for SEREVENT in 1995, which inform on this outcome, and the NHLBI's asthma guidelines recommendations in 1997.

ADVAIR:

- A review of all adverse events demonstrated that the relative reporting frequencies for ADVAIR were similar for children and adults with the exceptions of *chest pain*, *hypersensitivity*, *weight increased*, and *myalgia*, which were reported more frequently for children than adults. However, these differences between adults and children were small, and, importantly, the magnitude of these observations was modest (EB05 did not exceed 2). All of these events are included in the labeling for ADVAIR products.

- For events of interest, relative reporting frequencies for ADVAIR were low in both children and adults, with no differences between groups.

6. SALMETEROL LITERATURE REVIEW – PEDIATRICS

6.1. METHODS

A literature search encompassing MEDLINE, EMBASE and CINAHL was conducted for all references specific to salmeterol or salmeterol-containing products and safety in subjects <18 years of age. The search was inclusive of all references available through September 2007. To reduce the large number of citations retrieved via EMBASE, this collection was limited to those references where salmeterol was a major descriptor.

The search retrieved 459 references. Articles were reviewed and evaluated for inclusion in the synopsis provided below. The following criteria were applied:

- GSK-conducted or sponsored studies and analyses were excluded (as data from these studies are included in other sections of this document)
- Duplicate citations were excluded
- Studies evaluating subjects >18 years were excluded
- Non-English language references were excluded
- Cost-efficacy or other pharmacoeconomic analyses were excluded
- Clinical trials, case reports, letters to the editor and review articles specific to subjects <18 years of age were included

Epidemiological cohort studies are discussed in Section 8 of this document.

6.2. OVERVIEW OF LITERATURE REPORTS - PEDIATRICS

Fifty-eight (58) literature reports were identified with data evaluating the efficacy and/or safety of salmeterol for the treatment of asthma in the pediatric population.

Of the 58 literature reports, 23 enrolled or reviewed both pediatric patients and adult patients and 35 enrolled or reviewed only pediatric patients. None of the 23 studies enrolling both pediatric and adult patients separated results based on patient age. The information from these studies is not summarized in this section.

Of the 35 studies that enrolled only pediatric patients, 30 were randomized studies, 3 were observational studies and 2 were case studies (Table 29). Ten (10) of the randomized studies were single-dose studies and 20 studies had multiple dosing regimens.

These 35 studies are included in the summary information below.

Table 29 Summary Information for Pediatric Patients in Literature Reports

Literature Report	Drug (s) and Doses	N	No. M/F	Mean Age (range)	Extent of Exposure
Randomized, Multiple Dose Studies					
Baki 1998	Budesonide 200mcg BID Nedocromil sodium 2mg BID Salmeterol 25mcg BID Placebo	43	22/21	12 years (range 7-17)	3 weeks
Buchvald 2003	Budesonide 400mcg/day Montelukast 5mg/day Salmeterol 50mcg BID Placebo	23	11/12	12 years (range 7-14)	2 weeks
Cracco 1995	Nedocromil 4mg TID Salmeterol 50mcg BID	14	-	12 ± 1 years	12 weeks
del-Rio Navarro 2001a	Salmeterol 100mcg/day Salmeterol/Beclomethasone 100/400mcg/day	28	17/11	10 years (range 6-15)	12 weeks
del-Rio Navarro 2001b	Beclomethasone 200mcg x2 BID Beclomethasone/salmeterol 100/25mcg x2 BID	29	20/9	11 ± 2 years	6 weeks
Fuglsang 1995	Salmeterol 50mcg BID Budesonide 100mcg BID	23	-	12 years (range 7-16)	3 weeks
Fuglsang 1998	Salmeterol 50mcg BID Budesonide 200mcg BID	24	-	12 years (range 7-15)	3 weeks
Giroux 2003	Beclomethasone 100-200mcg + salmeterol 50-100mcg + albuterol 100-300mcg + formoterol 24mcg Budesonide 200-400mcg + salmeterol 50-100mcg + terbutaline 250-500mcg + formoterol 24mcg + albuterol 100-300mcg Salmeterol 100mcg Albuterol 100-400mcg Beclomethasone 250-500mcg Budesonide 250-500mcg	149	99/50	10 ± 3 years	Greater than 2 months
Jartti 1998	Salmeterol 50mcg BID Placebo	11	7/4	11 years (range 9-12)	4 weeks
La Grutta 2003	Short-acting β_2-agonists prn FP/ salmeterol 250/50 mcg Non-asthmatic controls	35	24/11	10 ± 3 years	-
Langton Hewer 1995	Salmeterol 100mcg BID Placebo	24	17/7	15 years (range 12-17)	8 weeks
Russell 1995	Salmeterol 50mcg BID Placebo	206	124/82	10 ± 3 years	12 weeks
Simons 1997a	Beclomethasone 200mcg BID Salmeterol 50mcg BID Placebo	241	140/101	9 ± 2 years	1 year
Simons 1997b	Salmeterol 50mcg QD Placebo	16	7/9	13 ± 1 years	28 days
Sorkness 2007	FP 100mcg BID FP/salmeterol 100/50mcg AM Plus Salmeterol 50mcg PM Montelukast 5mg PM	285	175/110	10 ± 2 years	48 weeks

Literature Report	Drug (s) and Doses	N	No. M/F	Mean Age (range)	Extent of Exposure
Tomac 1996	Salmeterol 50mcg BID	24	14/10	12 ± 3 years	4 weeks
Tunaoglu 1999	Salmeterol 200mcg BID	17	12/5	9 ± 2 years	3 weeks
Verberne 1996	Salmeterol 50mcg BID Albuterol 200mcg BID	30	20/10	10 ± 2 years	4 months
Verberne 1997	Salmeterol 50mcg BID Beclomethasone 200mcg BID	67	45/22	11 years (range 6-16)	1 year
Verini 1998	Albuterol 200mcg Procaterol 20mcg Salmeterol 50mcg Formoterol 24mcg Placebo	27	18/9	9 ± 3 years	5 days
Total No. Patients		**1316**			
Randomized, Single Dose Studies					
Adlington 2006	Salmeterol/FP 100/50mcg Placebo	14	7/7	9 years (range 6-11)	
Barbato 1995	Salmeterol 50mcg Albuterol 200mcg Placebo	11	8/3	13 years (range 9-17)	
Carlsen 1995	Salmeterol 25mcg Salmeterol 50mcg Placebo	23	12/11	11 ± 2 years	X 3
De Benedictis 1996	Salmeterol 25mcg Salmeterol 50mcg Placebo	12	10/2	11 ± 2 years	X 3
Green 1992	Salmeterol 50mcg Placebo	13	8/5	12 years (range 8-15)	
Ortiz 2002	Albuterol (MDI) 400mcg Salmeterol (MDI) 100mcg Salmeterol (DISKUS) 50mcg Placebo MDI	10	7/3	53 months (range 34-66)	
Pohunek 2004	Formoterol MDI 6,12,24,48mcg Salmeterol MDI 50mcg Placebo	68	46/22	12 years (range 7-17)	
Primhak 1999	Salmeterol 25mcg Salmeterol 50mcg Salmeterol 100mcg Placebo	33	28/5	27 months (range 8-46)	
Quezada 1999	Albuterol 200 mcg Fenoterol 200 mcg Albuterol/beclomethasone 200/100 mcg Fenoterol/ipratropium bromide 200/80 mcg Salmeterol 50 mcg Placebo	214	119/95	8 years (range 4-17)	
Simons 1992	Salmeterol 25 or 50mcg Albuterol 200mcg Placebo	23	13/10	10 years (range 6-12)	
Total number of patients		**421**			
Observational or Case Reports					
Clark 1993	Salmeterol 50mcg BID	1	F	17 years	7 days
Nguyen	FP/salmeterol 100/50mcg BID	39 total	29/10	Range 5-16 years	1 year

Literature Report	Drug (s) and Doses	N	No. M/F	Mean Age (range)	Extent of Exposure
2005	FP/salmeterol 250/50mcg BID				
Palmer 2006	Salmeterol 50mcg BID	546	343/204	10 ± 4 years	
Sekhsaria 2004	FP/salmeterol	50	29/21	35 months (range 5-60)	
Weinberger 2006	ICS/salmeterol	2	2	-	-
Total number of patients		**638**			

6.3. OVERVIEW OF SAFETY RESULTS IN LITERATURE REPORTS - PEDIATRICS

The majority of the studies reviewed reported no clinically significant adverse events following either single dose or regular treatment with salmeterol in pediatric patients with asthma. The development of clinically significant pulmonary effects with the use of salmeterol in children was minimal. Safety results are summarized in the following section according to the type of clinical study.

6.3.1. Multiple Dose, Randomized Studies

Twenty (20) studies using a randomized design enrolled a total of 1,316 pediatric asthma patients ranging in age from 6 to 17 years of age as summarized in Table 29. The duration of salmeterol treatment ranged from 5 days to 1 year. Nine (9) of the studies were placebo-controlled and 14 included a study phase with an active drug other than, or in addition to salmeterol.

In studies that examined safety and efficacy of salmeterol alone or in combination with other active asthma drugs, no salmeterol-specific safety issues and/or drug-related adverse events were identified in any of the studies.

- Three studies monitored asthma exacerbations [Buchvald, 2002; Verberne, 1997; Langton-Hewer, 1995]. No increases in asthma exacerbations were observed during salmeterol treatment relative to placebo or other active agents in 2 of the studies. One study [Verberne, 1997] reported more asthma exacerbations and withdrawals due to exacerbations with salmeterol monotherapy than with beclomethasone over a 1 year period of time in patients with mild to moderate asthma. The authors did not report whether there were any asthma-related hospitalizations during the study.
- Seven studies specifically addressed pulmonary side effects including rebound hyper-responsiveness, deterioration or masking of asthma symptoms, attenuation of the bronchodilation response, or tolerance in patients treated with salmeterol and placebo or other active agents [Simons, 1997a; Fuglsang, 1998; Jartti, 1998; Simons, 1997b;Tomac, 1996; Verberne, 1996; Fuglsang, 1995).
    - In 4 of the 7 studies (n=306), no rebound responsiveness, masking/deterioration of symptoms, tolerance, and/or attenuation of the bronchodilator response were

noted following salmeterol treatment that ranged from 4 weeks to a 1 year duration.

- Three studies [Fuglsang, 1998; Simons, 1997b; Fuglsang, 1995] reported attenuation or possible attenuation of the bronchodilator response following salmeterol treatment (50mcg QD or BID) for 3 or 4 weeks. The salmeterol differences included a downward shift in a dose-response curve, increase in ED50 values, and reductions in bronchoprotection for exercise induced bronchospasm after 28 days of treatment.

- Four studies examined specific safety endpoints: oral outcomes [del-Rio Navarro, 2001a], cardiac toxicity [del-Rio Navarro, 2001b; Tunaoglu, 1999] and urinary creatinine [Grioux, 2003]. No cardiac-specific side-effects or oral outcome safety issues were found. Asthmatic children treated with ICS and a β_2-agonist had elevated urinary creatinine levels and higher creatinine/urinary urea ratios relative to non-asthmatic controls or children receiving β_2-agonists or ICS alone. No clinical significance was assigned to the changes in urinary creatinine levels.

6.3.2. Single Dose, Randomized Studies

Ten (10) studies using a randomized design enrolled a total of 421 pediatric asthma patients ranging in age from 8 months to 17 years of age as summarized in Table 29. All of the studies were placebo-controlled and 9 of the 10 included a study phase with an active drug other than or in addition to salmeterol.

None of the studies reported salmeterol-specific safety issues and/or clinically significant adverse events.

- One study [Simons, 1992] reported cardiac side effects following salmeterol administration. Pulse rate relative to the placebo group, was significantly increased after salmeterol 25mcg at 12 hours and from 1 to 12 hours after 50mcg salmeterol. The pulse rates were not given and the authors did not comment on the clinical relevance of the increases. One patient had a single supraventricular premature beat 1 hour after placebo inhalation; and another patient had a supraventricular beat 3 hours after albuterol and also 6 hours after salmeterol 25mcg.

6.3.3. Observational Studies and Case Reports

A survey by Palmer [Palmer, 2006] examined whether the Arg16 variant increased the likelihood of asthma exacerbations in children and young people with asthma who are prescribed the long-acting β_2-agonist salmeterol in combination with ICS. The Arg16 variant was associated with a greater frequency of asthma exacerbations in salmeterol treated patients compared to a cohort of asthma patients not taking salmeterol.

Two publications [Clark, 1993; Weinberger, 2006] reported 3 cases of pediatric asthma patients whose symptoms worsened significantly either after exercise, or without precipitating cause. Two patients were receiving treatment with ICS and salmeterol, and the third patient had recently added salmeterol to her treatment regimen that included

ICS. The authors concluded that an association between respiratory arrest and salmeterol introduction was suggested but not proven in the three cases.

Two publications [Nguyen, 2005; Sekhsaria, 2004] reported observational data in pediatric asthma patients. The study by Nguyen [Nguyen, 2005] measured ED visits and hospitalizations during the 12 months following introduction of fluticasone propionate/salmeterol combination therapy. Fluticasone/salmeterol combination was associated with a reduction in the risk of acute exacerbations of asthma compared to both pre-treatment and a control cohort. This study is discussed in greater detail in Section 8.1. The study by Sekhsaria [Sekhsaria, 2004] examined whether combination therapy with fluticasone propionate/salmeterol affected growth in children under 5 years of age. No height suppression or other side effects were reported.

6.4. OVERALL SUMMARY – LITERATURE

A review of the pediatric literature did not identify new safety information which changes the overall safety profile of salmeterol-containing products.

7. PHARMACOEPIDEMIOLOGY STUDIES IN ASTHMA

Epidemiological study methods, such as case-control and cohort studies, are well suited to determine whether use of a particular medication is associated with rare events. Epidemiological designs using observational data usually offer greater statistical power through use of large population-based patient databases and more efficient study conduct. Further, results of observational studies can be generalized to large populations treated in the community with a wider range of co-morbid conditions, disease severity, and demographic characteristics than highly selected patients enrolled in clinical trials.

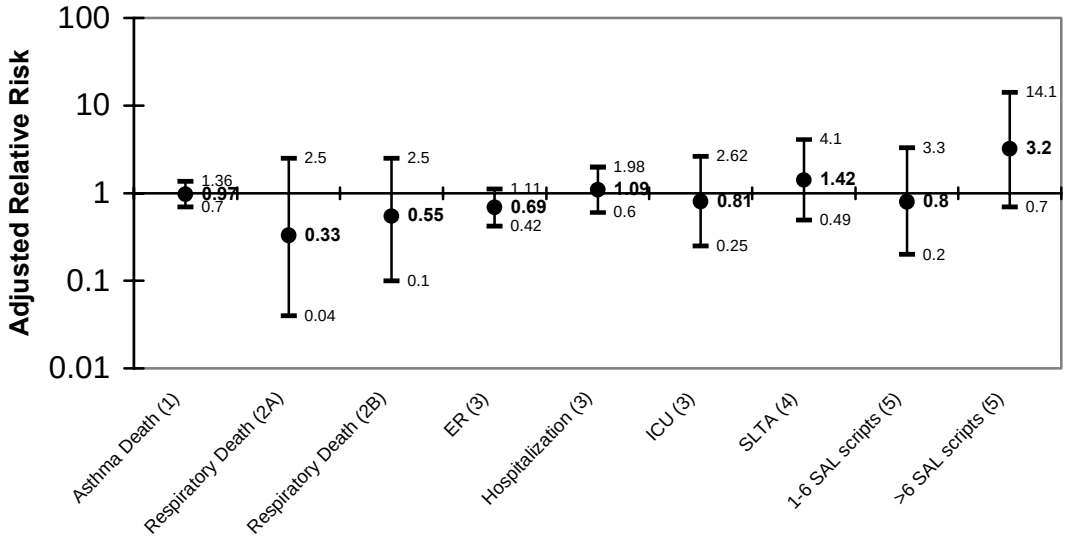
Generally, the primary limitations of pharmacoepidemiology studies are related to potential confounding since treatment assignment is not random and any observed effect of a drug or adverse event may be related to imbalances in underlying disease severity or other unmeasured factors by treatment group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

7.1. LITERATURE REVIEW OF OBSERVATIONAL STUDIES IN ASTHMA

Data in this section provide a summary of published epidemiological studies examining salmeterol safety, which are predominately in adults (>90% of patients). While not specific to children, these data provide additional safety information for salmeterol not covered in other sections of this document.

Three cohort studies [Mann, 1996; Lanes, 1998; Meier, 1997] and four case-control studies [Williams, 1998; Lanes, 2002; Anderson, 2005; Martin, 1998] have examined the association between salmeterol use and the risk of asthma mortality, ischemic events, and severe asthma morbidity. In summary, these large diverse studies show that salmeterol is not associated with a significant increase in the risk of severe asthma morbidity, asthma mortality, ischemic heart disease or cardiac failure after controlling for confounding by severity or preferential prescribing of salmeterol to patients with more severe asthma (Figure 8).

Figure 8 Adjusted Relative Risk (95% Confidence Intervals) of Asthma Mortality and Severe Asthma Morbidity Associated with Salmeterol Use from Published Observational Studies



1. Anderson, 2005 [salmeterol use in prior 3 months versus none]
2. Meier, 1997 [A: relative to theophylline use (OR=0.33); B: relative to ipratropium bromide (OR=0.55)
3. Lanes, 1998
4. Williams, 1998 [SLTA=Severe Life Threatening Attack of asthma]
5. Lanes, 2002 [Asthma Death, salmeterol users versus non-users]

Note: Mann 1996 (no relative risk data available) and Martin 1998 (ischemic/cardiac events) not presented in table

7.2. ECOLOGICAL ANALYSES

Examining changes in group-level data over time, or ecologic study design, is an important tool in drug safety evaluations. GSK conducted an ecologic study in the general population examining trends in sales of salmeterol- and ICS-containing products and US rates of asthma-related events from 1991-2005.

7.2.1. Methods

Annual age-adjusted rates of asthma-related hospitalization and asthma-related mortality from United States Centers for Disease Control and Prevention (CDC) population-based sources (National Hospital Discharge Survey and National Vital Statistics, respectively) were graphed along side annual dispensings of salmeterol- and ICS-containing products by year from 1991 through 2005 [Verispan, 2007]. For pediatric patients (<15 years of age), trends in dispensings of salmeterol-containing products (2002–2006) were plotted against event rates for 2002-2005. The age group younger than 15 years of age was chosen because CDC summary data on asthma-related hospitalizations and asthma-related mortality are presented for this group.

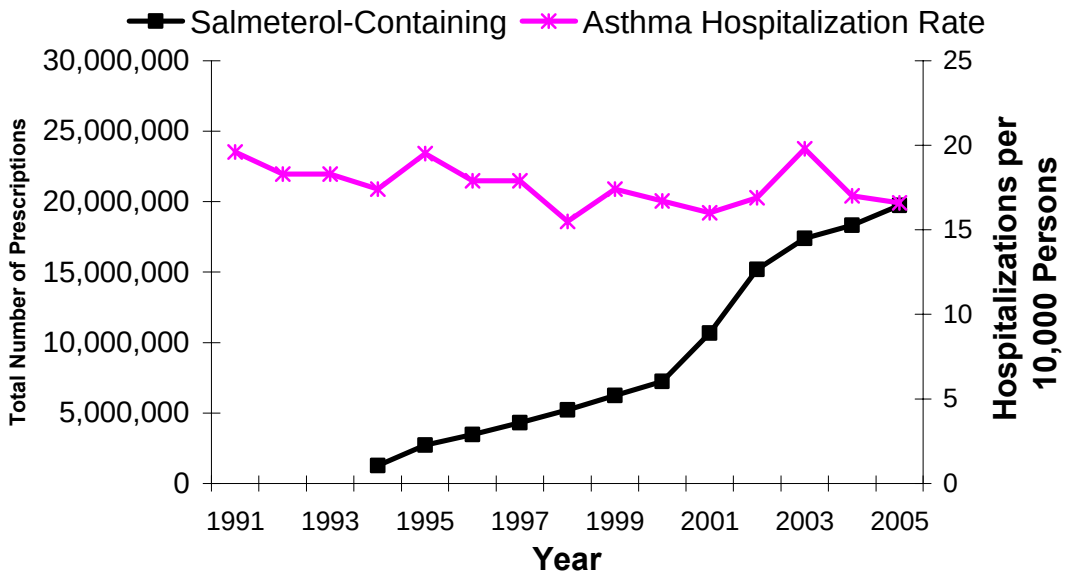
7.2.2. Results

Over the last 15 years, dispensings of salmeterol-containing products have increased while asthma-related hospitalization rates have decreased (Figure 9). In children younger than 15 years of age, asthma hospitalization rates have remained relatively stable over the period with minimal variation over time (Figure 9). Salmeterol-containing dispensing information by age was available for only four of the years for which hospitalization data were available (2002 to 2005), so no trend was discernable between dispensings and hospitalization with only four pairs of data points to evaluate.

As asthma-related mortality rates and the total number of asthma deaths declined, there was a rise in asthma dispensings of salmeterol-containing medications between 1991 and 2005 (Figure 10). In children younger than 15 years of age, asthma-related death was very uncommon, ranging from approximately 0.2 to 0.3 per 100,000 persons during the period 1991 through 2004 (age-specific preliminary estimates were unavailable for 2005). The trend in rates is relatively flat, with no upward or downward trend over the period (Figure 10). However, during the period 2002 to 2006, prescriptions of salmeterol-containing products increased and reached a peak in 2005. Sufficient data were not available to discern any relationships between dispensings and asthma-related deaths.

Figure 9 Age-Adjusted Asthma-Related Hospitalization Relative to Salmeterol-Containing Dispensings 1991-2005

General Population (1991-2005)



Children < 15 Years of Age (1991-2005)

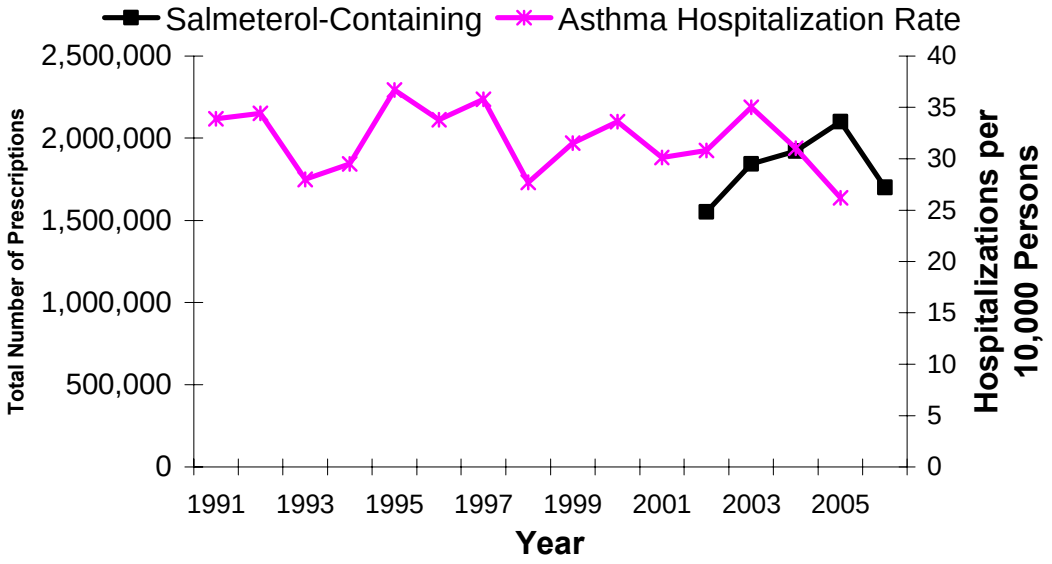
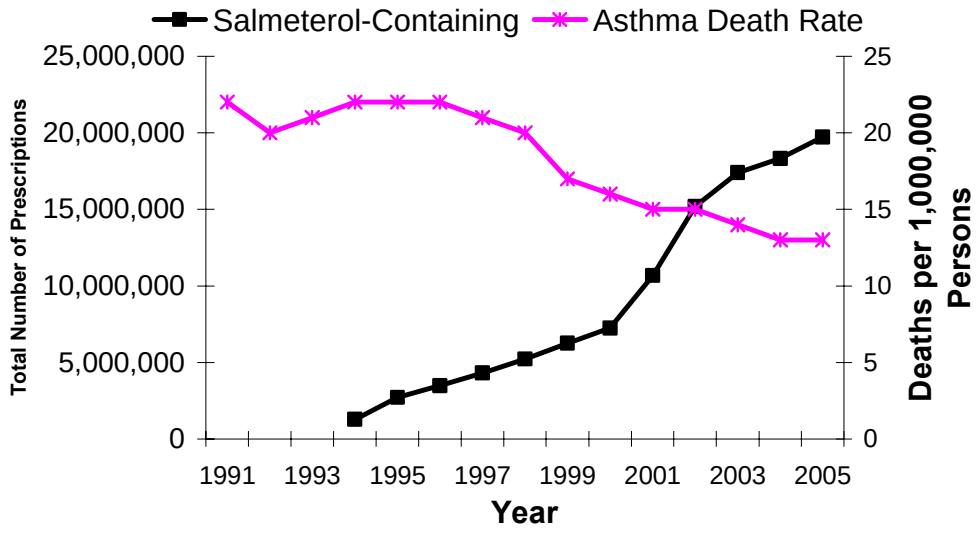
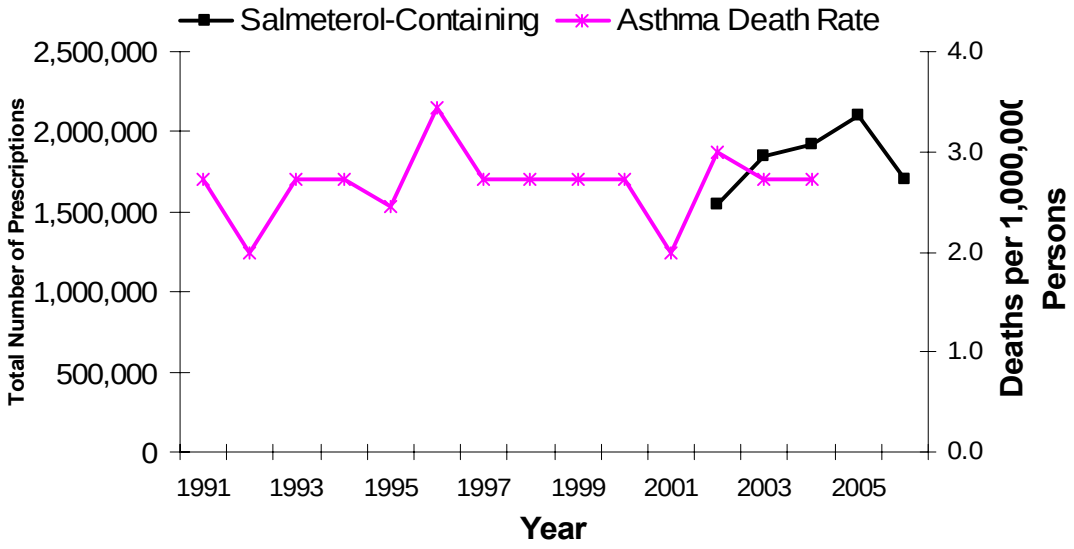


Figure 10 Age-Adjusted Asthma-Related Mortality Relative to Salmeterol-Containing Dispensings

General Population (1991-2005)



Children < 15 Years of Age (1991-2004)*



*Preliminary asthma-related death rates for 2005 are unavailable for pediatric patients (<15 years of age).

7.2.3. Discussion

This study provides population-level evidence that asthma-related deaths declined and asthma-related hospitalization rates were relatively constant over 15 years during a period of improvements in asthma management per treatment guidelines, including increased use of maintenance medications such as ICS and salmeterol. There was an increase in salmeterol-containing products during the 2002 to 2006 period with a peak in 2005, but the lack of availability of dispensings by age prior to 2002 and a lag in the availability of age-specific cause of death data after 2004 limits the ability to discern whether the same trends between dispensings and outcomes observed in adults is consistent for children. In addition, it was not possible to separate the trends of ICS- and salmeterol-containing products given that most salmeterol exposure was in the form of ADVAIR use by the final years of the study period.

7.3. SUMMARY

- Epidemiological studies examining salmeterol safety are largely in adults (>90% of patients); and, the use of salmeterol was not associated with a significant increase in the risk of severe asthma morbidity, asthma mortality, ischemic heart disease or cardiac failure in large US and UK studies to date.
- An ecological analysis in the general population (1991-2005) demonstrated that as dispensings of salmeterol-containing products increased, asthma-related hospitalizations and asthma-related deaths decreased. We were not able to discern whether the same trends were seen in children (<15 years of age) with only 4 years of data; however, these results do not show an association between salmeterol dispensings and asthma-related events.

8. HEALTH OUTCOMES STUDIES

Health outcomes studies (e.g., cohort studies. retrospective/prospective database studies and registry studies) are useful in ascertaining the long term benefits of a treatment on a given population of users in the "real world" [Concato, 2000]. These types of studies use established and current pharmacoepidemiologic and statistical methods. In a health outcomes study design, patients are enrolled based on exposure status (e.g., drug of interest versus comparator) and followed until an outcome (e.g., ED visit/hospitalization) is observed. Detailed information on the strengths and limitations of observational studies are provided in Section 7.

8.1. NGUYEN ET AL

This single-center study was a 1-year longitudinal observational study designed to assess the effect of ADVAIR on hospitalizations and ED visits in children with asthma. Patients 4-17 years of age with a history of frequent ED visit/hospitalizations in the previous 2 years and prescribed ADVAIR were studied. A corresponding control group was identified from hospital records. All control patients were taking ICS. The ADVAIR intervention group had a 33% reduction in the risk of experiencing an asthma related ED visit or hospitalization (adjusted RR 0.67, 95% CI 0.49, 0.90). In addition, the risk of experiencing asthma-related hospitalization alone was reduced 43% in the ADVAIR group compared to control (RR 0.57, 95% CI 0.19, 1.71). This publication is also included in Section 6.3.3.

8.2. STEMPEL ET AL

GSK study RES41153 was recently published by Stempel, et al [Stempel, 2006]. This study was excluded from the literature review (Section 6) because it is a cost and outcomes analysis; however, this study included asthma related ED visits and hospitalizations as outcomes, which are relevant safety outcomes. Therefore, it is summarized in this section.

This observational outcomes study utilized claims data from i3Innovus, an Ingenix Company, which has access to a proprietary, Health Insurance Portability and Accountability Act (HIPAA)-compliant research database containing information from a noncapitated, managed, fee-for-service national health plan. This database is geographically diverse and contains more than 13 million annual covered lives, with integrated enrollment, laboratory, pharmacy, and medical claims data. This retrospective, observational cohort study utilized this database from 01 January 2000 to 31 May 2003. The study involved the use of a pre-post design to compare the risk of treatment failure, and asthma related exacerbations (ED visit or hospitalization/inpatient) among patients receiving controller therapy for asthma.

The study population included patients 4-17 years of age with both a claim for asthma [International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code: 493.xx] and an initial pharmacy claim for ADVAIR, FP, montelukast, ICS + LABA, and ICS + montelukast at any time during 01 January 2001 and 31 May 31 2002.

The initial prescription was considered the index event. Patients were required to be continuously enrolled in their health plan for at least 12 months before and at least 60 days after their index date. Subjects were followed for up to 12 months following the index date. Patients with a diagnosis of cystic fibrosis, COPD or respiratory tract cancer were excluded from the analysis. The use of inhaled anti-cholinergic therapy in the pre- or post-index periods was not permitted. Patients were new users of their index therapy during the 12 months prior to their index date, but may have used other asthma controllers in the baseline period.

A total of 9192 subjects were identified, 1168 ADVAIR, 2473 FP, 4246 montelukast, 1009 ICS + montelukast and 296 ICS + LABA. The asthma-related ED visit/inpatient (combined endpoint) rate was 6.9% for the ADVAIR group post index and 7.4% for the FP cohort. Analysis from the regression model controlling for baseline differences, showed a similar risk for an asthma-related ED visit/IP when the ICS cohort was compared to the ADVAIR cohort (OR 1.025, 95% CI, 0.772, 1.361). Similar trends were observed with the other treatments compared to ADVAIR.

8.3. OBSERVATIONAL STUDY: ADVAIR AND ICS USE ON ASTHMA-RELATED ED VISITS AND HOSPITALIZATIONS

A retrospective observational study was conducted to evaluate the seasonal use of ADVAIR in the summer and its associated effect on asthma outcomes in the fall. This study was conducted in a large managed care database that contains >45 US health plans representing 58.5 million covered lives during the observed time period, 01 December 2002 and 31 May 2006 (study ADA111394). As part of this study, asthma-related events for ADVAIR and ICS were profiled within given 12-month periods. The profile of these asthma-related events will be the focus of this section.

Asthma controller use (ADVAIR or ICS) was defined as any use (≥1 prescription [Rx]) of those medications within a designated 12 month period (January-December). Asthma-related ED visits and hospitalization events and ADVAIR/ICS exposure were assessed in each year of observation. Study subjects were categorized into the following age cohorts and analyzed: 4-5 years, 6-11 years, 12-18 years, and overall 4-18 years.

8.3.1. Study Design

The cross sectional observational analysis of managed care medical and pharmacy administrative claims was used to profile asthma related hospitalizations and ED visits in subjects with asthma who were dispensed either ADVAIR or inhaled corticosteroid (ICS). This cross-sectional analysis is the focus of this section; however, the results of the seasonal analysis of ADVAIR users is also reported.

The study population included subjects 4 to 55 years of age with the diagnosis of asthma [International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code: 493.xx]. Subjects were required to have a pharmacy claim for ADVAIR (all strengths) or ICS during 01 December 2001 to 31 May 2006 (at least once in each year of observation), and at least one medical diagnosis claim for asthma identified anywhere in the medical claim file in each year of observation. Subjects also had to have both

medical and pharmacy benefits within the dataset. At least 12 months of continuous enrollment in their health plan during in each year of observation was required. Subjects were excluded from analysis if they had pharmacy records of both ADVAIR and ICS in the same year. Subjects could give multiple years of observation, but in order for that to occur, subjects had to meet these criteria for each year of eligibility. For example, a subject who met all defined criteria in year 2002 but not in 2003, only the data from 2002 were included. This was used to help ensure that the study population had current asthma. Asthma-related outcomes were converted to rates per 10,000 person years from the original seasonal analysis.

8.3.2. Results

A total of 305,137 subjects 4-18 years of age were identified: 193,707 for ADVAIR and 111,707 for ICS. Overall, the ADVAIR cohort was older (12.2 vs 8.6), with fewer males (58.5% vs 60.6%), and had a greater number of pharmacy claims for ADVAIR/ICS (2.8 vs 2.1) than the ICS cohort. Both cohorts used a similar amount of albuterol (1.8 vs 2.1) (Table 30). Demographics for the sub-categories are reported in Table 30.

Table 30 Baseline Characteristics of ADVAIR and ICS Users[a]

Age Group	Parameter	ADVAIR	ICS
Age 4 & 5	# of observations	2,408	53,608
	Mean age	4.8	4.5
	Male (%)	60.1	62.3
	Average # of Advair/ICS Rx[b]	2.5	2.5
	Average # of SABA Rx	1.4	2.1
Age 6 - 11	# of observations	45,842	92,595
	Mean age	9.0	8.1
	Male (%)	62.9	62.4
	Average # of Advair/ICS Rx	2.9	2.1
	Average # of SABA Rx	1.6	2.0
Age 12 - 18	# of observations	63,457	47,227
	Mean age	14.7	14.5
	Male (%)	55.3	55.1
	Average # of Advair/ICS Rx	2.7	1.8
	Average # of SABA Rx	2.0	2.2
Age 4 - 18	# of observations	111,707	193,430
	Mean age	12.2	8.6
	Male (%)	58.5	60.6
	Average # of Advair/ICS Rx	2.8	2.1
	Average # of SABA Rx	1.8	2.1

a. Total # of subjects = 780,426 (age 4 ~ 55)
b. Average # of Rx per year

8.3.3. Cross-Sectional Outcomes

For subjects aged 4 to 18 age, asthma-related ED visit event rates were 15.3 for ADVAIR and 16.5 for ICS (Incidence Relative Risk (IRR) 0.92, 95% CI 0.91-0.94, p<0.01) and hospitalization event rates of 2.8 and 3.7; (IRR 0.76, 95% CI 0.73-0.79, p<0.01) for ADVAIR and ICS, respectively, over the 4.25 year period.

Across the two youngest age groups (4-5 years and 6-11 years), hospitalization rates were lower with ADVAIR compared to ICS, whereas, in adolescents (12 to 18 years), similar hospitalization rates were seen with both ADVAIR and ICS (Table 31).

Table 31 Comparison Between ADVAIR and ICS Users

Age Group	Parameter[a]	Advair	ICS	Incidence relative risk[b] (Advair vs. ICS)
Age 4 & 5	ED visit rate	19.2	20.1	0.95 (0.88 - 1.04)
	Hospitalization rate	3.8	5.3	0.72** (0.58 - 0.88)
Age 6 -11	ED visit rate	14.9	15.3	0.98 (0.95 ~ 1.00)
	Hospitalization rate	2.8	3.2	0.89** (0.84 ~ 0.95)
Age 12 -18	ED visit rate	15.4	14.9	1.03* (1.00 ~ 1.06)
	Hospitalization rate	2.7	2.8	0.97 (0.90 ~ 1.04)
Age 4 - 18	ED visit rate	15.3	16.5	0.92** (0.91 ~ 0.94)
	Hospitalization rate	2.8	3.7	0.76** (0.73 ~ 0.79)

a. # of observations is in person year. Rates are in per 10,000 patient-year
b. * p <0.05 ; ** p <0.01

8.3.4. Seasonal Analysis

Among ADVAIR users aged 4-18 years, exposure to ADVAIR in the summer months was associated with reduction in the risk of having an asthma-related hospitalization (RR 0.56, 95% CI 0.48-0.67) and asthma-related ED visits (RR 0.55, 95% CI 0.48-0.67) in the fall compared with no exposure to ADVAIR in the summer. This effect was observed across all age groups.

8.4. SUMMARY

These large administrative claims and prospective health outcome studies conducted in North America indicate that the use of salmeterol in combination with an inhaled corticosteroid (ADVAIR) do not suggest any associated increase in the risk of asthma-related ED visits/hospitalization or asthma-related hospitalization when used in clinical practice. This finding was consistent across different asthma populations, in different clinical settings and using various pharmacoepidemiologic methods. In addition,

ADVAIR exposure in the summer months was associated with a reduction in the risk of an asthma-related event in the fall.

9. LABELING SUMMARY

The approved product label for SEREVENT DISKUS, ADVAIR DISKUS and ADVAIR HFA provide specific information for the safe and effective use of the products for the patient populations indicated.

In this section, specific references to important information pertinent to the pediatric population have been included.

9.1. BOXED WARNING

Both SEREVENT and ADVAIR contain a similar important Warning concerning the risk of asthma related death. This Warning is based on the results of SMART and is applicable to the use of the products in pediatric patients. The Warning from the SEREVENT DISKUS labeling is provided below:

> **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*).

9.2. APPROVED INDICATIONS

The approved Indications and Usage of SEREVENT and ADVAIR are provided below. The indications section of the label define the population appropriate for the use of salmeterol in the treatment of asthma (Indications for COPD have not been included). The approved indication for SEREVENT DISKUS, ADVAIR DISKUS, and ADVAIR HFA are shown below:

SEREVENT DISKUS: 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.

ADVAIR DISKUS: INDICATIONS AND USAGE

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

Long-acting $beta_2$-adrenergic agonists, such as salmeterol, one of the active ingredients in ADVAIR DISKUS, may increase the risk of asthma-related death (see WARNINGS). 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. ADVAIR DISKUS is not indicated in patients whose asthma can be successfully managed by inhaled corticosteroids along with occasional use of inhaled, short-acting $beta_2$-agonists. ADVAIR DISKUS is NOT indicated for the relief of acute bronchospasm.

ADVAIR HFA: 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.

9.3. CLINICAL TRIALS

While ADVAIR HFA is only approved for use of the treatment of asthma in patients 12 years of age and older, both SEREVENT DISKUS and ADVAIR DISKUS are approved for use in patients 4 years of age or older. Therefore the labeling for both SEREVENT DISKUS and ADVAIR DISKUS contain specific safety and efficacy information from studies in the pediatric population in the CLINICAL TRIALS and ADVERSE REACTIONS section each of label. In addition, specific pediatric pharmacokinetic and pharmacodynamic information is provided in the ADVAIR DISKUS labeling.

Further, as the PRECAUTIONS, Pediatric Use subsection within the ADVAIR DISKUS labeling, the following text is provided to describe the data supporting the use in pediatric patients:

> **Pediatric Use:** Use of ADVAIR DISKUS 100/50 in patients 4 to 11 years of age is supported by extrapolation of efficacy data from older patients and by safety and efficacy data from a study of ADVAIR DISKUS 100/50 in children with asthma aged 4 to 11 years (see CLINICAL TRIALS: Asthma: *Pediatric Patients* and ADVERSE REACTIONS: Asthma: *Pediatric Patients*). The safety and effectiveness of ADVAIR DISKUS in children with asthma under 4 years of age have not been established.

9.4. DOSAGE AND ADMINISTRATION

Importantly, the approved dosage of ADVAIR DISKUS in patients aged 4 to 11 years is specifically defined in the DOSAGE AND ADMINISTRATION section of the labeling and is limited to the lowest strength 100/50mcg.

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

10. CONCLUSION

Based on a comprehensive review of the safety of salmeterol-containing products, GSK believes that salmeterol continues to exhibit a favorable safety profile in pediatric subjects and the safety profile is similar to that seen in adults. SEREVENT and ADVAIR are appropriately labeled to reflect the safety profile of these products. Salmeterol when used as described in the approved labeling offers an important therapeutic option for patients and clinicians and has been shown to improve the level of care in children with asthma.

11. REFERENCES

Aldington S, Williams M, Weatherall M, et al. Duration of action of the salmeterol/fluticasone propionate combination inhaler administered in the evening: a randomized controlled trial in childhood asthma. *Respirology*. 2006;11(5):638-42.

American Lung Association (ALA), Epidemiology and Statistics Unit. Trends in Asthma Morbidity and Mortality. July, 2006.

Anderson HR, Ayres JG, Sturdy PM, et al. Bronchodilator treatment and deaths from asthma: case-control study. *Br Med J.* 2005;330:117-24.

Baki A, Karaguzel G: Short-term effects of budesonide, nedocromil sodium and salmeterol on bronchial hyperresponsiveness in childhood asthma. *Acta Paediatr Jpn.* 1998;40(3):247-51.

Barbato A, Cracco A, Tormena F, et al. The first 20 minutes after a single dose of inhaled salmeterol in asthmatic children. *Allergy.* 1995;50(6):506-10.

Bleecker ER, Yancey SW, Baitinger LA, Edwards LD, Klotsman M, Anderson WH, Dorinsky PM. Salmeterol response is not affected by b_2-adrenergic receptor genotype in subjects with persistent asthma. *J Allergy Clin Immunol.* 2006;118:809-16.

Buchvald F, Bisgaard H. Comparisons of the complementary effect on exhaled nitric oxide of salmeterol vs montelukast in asthmatic children taking regular inhaled budesonide. *Ann Allergy Asthma Immunol.* 2003;91(3):309-13.

Carlsen KH, Roksund O, Olsholt K, et al. Overnight protection by inhaled salmeterol on exercise-induced asthma in children. *Eur Respir J.* 1995;8(11):1852-5.

Castle W, Fuller R, Hall J, Palmer J. SEREVENT nationwide surveillance study: comparison of salmeterol with salbutamol in asthmatic patients who require regular bronchodilator therapy. *Br Med J.* 1993;306(6884):1034-7.

Centers for Disease Control and Prevention (CDC). National Surveillance for Asthma, United States 1980-2004. Surveillance Summaries. Oct 19, 2007, Vol 56 (No SS-8).

Clark CE, Ferguson AD, Siddorn JA. Respiratory arrests in young asthmatics on salmeterol. *Respir Med.* 1993;87(3):227-8.

Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. *N Engl J Med*. 2000;342(25):1887-92.

Cracco G, Dal Negro R, Boer LA, et al. Salmeterol (50mcg bid) versus nedocromil (4mg tid): protective effect against hyperreactivity to ultrasonically nebulised distilled water in asthmatic children. *Riv Ital Pediatr.* 1995;21:807-12.

de Benedictis FM, Tuteri G, Pazzelli P, et al. Salmeterol in exercise-induced bronchoconstriction in asthmatic children: comparison of two doses. *Eur Respir J.* 1996;9(10):2099-103.

del-Rio Navarro B, Sienra-Monge J, Alvarez-Amador M, et al. Serum potassium levels, CPK-MB and ECG in children suffering asthma treated with beclomethasone or beclomethasone-salmeterol. *Allergol Immunopathol (Madr).* 2001(a);29(1):16-21.

del-Rio Navarro BE, Corona-Hernandez L, Fragoso-Rios R, et al. Effect of salmeterol and salmeterol plus beclomethasone on saliva flow and IgA in patients with moderate-persistent chronic asthma. *Ann Allergy Asthma Immunol.* 2001(b);87(5):420-3.

DuMouchel W. Bayesian data mining in large frequency tables, with an application to the FDA Spontaneous Reporting System. *The American Statistician*. 1999;53(3):177-202.

DuMouchel W, Pregibon D. Empirical Bayes screening for multi-item associations. In: Seventh ACM SigKDD International Conference on Knowledge Discovery and Data Mining. San Francisco: ACM Press. 2001.

Fuglsang G, Agertoft L, Vikre-Jorgensen J, et al. Influence of budesonide on the response to inhaled terbutaline in children with mild asthma. *Pediatr Allergy Immunol.* 1995;6(2):103-8.

Fuglsang G, Vikre-Jorgensen J, Agertoft L, et al. Effect of salmeterol treatment on nitric oxide level in exhaled air and dose-response to terbutaline in children with mild asthma. *Pediatr Pulmonol.* 1998;25(5):314-21.

Giroux M, Ferrieres J. Creatininuria in asthmatic children treated with a combination of glucocorticoid and beta-agonist. *J Asthma.* 2003;40(1):41-8.

Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. NHLBI/WHO Workshop Report. National Heart, Lung and Blood Institute. Revised 2002; Publication Number 02-3659.

Green CP, Price JF. Prevention of exercise induced asthma by inhaled salmeterol xinafoate. *Arch Dis Child* 1992;67(8):1014-7.

Israel E, Drazen JM, Liggett SB, et al. The effect of polymorphisms of the b_2-adrenergic receptor on the response to regular use of albuterol in asthma. *Am J Respir Crit Care Med.* 2000; 162:75-80.

Jartti TT, Kaila TJ, Tahvanainen KU, et al. Altered cardiovascular autonomic regulation after salmeterol treatment in asthmatic children. *Clin Physiol*. 1998;18(4):345-53.

La Grutta S, Gagliardo R, Mirabella F, et al. Clinical and biological heterogeneity in children with moderate asthma. *Am J Respir Crit Care Med.* 2003;167(11):1490-5.

Lanes SF, Garcia Rodriquez LA, Hueta C. Respiratory medications and risk of asthma death. *Thorax.* 2002;57:683-6.

Lanes SF, Lanza L, Wentworth CE. Risk of emergency care, hospitalization and ICU stays for acute asthma among recipients of salmeterol. *Am J Resp Crit Care Med.* 1998;158:857-61.

Langton Hewer S, Hobbs J, French D, et al. Pilgrim's progress: the effect of salmeterol in older children with chronic severe asthma. *Respir Med.* 1995;89(6):435-40.

Leineweber K, Brodde O-E. B_2-adrenoceptor polymorphisms: relation between *in vitro* and *in vivo* phenotypes. *Life Sciences.* 2004;74:2803-14.

Liggett SB. B_2-Adrenergic Receptor Pharmacogenetics. *Am J Respir Crit Care Med.* 2000;161:S197-S201.

Mann RD, Kubota K, Pearce G, Wilton L. Salmeterol: a study by prescription-event monitoring in a UK cohort of 15,407 patients. *J Clin Epidemol.* 1996;49:247-50.

Martin RM, Dunn NR, Freemantle SN, Mann RD. Risk of non-fatal cardiac failure and ischaemic heart disease with long-acting $beta_2$ agonists. *Thorax.* 1998;53:558-62.

Meier CR, Jick H. Drug use and pulmonary death rates in increasing symptomatic asthma patients in the UK. *Thorax.* 1997;52:612-7.

National Institutes of Health. National Asthma Education and Prevention Program (NAEPP). The NAEPP Expert Panel Report 3 (EPR-3) Summary Report 2007: Guidelines for the Diagnosis and Management of Asthma. US Department of Health and Human Services; National Institutes of Health. October 2007; NIH Publication No. 08-5846.

Nguyen WT, Stewart C, Fisher K, Trolley E, Dukhee BL. Self TH. Maintenance asthma treatment with fluticasone propionate/salmeterol combination via Diskus: effect on outcomes in inner-city children enrolled in TennCare. *Allergy and Asthma Proc.* 2005;26:129-34.

Ortiz G, Menendez R. The effects of inhaled albuterol and salmeterol in 2- to 5-year-old asthmatic children as measured by impulse oscillometry. *J Asthma.* 2002;39:531-6.

Palmer CN, Lipworth BJ, Lee S, et al. Arginine-16 $beta_2$ adrenoceptor genotype predisposes to exacerbations in young asthmatics taking regular salmeterol. *Thorax.* 2006;61(11):940-4.

Pohunek P, Matulka M, Rybnicek O, et al. Dose-related efficacy and safety of formoterol (Oxis) turbuhaler compared with salmeterol diskhaler in children with asthma. *Pediatr Allergy Immunol.* 2004;15(1):32-9.

Primhak RA, Smith CM, Yong SC, et al. The bronchoprotective effect of inhaled salmeterol in preschool children: a dose-ranging study. *Eur Respir J.* 1999;13(1):78-81.

Quezada A, Mallol J, Moreno J, et al. Effect of different inhaled bronchodilators on recovery from methacholine-induced bronchoconstriction in asthmatic children. *Pediatr Pulmonol.* 1999;28(2):125-9.

Russell G, Williams DA, Weller P, et al. Salmeterol xinafoate in children on high dose inhaled steroids. *Ann Allergy Asthma Immunol.* 1995;75(5):423-8.

Sekhsaria S, Alam M, Sait T, et al. Efficacy and safety of inhaled corticosteroids in combination with a long-acting beta$_2$-agonist in asthmatic children under age 5. *J Asthma.* 2004;41(5):575-82.

Simons FE, Soni NR, Watson WT, et al. Bronchodilator and bronchoprotective effects of salmeterol in young patients with asthma. *J Allergy Clin Immunol.* 1992;90(5):840-6.

Simons FE. A comparison of beclomethasone, salmeterol, and placebo in children with asthma. Canadian Beclomethasone Dipropionate-Salmeterol Xinafoate Study Group. *N Engl J Med.* 1997(a);337(23):1659-65.

Simons FE, Gerstner TV, Cheang MS. Tolerance to the bronchoprotective effect of salmeterol in adolescents with exercise-induced asthma using concurrent inhaled glucocorticoid treatment. *Pediatrics.* 1997(b);99(5):655-9.

Sorkness CA, Lemanske RF, Jr., Mauger DT, et al. Long-term comparison of 3 controller regimens for mild-moderate persistent childhood asthma: the pediatric asthma controller trial. *J Allergy Clin Immunol.* 2007;119(1):64-72.

Stempel DA, Riedel AA and Carranza Rosenzweig JR. Resource utilization with fluticasone propionate and salmeterol in a single inhaler compared with other controller therapies in children with asthma. *Current Medical Research and Opinion.* 2006;22(3): 463–47.

Szarfman A, Machado SG, O'Neill RT. Use of screening algorithms and computer systems to efficiently signal higher-than-expected combinations of drugs and events in the US FDA's spontaneous reports database. *Drug Safety.* 2002;25:381-92.

Taylor DR, Drazen JM, Herbison GP, Yandava CN, Hancox RJ, Town GI. Asthma exacerbations during long term β agonist use: influence of b_2 adrenoceptor polymorphism. *Thorax.* 2000;55:762-7.

Tomac N, Tuncer A, Saraclar Y, et al. Efficacy of salmeterol in the treatment of childhood asthma. *Acta Paediatr Jpn.* 1996;38(5):489-94.

Tunaoglu FS, Turktas I, Olgunturk R, et al. Cardiac side effects of long-acting beta-$_2$ agonist salmeterol in asthmatic children. *Pediatr Int.* 1999;41(1):28-31.

U.S. Department of Health and Human Services (US HHS). Food and Drug Administration. Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment. March 2005.

U.S. Public Health Service and Health Care Financing Administration. International Classification of Diseases. Ninth Revision. Clinical Modification [ICD-9-CM]. Practice Management Information. 1996.

Verberne AA, Hop WC, Creyghton FB, et al. Airway responsiveness after a single dose of salmeterol and during four months of treatment in children with asthma. *J Allergy Clin Immunol.* 1996;97(4):938-46.

Verberne AA, Frost C, Roorda RJ, et al. One year treatment with salmeterol compared with beclomethasone in children with asthma. The Dutch Paediatric Asthma Study Group. *Am J Respir Crit Care Med.* 1997;156(3 Pt 1):688-95.

Verini M, Verrotti A, Greco R, et al. Comparison of the bronchodilator effect of inhaled short- and long-acting β2-agonists in children with bronchial asthma a randomized trial. *Clin Drug Inv*. 1998;16:18-24.

Verispan Vector One National [database]. Verispan, Inc. Yardley, PA; 2007.

Weinberger M, Abu-Hasan M. Life-threatening asthma during treatment with salmeterol. *N Engl J Med.* 2006;355(8):852-3.

Williams C, Crossland L, Finnerty J, et al. A case-control study of salmeterol and near-fatal attacks of asthma. *Thorax.* 1998;53:7-13.