MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

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TO: Lisa L. Mathis, MD, Associate Director
Pediatric and Maternal Health Staff (PMHS)
Office of New Drugs (OND), CDER
and
M. Dianne Murphy, MD, Director
Office of Pediatric Therapeutics (OPT), OC

FROM: Ann Corken Mackey, RPh, MPH, Postmarketing Safety Evaluator
Andrew D. Mosholder, MD, MPH, Medical Officer
Division of Drug Risk Evaluation (DDRE)

THROUGH: Ann McMahon, MD, MS for Mark Avigan, M.D, CM, Director
Division of Drug Risk Evaluation

SUBJECT: 1-year Post-Pediatric Exclusivity Postmarketing Adverse Event Review
Drug: Salmeterol xinafoate (Serevent)
Pediatric Exclusivity Approval Date: March 9, 2006

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1. EXECUTIVE SUMMARY

This document summarizes salmeterol xinafoate (Serevent) pediatric adverse event reports identified in the Adverse Event Reporting System (AERS) database. The Office of Pediatric Therapeutics requested this information in preparation for the Pediatric Advisory Committee (PAC) meeting scheduled for November 2007.

Serevent Diskus (NDA# 20-692) delivers 50 mcg of salmeterol xinafoate inhalation powder. The product was approved in the US on September 16, 1997. Serevent inhalation aerosol was previously available (beginning in 1994) in a metered dose inhaler (MDI), but this was phased out as part of the effort to replace MDIs containing chlorofluorocarbons (CFCs). Salmeterol is also one of two active ingredients in the drug product Advair, in combination with fluticasone. Salmeterol is a selective, long-acting β_2-adrenergic agonist (LABA) indicated for long-term, twice-daily administration in the maintenance treatment of asthma and in the prevention of bronchospasm in patients 4 years of age and older with reversible obstructive airway disease, including patients with symptoms of nocturnal asthma who require regular treatment with inhaled, short-acting β_2-agonists. It also is approved for prevention of exercise-induced bronchospasm (EIB) in patients 4 years of age and older and for use in the maintenance treatment of bronchospasm associated with COPD in adults. Salmeterol is a smooth muscle relaxant. In November 2005, salmeterol was given a boxed warning and an FDA Public Health Advisory was issued because of increased risk of severe episodes of asthma and death associated with its use (this was based on data from The Salmeterol Multicenter Asthma Research Trial [SMART], a study that included children).[1,2,3]

The AERS database was searched for reports of adverse events (serious and non-serious) occurring with the use of salmeterol (excluding the combination product Advair) in pediatric patients (ages 0 to 16 years of age). Up to the "data lock" date of April 9, 2007, AERS contained 4205 cases for salmeterol (raw counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). Pediatric cases represent approximately 4.9% of the total (205/4205). DDRE was asked to focus on the 1-year period following the approval of pediatric exclusivity, March 9, 2006 to April 9, 2007. We used an AERS data lock date of April 9, 2007 to allow time for reports received up to March 9, 2007 to be entered into AERS. During the first 13 months after pediatric exclusivity was granted, AERS received a total of 225 cases (raw counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). Pediatric cases represent approximately 4.0% of the total number of cases (9/225). We will refer to this 13-month interval as the pediatric exclusivity period in the remainder of this review.

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[1] Serevent Diskus product label, GlaxoSmithKline, revised March 31, 2006.
[2] FDA Public Health Advisory: Serevent Diskus (salmeterol xinafoate inhalation powder), Advair Diskus (fluticasone propionate & salmeterol inhalation powder), Foradil Aerolizer (formoterol fumarate inhalation powder), issued November 8, 2005.
[3] Nelson HS, Weiss ST, Bleecher ER, et al. The Salmeterol Multicenter Asthma Research Trial. Chest 2006; 129: 15-26.

Of the 9 cases in children received during the pediatric exclusivity period, the following events were reported: decreased therapeutic response/therapy nonresponder (2 [1 death]), overdose (3 [1 death]), dizziness/muscle spasm (1; this is the only case involving a CNS adverse event), reported leaking device (1 [death]), asthma/dyspnea/circulatory collapse (1 [death]), and death from unspecified cause (1). These cases are described below (see *Review of Postmarketing Pediatric Adverse Event Reports*, *Case Characteristics* and *Discussion of Cases Received*). See *Discussion* section below for a summary of adverse events from AERS identified in children since initiation of marketing for salmeterol. The consult request specifically asked about cases of lactose intolerance identified in children; AERS identified one nonserious case (see *AERS Search Results* below).

The review of the few salmeterol pediatric reports during the exclusivity period in the AERS database did not identify adverse events unique to the pediatric population as compared to the adult population. However the review was limited by the few number and incompleteness of some of the reports. A separate review of all pediatric fatalities (n=23) as reported to AERS associated with salmeterol use identified cases of death due to asthma exacerbation (at least 14); the search also identified cases of product misuse (n=9). Review of fatal reports for the combination product Advair revealed 15 fatalities reported with fluticasone/salmeterol combination use. Nine patients died of asthma exacerbation as stated in the report based on autopsy data (6) and/or physician assessment (3). The analysis identified misuse of the product (n=5), including noncompliance (3), overdose of albuterol (1), and overdose of fluticasone (1).

In adults, the most commonly-reported adverse events (per AERS reports) associated with salmeterol therapy were related to the respiratory system and cardiovascular system. Reports of overdose in adults using salmeterol also were identified in AERS. Respiratory and cardiac events along with overdose have been reported in children as well. Respiratory events and overdose are well labeled. Cardiovascular effects are seen with sympathomimetic amines (the label states that no effect on the cardiovascular system is usually seen after use of salmeterol at recommended doses); labeled cardiovascular events for salmeterol include arrhythmias (atrial fibrillation, supraventricular tachycardia, and extrasystoles), tachycardia, palpitations, and hypertension.

In summary:

1. The review of the few salmeterol pediatric reports in the AERS database did not identify adverse events unique to the pediatric population. However, the review was limited by the small number of reports, and incompleteness of some of the reports. There are too few reported adverse events in any one area to make a conclusion regarding safety signals unique to the pediatric population. A number of the fatal outcomes reported were attributed to asthma, but since this is also the indication for the drug, reliable assessment of drug-relatedness in individual AERS cases is not feasible. Data on serious asthma outcomes from controlled clinical trials are far more informative, and accordingly are summarized in this review.

2. Because 3 of the 9 adverse event reports received during the Exclusivity period (and 9 of 23 reports of all pediatric fatalities) represent misuse of Serevent Diskus, OSE Division of Medication Errors and Technical Support (DMETS) has been contacted to review this issue and provide a separate consult.

3. The four-fold increase in asthma-related deaths in subjects using salmeterol (as compared to placebo) identified in the SMART study (see above) is of concern; the data represent one excess asthma death per 1300 salmeterol-treated subjects. The similar results from the SNS trial, while not meeting the usual criteria for statistical significance, lend credence to the results of SMART.

4. In SMART, based on a hands-on review of case report forms by one of the authors (ADM), 12-18 year old patients on salmeterol had a higher frequency of hospitalizations for asthma compared to placebo, although this did not reach statistical significance.

5. A meta-analysis of placebo-controlled clinical trial data for salmeterol and formoterol in patients of all ages found that the long acting beta agonists (LABAs) were associated with statistically significant increases in asthma exacerbations requiring hospitalization, and in exacerbations requiring intubation and ventilation. In pediatric trials within the same meta-analysis, there was also a statistically significant increase in the risk of asthma hospitalizations with LABAs compared to placebo; pediatric trial data on serious asthma outcomes were generally sparse compared to adult data, however.

7. There is no available pediatric data to indicate that the increased risk of asthma death and life-threatening exacerbations observed in adults does not also apply to children.

8. With respect to the crucial issue of whether concomitant inhaled corticosteroid (ICS) therapy protects against severe asthma outcomes with LABA therapy, the NHLBI Expert Panel guidelines[4] state, "…while the data do not necessarily support an increased risk of severe or serious exacerbations in patients who are taking LABA and are receiving concomitant ICS, data are also insufficient to establish definitively that ICS therapy completely obviates the risk." Our overview of the available data focused on the pediatric age group was consistent with this assessment.

10. Recommendation for a study in children may be warranted, but may not be feasible because of the difficulties in enrolling a sufficient number of patients to assess infrequent but severe asthma events, thus making results unavailable for many years, as was the case for SMART. In addition, there may be ethical issues with randomized designs if we are not at equipoise with respect to the pediatric safety of LABAs.

Our overview of these various data sources has shown that (1) adult trial data show an increase in asthma mortality and severe asthma events with salmeterol; (2) available data do not provide any reason to believe that the pediatric population does not share the same risk; and (3) definitive evidence of a protective effect of ICS is lacking for LABAs, and

[4] National Heart, Lung, and Blood Institute. Expert Panel Report 3 (EPR 3): Guidelines for the Diagnosis and Management of Asthma. 2007. Available at http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm

in fact there is evidence that ICS is not protective in pediatric patients receiving formoterol.. Accordingly, we conclude that salmeterol may have an unfavorable risk-benefit ratio in the treatment of pediatric asthma. We recommend a more thoroughgoing, formal risk-benefit analysis of salmeterol in the treatment of pediatric asthma. Of course, such an analysis would also have to consider relevant data for adults and for the other long acting beta agonist, formoterol.

2. PRODUCTS, INDICATIONS, PEDIATRIC LABELING, AND PEDIATRIC FILING HISTORY

2.1 Salmeterol Products Available in the United States: Serevent Diskus (NDA# 20-692) delivers 50 mcg inhalation powder. The product was approved in the US on September 16, 1997. Serevent inhalation aerosol was previously available (beginning in 1994) as a metered dose inhaler (MDI). The MDI has been phased out as part of the effort to replace MDIs containing chlorofluorocarbons (CFCs). Salmeterol is also an active ingredient in the salmeterol/fluticasone combination drug product Advair, first approved in August 2000.

2.2 Salmeterol Approved Indications: Salmeterol is a selective, long-acting β_2-adrenergic agonist (LABA) indicated for long-term, twice-daily administration in the maintenance treatment of asthma and in the prevention of bronchospasm in patients 4 years of age and older with reversible obstructive airway disease, including patients with symptoms of nocturnal asthma who require regular treatment with inhaled, short-acting β_2-agonists. It also is approved for prevention of EIB in patients 4 years of age and older and for use in the maintenance treatment of bronchospasm associated with COPD in adults. (The other currently marketed LABA is formoterol, which carries similar indications. Salmeterol is a full agonist and formoterol is a partial agonist, with a more rapid onset of action with respect to bronchodilation.[5] The R,R isomer of formoterol was approved in October 2006 under the tradename Brovana, for treatment of chronic obstructive pulmonary disease.)

The National Health Interview Survey estimated that some 6.2 million children under 18 years of age, or approximately 8.5% of the population under 18 years old, had asthma in 2004.[6] In 2005, according to the National Hospital Discharge Survey, there were an estimated 159,000 hospitalizations for asthma among patients under 15 years old.[7] Fortunately, although the morbidity from pediatric asthma is substantial, pediatric asthma mortality is less common; in 2004 there were 186 pediatric asthma deaths (<18 years)

[5] National Heart, Lung, and Blood Institute. Expert Panel Report 3 (EPR 3): Guidelines for the Diagnosis and Management of Asthma. 2007. Available at http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm

[6] Centers for Disease Control and Prevention. National Surveillance for Asthma—United States, 1980-2004. Surveillance Summaries, October 19, 2007. MMWR 2007;56(No. SS-8). Available at www.cdc.gov/mmwr/PDF/ss/ss5608.pdf

[7] DeFrances CJ, Hall MJ. 2005 National Hospital Discharge Survey. Advance data from vital and health statistics, no. 385, Hyattsville, MD: US Department of Health and Human Services, CDC, National Center for Health Statistics; 2007. Available at http://www.cdc.gov/nchs/data/ad/ad385.pdf

nationwide, representing approximately 3 deaths per 100,000 children with asthma per year.[8]

Medications used for long-term control of asthma in children include the following[9].: inhaled anti-inflammatory agents (i.e., cromolyn sodium, corticosteroids, nedocromil sodium), leukotriene modifiers (i.e., montelukast, zafirlukast), long-acting β_2-agonists (i.e., salmeterol, formoterol), oral corticosteroids, and oral bronchodilators (i.e., sustained-release theophyllin). Quick-relief medications used for treatment of asthma in children include short-acting inhaled or oral β_2-agonists, oral corticosteroids (short course), and bronchodilators (i.e., ipratropium bromide). The monoclonal antibody omalizumab (anti-IgE) is also approved for use in children.

2.3 Pediatric Labeling:
The labeling for salmeterol contains a boxed warning regarding the results of the SMART study, a large placebo-controlled study that showed a significant increase in asthma-related deaths in patients receiving salmeterol compared to placebo:

WARNING: Data from a large placebo-controlled US study that compared the safety of salmeterol (SEREVENT® Inhalation Aerosol) or placebo added to usual asthma therapy showed a small but significant increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176 patients treated for 28 weeks) versus those on placebo (3 of 13,179) (see WARNINGS and CLINICAL TRIALS: Asthma: *Salmeterol Multi-center Asthma Research Trial*). 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 in those whose disease severity clearly warrants initiation of treatment with two maintenance therapies, including SEREVENT DISKUS.

The *Warnings* section of the salmeterol labeling provides additional information regarding the SMART study. This section of the labeling advises that salmeterol should not be initiated in a patient with deteriorating asthma, that paradoxical bronchospasm can occur with salmeterol, and that patients should not use salmeterol for the relief of acute symptoms. In addition, this section warns that salmeterol should not be used in conjunction with another inhaled, long-acting β_2-agonist and that salmeterol should be used with caution in patients with cardiovascular disorders.

Summary of Other Information from Labeling[10]

Pregnancy

[8] Centers for Disease Control and Prevention. National Surveillance for Asthma—United States, 1980-2004. Surveillance Summaries, October 19, 2007. MMWR 2007;56(No. SS-8). Available at www.cdc.gov/mmwr/PDF/ss/ss5608.pdf
[9] American Academy of Allergy Asthma and Immunology website www.aaaai.org, accessed on May 24, 2007.
[10] Adapted from Serevent prescribing information. Available at www.serevent.com

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

New Zealand rabbits were less sensitive since only delayed ossification of the frontal bones was seen at an oral dose of 10 mg/kg (approximately 1,600 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis). Extensive use of other beta-agonists has provided no evidence that these class effects in animals are relevant to their use in humans. There are no adequate and well-controlled studies with salmeterol in pregnant women. Salmeterol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Salmeterol crossed the placenta following oral administration of 10 mg/kg to mice and rats (approximately 410 and 810 times, respectively, the maximum recommended daily inhalation dose in adults on a mg/m^2 basis).

Nursing Mothers

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

Pediatric Use

The safety and efficacy of salmeterol has been evaluated in over 2,500 patients aged 4 to 11 years with asthma, 346 of whom were administered salmeterol for 1 year. Based on available data, no adjustment of dosage of salmeterol in pediatric patients is warranted for either asthma or EIB.

In 2 randomized, double-blind, controlled clinical trials of 12 weeks' duration, salmeterol 50 mcg was administered to 211 pediatric patients with asthma who did and who did not receive concurrent inhaled corticosteroids. The efficacy of salmeterol was demonstrated over the 12-week treatment period with respect to peak expiratory flow (PEF) and forced expiratory volume (FEV_1). Salmeterol was effective in demographic subgroups (gender and age) of the population. Salmeterol was effective when coadministered with other inhaled asthma medications, such as short-acting bronchodilators and inhaled corticosteroids. Salmeterol was well tolerated in the pediatric population, and there were

no safety issues identified specific to the administration of salmeterol to pediatric patients.

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

Dosing and Administration

For maintenance of bronchodilatation and prevention of symptoms of asthma, including the symptoms of nocturnal asthma, the usual dosage for adults and children 4 years of age and older is 1 inhalation (50 mcg) twice daily (morning and evening, approximately 12 hours apart). If a previously-effective dosage regimen fails to provide the usual response, medical advice should be sought immediately as this is often a sign of destabilization of asthma.

For prevention of EIB, the dose is one inhalation of salmeterol at least 30 minutes before exercise has been shown to protect patients against EIB. When used intermittently as needed for prevention of EIB, this protection may last up to 9 hours in adolescents and adults and up to 12 hours in patients 4 to 11 years of age.

Pediatric Filing History: Pediatric exclusivity was granted on March 9, 2006. On November 18, 2004, a Written Request letter was issued for salmeterol and the following four studies were requested:

Study 1: Dose-ranging safety of salmeterol xinafoate for treatment of asthma in children between the ages of ≥2 years to <4 years.
Study 2: Efficacy and safety of salmeterol xinafoate for treatment of asthma in children between the ages of ≥2 years to <4 years.
Study 3: Dose-ranging safety of salmeterol xinafoate for treatment of asthma in children between the ages of ≥6 months to <2 years.
Study 4: Efficacy and safety of salmeterol xinafoate for treatment of asthma in children between the ages of ≥6 months to <2 years.

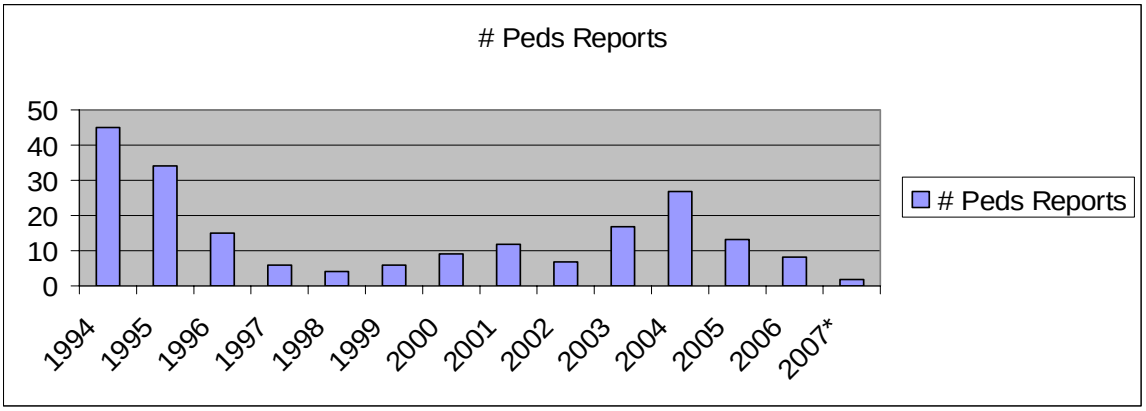
3. AERS SEARCH RESULTS: Salmeterol xinafoate (excludes salmeterol/fluticasone combination product)

3.1 Count of Reports: AERS Search including all sources - U.S. & foreign from marketing approval date (Table 1)

Table 1: Crude counts[1] of AERS Reports for All Sources from Marketing Approval Date (US counts in parentheses)			
	All reports	Serious[2]	Death
Adults (≥ 25yrs.)	2497 (1990)	1053 (562)	385 (136)
Adults (17-25 yrs.)	96 (71)	69 (44)	23 (14)
Pediatrics (0-16 yrs.)	205 (152)	123 (72)	45 (31)
Age unknown (Null values)	1407 (1321)	242 (160)	70 (47)
Total	4205 (3534)	1487 (838)	523 (228)

[1] May include duplicates
[2] Serious adverse drug experience per regulatory definition (CFR 314.80), which includes death, life-threatening, hospitalization (initial or prolonged), disability, and congenital anomaly.

Figure 1: Reporting trend for pediatric reports (ages 0-16 years) from approval date (February 4, 1994) through March 31, 2007:



* January 1, 2007 through March 31, 2007.

3.2 Count of Reports: AERS Search including all sources - U.S. & foreign from Pediatric Exclusivity approval date (Table 2)

Table 2: Crude counts[1] of AERS Reports for All Sources from date Pediatric Exclusivity was Granted (US counts in parentheses)			
	All reports (US)	Serious[2] (US)	Death (US)
Adults (≥ 25 yrs.)	151 (124)	67 (42)	9 (8)
Adults (17-25 yrs)	3 (2)	3 (2)	2 (2)
Pediatrics (0-16 yrs)	9 (7)	6 (4)	5 (3)
Age unknown (Null Values)	62 (54)	20 (13)	5 (3)
Total	225 (187)	96 (61)	21 (16)

[1] May include duplicates
[2] Serious adverse drug experience per regulatory definition (CFR 314.80), which includes death, life threatening, hospitalization, disability, and congenital anomaly.

4. REVIEW OF POSTMARKETING PEDIATRIC ADVERSE EVENTS REPORTS RECEIVED DURING THE ONE-YEAR AFTER A DRUG RECEIVES PEDIATRIC MARKET EXCLUSIVITY

4.1 Case Characteristics:

Table 3: Characteristics of pediatric cases reported during the pediatric exclusivity period (Beginning Date through End Date) n=9	
Gender [n=9]	Male: 6 Female: 3
Age [n=9]	0- 5 yrs: 1 6-11 yrs: 6 12-16 yrs: 2 Mean 10 years; Median 10 years; Range 3 to 15 years
Origin [n=9]	US (7), Foreign (2)
Report source [n=9]	Health care professional: 3 Consumer: 3 Attorney: 3
Event dates (n=9)	2000=1 2002=1 2004=1 2005=2 2006=3 2007=1
Daily dose [n=2]	2 puffs per day (2)
Duration of therapy [n=2]	2 days (1), 3 years (1)
Indications [n=5]	Asthma (5)
Primary Reported Adverse Events Decreased therapeutic response/therapy nonresponder: 2 Overdose: 3* Dizziness/muscle spasm: 1 Pharmaceutical product complaint (inhaler leaked): 1 Asthma/dyspnea/pulmon edema/circulatory collapse: 1 Death from unspecified cause: 1	
Outcomes [n=6]	Death=5 Life-Threatening/Hospitalization=1

* Cause of death for one patient who received an overdose was viral pneumonia, it is not know if the overdose contributed to the patient's death.

Cases of Lactose Intolerance in Children

The consult request specifically asked about cases of lactose intolerance reported in children. An AERS search identified only one reported case since marketing of salmeterol. This case involved a 5-year-old male who experienced "lactose intolerance" and a sinus infection with no reported outcome (consumer report; very little information provided). The search identified six cases reported as lactose intolerance in adults or patients of unknown age. All but one of these cases was reported by a consumer; most provided little information. One case described a milky white substance in the bottom of the lungs (per bronchoscopy) of a 63-year-old male who was hospitalized with dyspnea and pneumonia; the physician thought that the patient was reacting to the lactose in the Serevent or Advair products (this report was submitted by a consumer).

4.2 DISCUSSION OF CASES RECEIVED

Of the 9 cases in children received by the FDA during the one-year period following the date pediatric exclusivity was granted (March 9, 2006 to April 9, 2007), the following events were reported: decreased therapeutic response/therapy nonresponder (2 [1 death]), overdose (3 [1 death]), dizziness/muscle spasm (1), reported leaking device (1 [death]), asthma/dyspnea/circulatory collapse (1 [death]), and death from unspecified cause (1 [death]).

Decreased therapeutic response or therapy nonresponder (n=2[1 death]): Two reports coded as decreased therapeutic response/therapy nonresponder were received during the exclusivity period. The first nonfatal case was submitted by a consumer and described a 3-year-old male who experienced decreased therapeutic response after using salmeterol (indication for use, concomitant medications, and dose/duration were not specified); very little information was provided. The second case (reported by an attorney) involved a 10-year-old male who *died* of underlying asthma/respiratory arrest (asthma listed as cause of death on death certificate; no autopsy performed). Dose and duration of use of salmeterol were not reported; indication for salmeterol use was not specified, but the patient had underlying asthma. The patient's medical history included systolic murmur, ventricular septal defect, attention deficit/hyperactivity disorder, eczema, allergic conditions (oats and eggs) and otoplasty; he had been hospitalized several times for asthma and bronchiolitis/wheezing. His concomitant medications included fluticasone and salmeterol combination product, methylphenidate, pimecrolimus cream, salbuterol, desloratadine, and amoxicillin and potassium clavulanate combination.

Overdose (n=3[1 death]): Three cases coded as overdose were received during the exclusivity period. The first case involved a 15-year-old female who used three puffs of salmeterol rather than her prescribed dose of one puff because she could not feel or taste anything when she inhaled through the Diskus; no adverse event was specified and treatment with salmeterol continued (the reporting pharmacist found no defects with the device). In the second case, a 7-year-old male *died* of viral pneumonia (per MD, an autopsy was performed, but he was not willing to provide the results because of pending legal action); prior to the child's death, he had received 9 inhalations of his salmeterol (timeframe not specified) and the physician considered the events as possibly related to salmeterol. This case provided little information on use of salmeterol, medical history, and concomitant medications. The third case involved a 9-year-old male who experienced tachyarrhythmia after using 13 inhalations of salmeterol within 2 hours due to shortness of breath during his physical education class. He was seen by his physician (heart rate=140 at that time) and hospitalized with "tachycardia without arrhythmia;" he also was found to have hypokalemia (value=2.4). His cardiac enzyme test was reported as negative and he had no history of underlying cardiovascular disease. Dose and duration of use for salmeterol were not reported; indication for use was not reported, but the patient had underlying asthma. Concomitant medications were not specified. He was treated with potassium supplementation and recovered; treatment with salmeterol was discontinued and the patient was started on fluticasone propionate and salmeterol combination at 1 puff daily.

Dizziness/muscle spasm (n=1) An 8-year-old female experienced dizziness and leg cramps at some point in her 3-year asthma treatment with salmeterol and fluticasone propionate. Her dose for salmeterol was reported as 2 puffs per day. The events resolved and she was switched to fluticasone and salmeterol combination. In addition to asthma, she had multiple unspecified allergies; concomitant medication included certirizine. Very little information was provided.

Pharmaceutical product complaint (n=1[death]) A 13-year-old male *died* of an unspecified cause after using salmeterol to treat asthma for an unspecified duration. After he passed away, his mother found that the drug was leaking from the pivot point of his inhaler (the sponsor requested that the parents return the product for testing, but the product was never returned). Very little information was provided (consumer report).

Asthma/dyspnea/pulmonary edema/circulatory collapse (n=1[death]) An attorney submitted a report involving an 11-year-old female who *died* after using salmeterol (25 mcg, unknown dosing) for one day to treat asthma. The patient presented at a medical center unable to breathe; she collapsed and *died*. Two weeks prior to death, she had complained of difficulty breathing. Per post-mortem, the cause of death was asthma; examination of the bronchi identified partly-digested food. The patient had been diagnosed with asthma for only 2 weeks; concomitant medication included albuterol. An examination of the inhaler by the sponsor found that 9% of the contents had been expelled. (**Reviewer comment:** It is difficult to know if the patient received an overdose based on this analysis.)

Death from unspecified cause (n=1) Per attorney report, a 10-year-old male died of unspecified causes; he had used “Salmeterol xinafoate (Serevent) and/or Fluticasone propionate+salmeterol xinafoate (Advair)” for an unknown indication, dose, and duration of use. Very little information was provided.

In addition, all cases where no age was reported with a serious outcome (including death) were reviewed (n=18) in an attempt to determine if the patients who experienced adverse events were children. None of the cases stated that the patient was a child; several of the reports specified descriptions such as "young adult male" and "man in his 50s."

Discussion of 9 cases received during exclusivity period: In 5 of the 9 cases, the patients died. Two patients died from what was described as their underlying asthma and one patient died of viral pneumonia after receiving 9 inhalations of salmeterol in an unspecified timeframe (little information was provided; it is not known if the overdose contributed to the patient's death). The two remaining fatal cases (i.e., death possibly resulting from a leaking device and death from unspecified cause) did not provide sufficient information to draw any conclusions. Three of the 5 fatal cases were submitted by attorneys. One nonfatal case described a decreased therapeutic response; two nonfatal cases were coded as overdose (in one case no adverse outcome was reported and in the other case, a boy experienced tachycardia and was found to be hypokalemic [one study of 29 children with asthma using either beclomethasone or beclomethasone/salmeterol in a single-blind crossover design to treat asthma found no significantly-altered potassium

levels or EKGs, but the CPK-MB was increased]).[11] It is not known if the boy's overdose affected his potassium value. The consult request specifically asked about CNS adverse events; the search identified one case of dizziness/muscle cramps and spasms (case was nonfatal, nonserious; dizziness and muscle cramps are labeled events).

From a previous AERS review of fatal cases associated with salmeterol use before the exclusivity period, by Joyce Weaver, PharmD (see Attachment 1), asthma-related deaths have been reported for all ages. A separate chart of all pediatric deaths (n=23) associated with salmeterol use from initiation of marketing to April 9, 2007 is provided in Attachment 2, and a chart of pediatric deaths associated with fluticasone and salmeterol combination is provided in Attachment 3 [note that these data cannot be used to compare the safety of products]. Clinical and demographic characteristics for the 23 fatalities are presented below.

SALMETEROL: CLINICAL AND DEMOGRAPHIC CHARACTERISTICS OF ALL PEDIATRIC DEATHS AS REPORTED TO AERS FROM INITIATING OF MARKETING TO APRIL 9, 2007 (n=23)

Age (years): 13 mean/median, 7 to 16 range (n=23)
Gender: Female (8), male (15)
Source: Domestic (20), foreign (3)
Year: 1994 to 1995 (11), 1996 to 1999 (4), 2002 to 2007 (8)
Reporter: Physician (14), attorney (5), consumer (4)
Race: African American (3), Caucasian (4), Hispanic (1), not stated (15)
Indication for Use: Asthma (15), exercise-induced asthma (EIA) (3), asthma/EIA (1), not stated (4)
Inhaler type: Metered dose (1), Diskus (2), not reported (20)
Dose: 1-2 puffs BID (1), 2 puffs BID (8), 1 puff before exercise (1), unknown (13)
Onset after salmeterol initiation: 1 day (1), 22 to 35 days (5), 270 days (1), 330 to 385 days (4), 3 years (2), unknown (10)
Significant medical history (mutually exclusive):† "Mild to moderate" asthma (1), "moderate" asthma (1), "moderate to severe" asthma (1), "severe" asthma (5)
Concomitant inhaled corticosteroid use (as documented in report): 7
Circumstances at Death: Clutching inhaler (2), sports participation (4), exposure to trigger (cat) (1), camping/hike above tree line (1), vacation/sitting near swimming pool (1), partially digested food in bronchi upon autopsy (1)
Device malfunction: 1§
Product misuse (9): Overdose (3), off-label use for acute attack (2), noncompliance (3), overdose/patient not using "breathing attachment" (1)
Asthma exacerbation reported as cause of death:* 14
† Asthma status as specified by reporter

[11] Del Rio-Navarro BE, Sienra-Monge JJL, Reyes-Ruiz N, et al. Serum potassium levels, CPK-MB and EKG in children suffering asthma treated with beclomethasone or beclomethasone-salmeterol. Allergol Immunopathol 2001; 29: 16-21.

[§] Parents of child reported leaking inhaler, but never returned the product for testing

[*] Per autopsy report and/or physician assessment.

Of the 23 fatalities associated with salmeterol use, 14 patients died of asthma exacerbation as stated in the report based on autopsy data (6) and/or physician assessment (8). At least 7 of the 23 patients were reported as using a concomitant inhaled corticosteroid. The analysis of all pediatric fatalities identified misuse of the product (n=9), including overdose (3), off-label use for an acute attack (2), noncompliance (3), overdose/noncompliance with concomitant asthma medications (1); note that these numbers include data from the exclusivity period.

As noted by Dr. Weaver in her review, some patients with asthma will experience exacerbations of asthma even when receiving appropriate therapy. It is difficult to know from review of individual spontaneous adverse event reports whether the asthma pharmacotherapy increases the risk of serious asthma exacerbations. In the following section of this review, we will explore whether data from pediatric randomized controlled trials rather than AERS data can better address this issue.

The most frequently-reported adverse events in children using salmeterol since marketing include asthma, pharmaceutical product complaint, drug ineffective/condition aggravated, dyspnea/wheezing, cough, nausea/vomiting, headache, increased weight, overdose, cardiac arrest, and chest pain (note raw data). All events are labeled except for increased weight, cardiac arrest, and chest pain. Cases reporting cardiac arrest (nonlabeled event) were reviewed (n=21); many cases were coded as asthma attack and cardiac arrest.

In adults, the most commonly-reported adverse events (per AERS reports) associated with salmeterol therapy were related to the respiratory system and cardiovascular system. Reports of overdose in adults using salmeterol also were identified in AERS. Respiratory and cardiac events along with overdose have been reported in children as well. Respiratory events and overdose are well labeled. Cardiovascular effects are seen with sympathomimetic amines (the label states that no effect on the cardiovascular system is usually seen after use of salmeterol at recommended doses); labeled cardiovascular events for salmeterol include arrhythmias (atrial fibrillation, supraventricular tachycardia, and extrasystoles), tachycardia, palpitations, and hypertension.

4.3. Published Case Report

A PubMed search using the terms, "salmeterol" or "Serevent" and limited to English, Child (0 to 18 years), and Case Reports identified one article reporting two cases of adolescent boys with poorly controlled asthma and a history consistent with sudden asphyxial episodes during exertion while receiving inhaled corticosteroids and salmeterol. The patients were admitted to the hospital; both patients recovered. Salmeterol was replaced with theophylline and albuterol or pirbuterol.[12]

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

4.4 Pediatric Fatal AERS Reports for Salmeterol/Fluticasone (Advair)

For comparison, we also reviewed fatal AERS reports for the combination product Advair.

FLUTICASONE AND SALMETEROL COMBINATION: CLINICAL AND DEMOGRAPHIC CHARACTERISTICS OF ALL PEDIATRIC DEATHS AS REPORTED TO AERS FROM INITIATION OF MARKETING TO JULY 30, 2007 (n=15)

Age (years): 13 median, 12 mean, 5 to 16 range (n=15)
Gender: Female (6), male (9)
Source: Domestic (14), foreign (1)
Year: 1999 (1), 2003 to 2004 (6), 2005 to 2007 (8)
Reporter: Physician (7), nurse practitioner (1), attorney (7)
Race: African American (3), Caucasian (1), not stated (11)
Indication for Use: Asthma (15)
Inhaler type: Metered dose (1), Diskus (11), not reported (3)
Strength (fluticasone/salmeterol): 100/50 mcg (11), 250/50 mcg (2), 500/50 mcg (2)
Dose: 1 puff BID (9), not stated (6)
Onset after fluticasone/salmeterol initiation: 5 to 7 months (2), 1 to 2.75 years (4), 3 to 5 years (4), unknown (5)
Significant medical history:[†] "Mild" asthma (1), "severe" asthma (1), history of multiple hospitalizations/ER visits because of asthma (5)
Circumstances at Death: Sports participation (2), talking on phone (1)
Product misuse (5): Noncompliance (3), overdose of albuterol (1), overdose of fluticasone (1)
Asthma exacerbation reported as cause of death:[*] 9
[†] Asthma status as specified by reporter
[*] Per autopsy report and/or physician assessment

Of the 15 fatalities associated with fluticasone and salmeterol combination use, 9 patients died os asthma exacerbation as stated in the report based on autopsy data (6) and/or physician assessment (3). The analysis identified misuse of the product (n=5), including noncompliance (3), overdose of albuterol (1), and overdose of fluticasone (1).

5. REVIEW OF ADDITIONAL DATA SOURCES

To provide additional context for the pediatric spontaneous reports of fatal asthma events, in view of the concerns raised by the findings from the SMART trial, we undertook a review of clinical trial and epidemiologic data relevant to the assessment of the pediatric safety profile of salmeterol.

We will begin with a discussion of the findings regarding asthma mortality in the two large controlled trials of salmeterol, involving primarily adult subjects. One important metric of risk that will be discussed in connection with these two large trials is the number needed to harm (NNH). This is defined as the number of patients who would have to receive the test treatment in order to produce one additional adverse event, in comparison to patients receiving the control treatment. The NNH is calculated as the inverse of the attributable risk, which is the difference in frequency of the events between the two treatments; confidence limits on the NNH can be calculated by taking the inverse of the confidence limits for the attributable risk.[13] In the tables that follow we display the NNH for outcomes in which the risk was shown to be statistically significant, along with confidence limits (which we have calculated using Fishers Exact Test).

5.1 Clinical trial data relevant to severe asthma outcomes

SNS study

The Serevent Nationwide Surveillance (SNS) study[14] was a very large, randomized, double blind study, 16 weeks in duration, in which patients with asthma requiring regular bronchodilator treatment were randomized to receive either salmeterol 50 µg twice daily or albuterol 200 µg four times daily. The primary objective was to assess serious adverse events, and a large number (3516) of general practitioners served as the investigators. For subjects who withdrew prematurely, the investigator was to determine their vital status at the end of the study. A total of 16,787 and 8,393 patients were randomized to salmeterol or albuterol, respectively (2:1 randomization ratio). Most were adults, but 899 salmeterol patients and 421 albuterol patients were under 18 years of age. The percentage of patients receiving inhaled corticosteroids at entry was 69% for both treatment groups. Withdrawals from the study due to asthma were less frequent with salmeterol treatment, (relative risk = 0.77, p-value = 0.0002). However, asthma mortality showed the opposite pattern, with 12 asthma deaths among the salmeterol patients and 2 among the albuterol patients (relative risk = 3.0, p-value = 0.105). For all causes of death, there were 54 deaths with salmeterol and 20 with albuterol (relative risk 1.35, not statistically significant). These findings are summarized in the table below. Results from the pediatric subgroup were not reported in the publication. In a subsequent editorial, Hasford and Virchow suggested that a time-to-event analysis would have been a more appropriate statistical technique, given that 3256 patients dropped out of the study prematurely.[15]

[13] Citrome L. Show me the evidence: Using number needed to treat. South Med J. 2007;100(9):881-4.
[14] Castle W, Fuller R, Hall J, Palmer J. Serevent nationwide surveillance study: comparison of salmeterol with salbutamol in asthmatic patients who require regular bronchodilator treatment. BMJ. 1993 Apr 17;306(6884): 1034-7.
[15] Hasford J and Virchow JC. Excess mortality in patients with asthma on long-acting Beta-2 agonists. Eur Respir J 2006;28:900-902.

Table 4. Selected outcomes in SNS trial

Outcome	Number of pts.(all ages)		Relative Risk (p-value)
	Salmeterol (N=16,787)	Albuterol (N=8,393)	
Withdrawals related to asthma	488	318	0.77 (0.0002)
Asthma-related death	12	2	3.00 (0.105)
All cause death	54	20	1.35 (0.250)

SMART study

This was a very large, placebo controlled, safety study[16], 28 weeks in duration; the results are described within the current boxed warning in the Serevent labeling, as noted previously. The trial enrolled subjects over 12 years of age with asthma who had not used long acting beta agonists. A total of 13,176 patients were randomized to salmeterol 42 µg bid, and 13,179 to placebo. Subjects were allowed to use albuterol during the trial. After the initial clinic visit, safety outcomes were assessed via telephone calls. A National Death Index search provided verification of vital status for subjects lost to follow up. The primary endpoint was a combination of respiratory-related deaths or life-threatening events; relative risks were assessed with life table estimates. There were fifty salmeterol and 36 placebo patients with this primary endpoint, for a relative risk of 1.4 that was not statistically significant. Asthma deaths numbered 13 in the salmeterol group and 3 in the placebo group, yielding a relative risk of 4.4 (95% confidence intervals 1.25-15.3), and in terms of number needed to harm, one excess asthma death compared to placebo for every 1318 patients who received salmeterol. The somewhat broader secondary outcome category of respiratory-related deaths also showed an increase with salmeterol (relative risk of 2.16, with 95% confidence interval 1.06-4.41). Subgroup analyses showed even higher relative risks among African-Americans, including a relative risk of 4.1 on the primary endpoint that was statistically significant. Similar to the SNS findings, data on withdrawals for worsening asthma showed an advantage for salmeterol over placebo, suggesting that the drug can at the same time offer symptomatic improvement while elevating the risk of a catastrophic outcome. The risk for asthma-related death with salmeterol appeared greater among patients who did not receive inhaled corticosteroids (ICS) at baseline, but the trial was not designed to assess this, and data on concomitant inhaled corticosteroids was collected only at baseline.

[16] Nelson HS, Weiss ST, Bleecher ER, et al. The Salmeterol Multicenter Asthma Research Trial. Chest 2006; 129: 15-26.

Table 5. Selected outcomes from SMART trial, all subjects

Outcome	Number of pts. (all ages)		Relative Risk (95% c.i.)	Number needed to harm (95% c.i.)
	Salmeterol (N=13,176)	Placebo (N=13,179)		
Primary: Combined resp-related death or life-threatening experience	50	36	1.40 (0.91-2.14)	-
Asthma death	13	3	4.37 (1.25-15.34)	1317 (739-6086)
Respiratory-related death	24	11	2.16 (1.06-4.41)	1013 (536-9302)
All cause hospitalization	469	420	1.11 (0.98-1.26)	-

Additional data specifically on the subjects who were aged 12-18, taken from the sponsor's submission regarding this study, are shown in the table below. In the initial analysis, specific reasons for hospitalization were not recorded. However, the sponsor provided to us the case report forms for the 53 pediatric subjects who were hospitalized. One of the authors of this review (ADM) performed a hands-on review of these case report forms, to classify the reason for hospitalization as asthma-related or related to some other condition. Once the case reports were so classified, the treatment assignment was determined from a separate listing provided by the sponsor. These results are shown in the final row in Table 6.

Table 6. Selected SMART study outcomes for pediatric subgroup (12-18 y.o.)

Outcome	Number of pediatric pts.		Relative Risk (95% c.i.)	Number Needed to Harm (95% c.i.)
	Salmeterol (N=1648)	Placebo (N=1619)		
Primary: Combined resp-related death or life-threatening experience	2	2	0.98 (0.14-6.97)	-
Secondary: Respiratory-related death	1	0	Undefined	-
All cause hospitalization	37	16	2.27 (1.27-4.07)	80 (47-254)
Respiratory-related death, life-threatening experience, or asthma hospitalization (from hands-on review of case report forms)	15[17]	9[18]	1.64 (0.72-3.73)	-

[17] Patient numbers for asthma hospitalizations (hands-on review): 03899-022432, 43016-016494, 44206-013949, 44397-011777, 46348-020399, 37584-024115, 47676-022337, 47873-023829, 47874-023775, 51374-007812, 53210-038889, 77633-041523, 82105-057102

As shown, in the pediatric subjects, there were very few deaths or life threatening events, but there was a statistically significant increase in hospitalizations for any cause with salmeterol. This finding was not observed in the adult subgroup, in which (by subtraction) there were 432 hospitalizations among 11,096 salmeterol patients, and 404 hospitalizations among 11,156 placebo patients (relative risk = 1.07, not statistically significant (Fisher's exact test)). With respect to asthma hospitalizations specifically, our review of the case report forms disclosed that such hospitalizations occurred more frequently with salmeterol, but this imbalance was not statistically significant.

> *Conclusions from large safety studies of salmeterol*: Two randomized, controlled trials of salmeterol demonstrated a several-fold increase in asthma mortality in comparison to treatment with either a defined daily dose of albuterol (SNS) or albuterol as needed (SMART). Calculation of the number needed to harm showed one excess asthma death for every 2099 salmeterol treated patients in the SNS, and 1 in 1317 in SMART; these two estimates are very consistent if one recalls that SNS was the shorter of the two trials. In addition, increased mortality of this magnitude would not be apparent to prescribers, especially since salmeterol is effective with respect to acute asthma symptoms (e.g., fewer withdrawals for asthma symptoms in SNS). In SNS, increased asthma mortality was marginally statistically significant, and in SMART met usual criteria for statistical significance. There was a suggestion from the data in SMART that inhaled corticosteroid treatment mitigated the risk, but data on concomitant ICS were not systematically collected. With respect to the pediatric subpopulation in SMART, there was a statistically significant increase in hospitalization for any cause with salmeterol treatment, as well as a greater frequency of asthma hospitalizations with salmeterol which did not reach statistical significance. While the only respiratory death among pediatric subjects occurred in a salmeterol subject, this single event was of course insufficient to measure a difference between the treatments.

5.2 Evidence for biological plausibility and potential mechanisms

Salmeterol has therefore been associated with increased asthma mortality despite its unquestioned efficacy with respect to asthma symptoms and improvement in lung function measurements. We may ask whether there are any biologically plausible explanations for such an apparently paradoxical finding. Several hypotheses have been proposed, and for some there is experimental evidence. One hypothesis is masking of progression of asthma by the bronchodilating effects of the LABA. In a small crossover design study by McIvor and colleagues[19] in 13 asthmatic adults, salmeterol appeared to mask symptoms of progression of asthma (as measured by the level of sputum eosinophilia) during withdrawal of an inhaled corticosteroid. Another possible

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[18] Patient numbers for asthma hospitalizations (hands-on review): 42273-044663, 44195-010004, 44217-0188868, 44467-022252, 74598-041413, 82016-043050, 89106-050176, 97874-050995

[19] McIvor RA, Pizzichini E, Turner MO, Hussack P, Hargreave FE, Sears MR. Potential masking effects of salmeterol on airway inflammation in asthma. Am J Respir Crit Care Med 1998;158:924–930.

explanation is that some asthmatic patients possess a mutant beta-2 adrenergic receptor and may not be responsive to LABAs. Patients with a specific genotype have been found to respond poorly to albuterol in a prospective trial,[20] and there is some data supporting such an effect with salmeterol as well. A study by Wechsler et al. involved retrospective genotyping of 43 subjects in two salmeterol clinical trials.[21] They found that subjects homozygous for arginine at the 16th amino acid of the beta adrenergic receptor had poorer clinical outcomes in the trials compared to subjects homozygous for glycine at that location. Similar findings for pediatric patients come from a cross sectional survey conducted in Scotland, involving genotyping of 546 pediatric asthma clinic patients.[22] The investigators reported an increased risk of asthma exacerbations over a 6 month period for patients with the homozygous Arg/Arg genotype, in comparison to Gly/Gly, and in addition, this risk was higher still among salmeterol-treated Arg/Arg patients. However, an abstract presented at this year's meeting of the American Thoracic Society did not report an association between salmeterol response and adrenergic receptor genotype among a genotyped subgroup of adult clinical trial subjects.[23] Another hypothesis is that tolerance to the effects of an LABA develops over time. One implication would be that short-term trials may not be relevant for assessment of this possible effect.[24] For pediatric exercise-induced asthma, tolerance to salmeterol has been demonstrated. Simons and colleagues studied subjects aged 12-18 years with exercise induced asthma in a crossover placebo-controlled study of low dose salmeterol.[25] Notably, all subjects were receiving inhaled corticosteroid treatment. The investigators found that a 50 µg daily dose of salmeterol had a prophylactic effect relative to placebo in an exercise challenge test at the beginning of the study, but this effect was lost after 4 weeks of administration. Along with the phenomenon of tolerance, there is some evidence of rebound, or worsening upon withdrawal. In one of the pediatric trials described in the current Serevent labeling,[26] 207 pediatric asthma patients were randomized to either placebo or salmeterol 50 µg daily via a non-marketed inhalation device. The 12-week trial demonstrated efficacy with respect to lung function measurements, but in the first 1-2 weeks after discontinuation of treatment, asthma exacerbations were reported more frequently by salmeterol-treated children (12/102) than placebo-treated children (2/105).[27] Finally, we note that increased asthma deaths have

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[20] Israel E, Chinchilli VM, Ford JG, Boushey HA, Cherniack RM, Craig TJ, Deykin A, Fagan JK, Fahy JV, Fish J, et al., for the National Heart Lung and Blood Institute's Asthma Clinical Research Network. Genotype stratified prospective trial of regularly scheduled albuterol treatment in asthma. Lancet 2004;364:1505–1512.

[21] Wechsler ME, Lehman E, Lazarus SC, et al. Beta-adrenergic receptor polymorphisms and response to salmeterol. Am J Respir Crit Care Med 2006:173:519-526.

[22] Palmer CNA, Lipworth BJ, Lee S, Ismail T, et al. Arginine-16 beta-2 adrenoreceptor genotype predisposes to exacerbations in young asthmatics taking regular salmeterol. Thorax 2006;61:940-944.

[23] Ortega H, Klotsman M, Yancey S, et al. Pharmacogenetics in patients with asthma: associations between genetic polymorphisms and drug response phenotypes. Am J Respir Crit Care Med. 2007;175:A57.

[24] Salpeter SR. Safety of long-acting beta-agonists (author's response). Ann Intern Med 2006;145:708-710

[25] Simons FER, Gerstner TV, Cheange MS. Tolerance to the bronchoprotective effect of salmeterol in adolescents with exercise-induced asthma using concurrent inhaled glucocorticoid treatment. Pediatrics 1997;99:655– 659.

[26] Serevent prescribing information. Available at www.serevent.com

[27] Johnson S. Medical Officer Review, NDA 20-692 S001/002, September 22, 1998. Available at www.fda.gov/cder/foi/nda/98/20692S1,2_Serevent_medr_P1.pdf

been linked not only to LABAs, but previously to short acting beta agonists as well, such as use of high dose isoproterenol in the late 1960's.[28]

> *Conclusions regarding biological plausibility:* There is more than one hypothesis supported by empirical evidence that might explain an increased risk of severe asthma outcomes with LABA treatment, despite the efficacy of LABAs with respect to symptoms and measured lung function. The various hypotheses are not necessarily mutually exclusive.

5.3 Review of clinical trial data relevant to combination of LABA and ICS therapy

Because of the emerging consensus that LABAs should not be used without ICS, some have argued that trials in which this combination was not used are irrelevant to the safety profile of LABAs.[29] We conducted a focused review of existing clinical trial data to determine if there are data to support or refute the hypothesis that concomitant treatment with other maintenance therapy, particularly ICS, mitigates the risk of increased severe asthma events with LABA treatment. Some of the relevant trials to be described below were included in the aforementioned meta-analyses.

The current Serevent labeling[30] describes results from four controlled studies involving 1,922 adults and adolescents, in which salmeterol was shown to provide additional clinical benefits when added to ICS, relative to treatment with an increased dose of ICS alone. However, information on serious asthma outcomes is lacking.

One clinical trial involved an evaluation of salmeterol as add-on therapy to an inhaled corticosteroid in children.[31] In this year long three-armed study, 177 children requiring inhaled corticosteroid therapy were randomized to either twice daily salmeterol 50 µg plus beclomethasone 200 µg, twice daily beclomethasone 400 µg, or twice daily beclomethasone 200 µg. The study failed to distinguish an additional benefit from either the higher dose steroid or the use of concomitant salmeterol on lung function measurements; growth was retarded in the high dose beclamethasone arm. The publication did not report data on severe asthma adverse events.

Another year long trial involved 426 asthmatic children aged 5-15 years who were randomized to either salmeterol 50 µg twice daily or placebo, with albuterol as needed for all subjects.[32] Lung function measurements were improved with salmeterol; the authors reported that "exacerbation rates did not differ between groups and results were

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[28] Stolley PD. Asthma mortality: why the United States was spared an epidemic of deaths due to asthma. Am Rev Respir Dis 1972; 105:883–890

[29] Gustafsson PM, Kiri VA. Effect of long-acting beta2 agonists on exacerbation rates of asthma in children. Pediatr Pulmonol. 2004;38:362-4;

[30] Serevent prescribing information. Available at www.serevent.com

[31] Verberne AAPH, Frost C, Duiverman EJ, Grol MH, Kerribijn KF. Addition of salmeterol versus doubling the dose of beclomethasone in children with asthma. Am J Respir Crit Care Med 1998; 158:213–219.

[32] Von Berg A, de Blic J, la Rosa M, et al. A comparison of regular salmeterol vs 'as required' salbutamol therapy in asthmatic children. Respir Med 1998;92:292-299.

not dependent upon concurrent inhaled steroid use." However, as calculated by Bisgaard,[33] with 62% of the salmeterol treated children experiencing an exacerbation compared to 53% of placebo treated children, the relative risk for an exacerbation approached statistical significance (RR 1.18, 95% c.i. 1.00-1.40). The publication did not report data on serious asthma adverse events.

One large year-long randomized controlled trial provided some evidence that concomitant ICS treatment with salmeterol provides better clinical outcomes.[34] In this trial, which included subjects aged 12 years and older, but mostly adults, 1709 patients were randomized to combination therapy with salmeterol/fluticasone and 1707 were randomized to therapy with fluticasone alone. Flexible dosing in both arms was designed to allow the investigators to titrate therapy for optimal benefits. More patients in the combination arm met prespecified criteria for optimal asthma control, the primary metric in the trial. With respect to serious asthma events, there were relatively few, with more in the ICS arm (8 in the combination arm and 12 in the fluticasone alone arm).

If we turn now to the other LABA, formoterol, there are several trials in the pediatric population that are relevant to the hypothesis of protective effects of ICS.

Bensch et al.[35] reported a multisite, one-year trial in which 518 asthma patients aged 5-12 years were randomized to either placebo, low dose formoterol (12 µg twice daily) or high dose formoterol (24 µg twice daily). At entry, subjects were using either sodium cromoglycate, nedocromil sodium, and/or inhaled corticosteroids, in addition to daily albuterol. (In other words, formoterol was added to existing asthma maintenance medication, as recommended in the Boxed Warning on asthma-related deaths currently in the formoterol label).[36] With respect to efficacy outcomes, both doses of formoterol were associated with improvements of forced expiratory volumes in 1 second (FEV1), and peak expiratory flow rates, compared to placebo. However, data on severe asthma events favored placebo. The table below summarizes the occurrence of asthma-related hospitalizations, for which the increase in asthma hospitalizations over placebo was statistically significant for either dose considered separately (Fisher's Exact test using Stata[37] software). The authors proposed that this imbalance might have been the result of seven placebo patients discontinuing for asthma events that did not require hospitalization. The table below is from the data reported in the publication; a similar table appears in the current Foradil label, which advises against the use of the higher dose

[33] Bisgaard H. Effect of long-acting beta-2 agonists on exacerbation rates of asthma in children. Pediatr Pulmonol. 2003;36:391-398

[34] Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJ, Pauwels RA, et al. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma ControL study. Am J Respir Crit Care Med. 2004;170:836-44.

[35] Bensch G, Berger WE, Blokhin BM, Socolovsky AL, Thomson MH, Till MD, et al. One-year efficacy and safety of inhaled formoterol dry powder in children with persistent asthma. Ann Allergy Asthma Immunol. 2002;89:180-90.

[36] Foradil prescribing information. Available at www.spfiles.com/piforadil.pdf

[37] Stata Corporation, College Station, Texas.

of 24 µg twice daily.[38] Two other trials of formoterol 24 µg twice daily in adults also showed a higher frequency of serious asthma exacerbations versus placebo.[39]

Table 7. Asthma-related hospitalizations in Bensch et al.[40] 1-yr. pediatric trial of formoterol

Treatment	Formoterol 24 µg twice daily	Formoterol 12 µg twice daily	Placebo
N	171	171	176
Number (%) of asthma-related hospitalizations	10 (5.8%)	8 (4.7%)	0
Number needed to harm (95% c.i.)	17 (11-43)	21 (13-66)	Ref.

Similarly, Tal et al. reported a 12-week, randomized, controlled trial of combined therapy with budesonide plus formoterol versus a higher dose of budesonide alone in children with asthma (Table 8).[41] This design is potentially informative because it compared the use of a LABA plus ICS to ICS alone. Although PEF and FEV1 were improved with the combination treatment versus budesonide alone, 5 out of 148 combination-treated subjects were hospitalized for asthma during the 12 month trial, versus zero higher dose budesonide alone subjects, a difference that approached statistical significance (p-value = 0.06, Fisher's exact).

Table 8. Asthma-related hospitalizations in Tal et al. 12-wk. pediatric trial of formoterol

Treatment	Budesonide/formoterol 80/4.5 µg, two inhalations twice daily	Budesonide 100 µg, two inhalations twice daily
N	148	138
Number (%) of asthma-related hospitalizations	5 (3.4%)	0

Finally, a recently published trial of formoterol plus an inhaled corticosteroid evaluated a novel treatment regimen for pediatric asthma.[42] In this year long trial, 341 children aged 4-11 years were randomized to daily budesonide 80 µg plus formoterol 4.5 µg, the same regimen plus additional inhalations as needed, or budesonide 320 µg daily without formoterol. Asthma exacerbations were less frequent with the as-needed regimen versus the other two treatment arms; growth velocity was slower in the higher dose steroid arm. With respect to severe exacerbations requiring hospitalization or emergency room

[38] Foradil prescribing information. Available at www.spfiles.com/piforadil.pdf
[39] Mann M, Chowdhury B, Sullivan E, Niclas R, Antracite R, Meyer RJ. Serious asthma exacerbations in asthmatics treated with high-dose formoterol. Chest 2003;124:70-74.
[40] Bensch G, Berger WE, Blokhin BM, Socolovsky AL, Thomson MH, Till MD, et al. One-year efficacy and safety of inhaled formoterol dry powder in children with persistent asthma. Ann Allergy Asthma Immunol. 2002;89:180-90.
[41] Tal A, Simon G, Vermeulen JH, Petru V, Cobos N, Everard ML, de Boeck K. Budesonide/formoterol in a single inhaler vs. inhaled corticosteroids alone in the treatment of asthma. Pediatr Pulmonol 2002;34:342–350.
[42] Bisgaard H, Le Roux P, Bjamer D, et al. Budesonide/formoterol maintenance plus reliever therapy : A new strategy in pediatric asthma. Chest 2006;130:1733-1743.

treatment, there was one such event in both the as-needed treatment arm and the higher dose budesonide arm, versus 8 in the fixed-dose combination arm. The higher number of such events in the fixed dose arm was associated with a p-value of 0.04 compared to the high dose budesonide arm. The results are summarized in the table below.

Table 9. Asthma exacerbations requiring emergency room or hospital treatment, Bisgaard et al., 2006

Treatment	Budesonide/formoterol 80/4.5 µg daily	Budesonide/formoterol 80/4.5 µg daily, plus as needed	Budesonide 320 µg daily
N	117	118	106
Number (%) of asthma-related hospitalizations or ER visits	8 (6.8%)	1 (0.8%)	1 (0.9%)
Number needed to harm (95% c.i.)	17 (9-104)	Not applicable	Reference

This trial also demonstrates a higher frequency of severe exacerbations with formoterol, as seen in other studies, but suggests that the as-needed administration may mitigate this effect.

> *Conclusions regarding clinical trials evaluating LABA plus ICS*: The available data set on severe asthma events with salmeterol plus ICS in pediatric trials, which might help to evaluate the hypothesis that ICS protects against salmeterol-related severe asthma exacerbations, is rather limited. One trial involving both adults and children did show a numerically higher number of serious asthma events in the ICS alone treatment group. In the case of formoterol, the available pediatric clinical trial data are more robust, and are actually not consistent with the hypothesis that ICS is protective against LABA-related severe asthma exacerbations.

5.4 Observational studies

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

GlaxoSmithKline undertook a feasibility study to determine if a case-control study of asthma deaths could evaluate whether there is an association between salmeterol use and death from asthma, and whether such an effect might be ameliorated by concomitant ICS. They planned to use five years of Medicaid data from six different states. Unfortunately, they determined that the level of use of salmeterol, and the number of asthma deaths in these databases, were insufficient to provide statistical power, and accordingly they abandoned this study.[43] A case-control study of non-fatal asthma episodes requiring

[43] Davis KJ, DiSantostefano RL, Beasley R., et al. Rare events and exposures; Long-acting beta2-agonists and risk of asthma-related mortality in Medicaid enrollees. Pharmacoepidemiol Drug Safe 2007;16:S169.

intensive care unit (ICU) admission, with 48 cases and 185 controls, showed an association between salmeterol use and ICU admission (unadjusted relative risk 2.32, 95% CI 1.05-5.16), but this association appeared to be due to more frequent use of salmeterol by patients with more severe asthma.[44] With respect to studies not focused specifically on salmeterol, findings from case-control studies have included an association between asthma deaths and life-threatening asthma attacks with use of beta-2 agonists in Japan.[45] A case-control study of 532 patients who died from asthma (and an equal number of controls) found an association between asthma deaths and use of short acting beta-2 agonists in the period 1-5 years prior to death. However, for use of long-acting beta-2 agonists during the same period, there was a reduction in the risk of asthma deaths that almost reached statistical significance.[46]

A cohort study of health care insurance claims compared emergency asthma care, hospitalization, and intensive care unit stays for 2708 patients prescribed salmeterol and 3825 patients receiving theophylline. This study failed to find any differences in outcomes, although there was evidence that salmeterol was prescribed for patients with more severe asthma.[47] This study did not examine asthma deaths. Another observational study used the UK's General Practice Research Database to assess respiratory mortality with salmeterol, ipratropium, and theophylline. No differences between drugs were found, but there were only 5 deaths from respiratory causes among salmeterol patients, and the relative risk estimates had very wide confidence limits, suggesting a lack of statistical power.[48]

> *Conclusions from observational studies*: Findings regarding the safety of LABAs from health care claims databases and case-control studies have been mixed. Using observational methods has been challenging, because patients prescribed LABAs almost certainly differ from other asthma patients, and because deaths from asthma are relatively rare, and thereby difficult to study.

5.5 Meta-analyses of pediatric clinical trial data on long-acting β_2 agonists

One technique that is useful in the assessment of rare adverse events is to combine data from separate clinical trials in a meta-analysis. We describe here two such meta-analyses addressing the risks of LABAs, particularly in the pediatric population.

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[44] Williams C, Crossland L, Finnerty J, et al. Case-control study of salmeterol and near-fatal attacks of asthma. Thorax 1998;53:7-13.
[45] Tanihara S, Nakamura Y, Matsui T, Nishima S. A case-control study of asthma death and life threatening attack: their possible relationship with prescribed drug therapy in Japan. J Epidemiol 2002;12:223-8.
[46] Anderson HR, Ayres JG, Sturdy PM, et al. Bronchodilator treatment and deaths from asthma: case-control study. BMJ 2005;330:117. Epub 2004 Dec 23.
[47] Lanes SF, Lanza LL, Wentworth CE. Risk of emergency care, hospitalization, and ICU stays for acute asthma among recipients of salmeterol. Am J Respir Crit Care Med 1998;158:857-861.
[48] Meier CR, Jick H. Drug use and pulmonary death rates in increasingly symptomatic asthma patients in the U.K. Thorax 1997;52:612-617.

Review of pediatric trials of LABAs by Bisgaard

Bisgaard reviewed eight pediatric trials of LABAs, including five trials of salmeterol and three of formoterol, to assess the effect of the LABA on asthma exacerbations in pediatric asthma.[49] He concluded there was no clear evidence of a protective effect from LABAs on asthma exacerbations, despite findings of improved lung function measurements; in fact, he concluded that asthma exacerbations and hospitalizations tended to be increased with LABA treatment. He did not calculate any combined statistical parameters because he found that the eight clinical studies were too heterogeneous in nature to be suitable for a formal meta-analysis. He pointed out that data from adult studies may not always be suitable for extrapolation to the pediatric population because of age-related differences in the disease of asthma.

Meta-analysis of long acting beta-2 agonist trials by Salpeter et al.

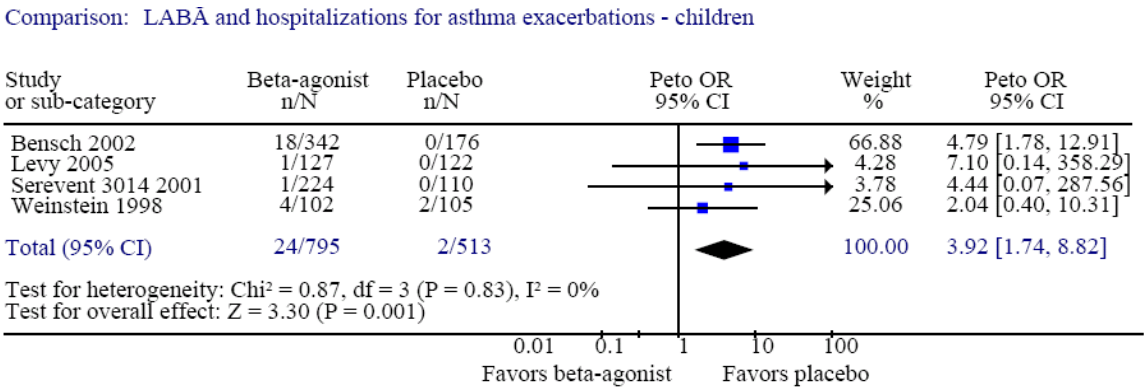
A more recently published formal meta-analysis examined data on asthma deaths, hospitalizations for asthma, and asthma exacerbations requiring intubation from 19 randomized, controlled trials of the two LABAs (salmeterol or formoterol) in patients of all ages..[50] The authors selected randomized, placebo-controlled trials at least 3 months in duration. Six of these trials were in pediatric patients (3 each with formoterol and salmeterol). The authors employed the Peto method for estimating combined odds ratios and confidence limits. Overall, they found that the LABAs were associated with statistically significant increases in asthma exacerbations requiring hospitalization (odds ratio 1.7), and in life-threatening exacerbations of asthma requiring intubation and ventilation (odds ratio 1.8), in comparison to placebo. The combined odds ratio for asthma deaths also showed an increase with LABAs, but since the SMART trial contributed 16 of the 18 total asthma deaths in the meta-analysis, this finding essentially reflected the results from SMART. For trials with at least 75% of subjects also receiving inhaled corticosteroids, the risk for asthma hospitalizations in association with LABAs was still present (OR 2.1, 95% CI 1.3-3.4).

With respect to pediatric data, a subgroup analysis of 4 pediatric trials which provided data on hospitalizations for asthma exacerbations was described in the article, and is displayed graphically below.[51]

[49] Bisgaard H. Effect of long-acting beta-2 agonists on exacerbation rates of asthma in children. Pediatr Pulmonol. 2003;36:391-398

[50] Salpeter SR, Buckley NS, Ormiston TM, Salpeter EE. Meta-analysis: Effect of long-acting beta-agonists on severe asthma exacerbations and asthma related deaths. Ann Intern Med 2006;144:904-912.

[51] Salpeter SR, personal communication.



As shown, there was an imbalance in hospitalizations for asthma which favored placebo, and a combined odds ratio which was statistically significant. The first two trials listed involved use of formoterol and the third and fourth trials involved use of salmeterol. We shall discuss the Bensch et al. trial, which showed the strongest association, in more detail below.

Meta-analyses focusing on LABAs combined with ICS

The question of whether a concomitant inhaled corticosteroid can mitigate potential risks from LABA treatment is that several meta-analyses of clinical trial data have attempted to address. First, two meta-analyses of clinical trials in which salmeterol plus ICS was compared to a higher ICS dose showed clinical benefits of salmeterol treatment; however, these analyses did not address serious asthma events.[52, 53] Two more recent meta-analyses that did focus on serious outcomes were presented at this year's meeting of the American Thoracic Society, both addressing the question of whether a concomitant inhaled corticosteroid (ICS) can mitigate the increase in severe asthma events with LABAs. Note that only abstracts of these analyses are currently available. The first was a meta-analysis of clinical trials in the salmeterol manufacturer's database involving comparisons of salmeterol plus ICS versus ICS alone.[54] This meta-analysis included data from 24 pediatric and adult trials of at least 2 weeks in duration with data on severe asthma exacerbations. A total of 32 out of 6,606 salmeterol plus ICS patients had an asthma hospitalization, compared to 35 out of 6,791 ICS alone patients (Peto odds ratio 0.94, 95% c.i. 0.57-1.53). These studies included 5 trials in pediatric age groups, involving 1,254 pediatric subjects exposed for 325 patient-years, with one asthma hospitalization observed (in an ICS alone subject). There was only one asthma death and one intubation for asthma in these trials, both occurring in combination therapy patients.

[52] Shrewsbury S, Pyke S, Britton M. Meta-analysis of increased dose of inhaled steroid or addition of salmeterol in symptomatic asthma (MIASMA). BMJ 2000;320:1368-73.
[53] Masoli M, Weatherall M, Holt S, Beasley R. Moderate dose inhaled corticosteroids plus salmeterol versus higher doses of inhaled corticosteroids in symptomatic asthma. Thorax 2005;60:730-734.
[54] Nelson HS, Beasley R, Yancey SW, et al. No increase in asthma-related hospitalizations following the addition of salmeterol to an inhaled corticosteroid in patients with asthma: a meta-analysis. Am J Respir Crit Care Med. 2007;175:A59.

A similar meta-analysis was presented at the same conference for formoterol.[55] In this analysis, trials of at least 12 weeks in duration were included, with 6,988 subjects receiving formoterol plus ICS, and 5,241 receiving ICS (age range not specified). They found fewer asthma-related hospitalizations in the formoterol plus ICS treatment group (34 versus 48, odds ratio 0.59, 95% c.i. 0.38-0.92). There were two asthma-related deaths, both in the formoterol plus ICS group, and no intubations for asthma, in these trials. Thus both meta-analyses provided reassuring results with respect to asthma hospitalizations, but included very few cases of fatal or life-threatening asthma exacerbations. As already noted, complete articles on these analyses have not yet been published in peer-reviewed journals.

> *Conclusions from clinical trial meta-analyses*: A recent meta-analysis of asthma clinical trials in subjects of all ages demonstrated an increase in life-threatening asthma exacerbations and asthma hospitalizations with LABA treatment. A meta-analysis examining severe asthma events with LABAs in pediatric asthma trials was limited by the amount of data available, but suggested an increase in asthma hospitalizations with LABA. Finally, two recent meta-analyses (not limited to pediatric trials), available only as abstracts, would appear to support the hypothesis that concomitant ICS mitigates the risk of increased asthma hospitalizations with LABA therapy.

6. SUMMARY AND RECOMMENDATIONS

1. The review of the few salmeterol pediatric reports in the AERS database did not identify adverse events unique to the pediatric population. However, the review was limited by the small number of reports, and incompleteness of some of the reports. There are too few reported adverse events in any one area to make a conclusion regarding safety signals unique to the pediatric population. A number of the fatal outcomes reported were attributed to asthma, but since this is also the indication for the drug, reliable assessment of drug-relatedness in individual AERS cases is not feasible. Data on serious asthma outcomes from controlled clinical trials are far more informative, and accordingly are summarized in this review.

2. Because 3 of the 9 adverse event reports received during the Exclusivity period (and 9 of 23 reports of all pediatric fatalities) represent misuse of Serevent Diskus, OSE Division of Medication Errors and Technical Support (DMETS) has been contacted to review this issue and provide a separate consult.

3. The four-fold increase in asthma-related deaths in subjects using salmeterol (as compared to placebo) identified in the SMART study (see above) is of concern; the data represent one excess asthma death per 1300 salmeterol-treated subjects. The similar

[55] Jaeschke R, Mejza F, Lesniak W, et al. The safety of formoterol among patients with asthma using inhaled corticosteroids. Am J Respir Crit Care Med. 2007;175:A57.

results from the SNS trial, while not meeting the usual criteria for statistical significance, lend credence to the results of SMART.

4. In SMART, based on a hands-on review of case report forms by one of the authors (ADM), 12-18 year old patients on salmeterol had a higher frequency of hospitalizations for asthma compared to placebo, although this did not reach statistical significance.

5. A meta-analysis of placebo-controlled clinical trial data for salmeterol and formoterol in patients of all ages found that the long acting beta agonists (LABAs) were associated with statistically significant increases in asthma exacerbations requiring hospitalization, and in exacerbations requiring intubation and ventilation. In pediatric trials within the same meta-analysis, there was also a statistically significant increase in the risk of asthma hospitalizations with LABAs compared to placebo;; pediatric trial data on serious asthma outcomes were generally sparse compared to adult data, however.

7. There is no available pediatric data to indicate that the increased risk of asthma death and life-threatening exacerbations observed in adults does not also apply to children.

8. With respect to the crucial issue of whether concomitant inhaled corticosteroid (ICS) therapy protects against severe asthma outcomes with LABA therapy, the NHLBI Expert Panel guidelines[56] state, "…while the data do not necessarily support an increased risk of severe or serious exacerbations in patients who are taking LABA and are receiving concomitant ICS, data are also insufficient to establish definitively that ICS therapy completely obviates the risk." Our overview of the available data focused on the pediatric age group was consistent with this assessment.

10. Recommendation for a study in children may be warranted, but may not be feasible because of the difficulties in enrolling a sufficient number of patients to assess infrequent but severe asthma events, thus making results unavailable for many years, as was the case for SMART. In addition, there may be ethical issues with randomized designs if we are not at equipoise with respect to the pediatric safety of LABAs.

Our overview of these various data sources has shown that (1) adult trial data show an increase in asthma mortality and severe asthma events with salmeterol; (2) available data do not provide any reason to believe that the pediatric population does not share the same risk; and (3) definitive evidence of a protective effect of ICS is lacking for LABAs, and in fact there is evidence that ICS is not protective in pediatric patients receiving formoterol.. Accordingly, we conclude that salmeterol may have an unfavorable risk-benefit ratio in the treatment of pediatric asthma. We recommend a more thoroughgoing, formal risk-benefit analysis of salmeterol in the treatment of pediatric asthma. Of course, such an analysis would also have to consider relevant data for adults and for the other long acting beta agonist, formoterol.

[56] National Heart, Lung, and Blood Institute. Expert Panel Report 3 (EPR 3): Guidelines for the Diagnosis and Management of Asthma. 2007. Available at http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm

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Ann Corken Mackey, RPh, MPH
Safety Evaluator

_____
Andrew D. Mosholder, MD, MPH
Medical Officer

_____
Lanh Green, PharmD, MPH
Safety Evaluator Team Leader

Appendix

Standard Searches:

A. Adults (17 yrs and above)
    1. All outcomes from approval date (no set criteria)
    2. Serious outcomes from AP date
    3. Death as an outcome from AP date
    4. All outcomes from PE date to present or any desired date
    5. Serious outcomes from PE date to present or any desired date
    6. Death as an outcome from PE date to present or any desired date

B. Ages 0-16 yrs ONLY
    1. Same as above 1-6
    2. Retrieve case reports for hands-on review

Drug Product Information
Cut and paste relevant pediatric labeling

Limitations of the Adverse Event Reporting System (AERS)
The voluntary or spontaneous reporting of adverse events from health care professionals and consumers in the U.S reflects underreporting and also duplicate reporting. For any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s). The main utility of a spontaneous reporting system, such as AERS, is to provide signals of potential drug safety issues. Therefore, counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing drug risk between drugs.

Other appendices (e.g., line listings, AERS printouts) up to the discretion of the reviewer

Attachment #1: DDRE Postmarketing Safety Review (PID# 050138): Salmeterol and formoterol: Review of US Death Cases (abstract only)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
MEMORANDUM
PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 28, 2005

FROM: Joyce Weaver, Pharm.D., Safety Evaluator
Division of Drug Risk Evaluation, HFD-430

THROUGH: Mark Avigan, M.D., C.M., Director
Division of Drug Risk Evaluation, HFD-430

TO: Badrul Chowdhury, M.D., Director
Division of Pulmonary and Allergy Drug Products, HFD-570

SUBJECT: Postmarketing Safety Review; PID # 050138
Drugs: Salmeterol (Serevent NDAs # 020236, 020692, Advair NDA # 021077; GlaxoSmithKline); Formoterol (Foradil NDA # 020831; Novartis)
Event: Review of US Death Cases

CONFIDENTIAL: CONTAINS USE DATA FROM IMS HEALTH— DO NOT RELEASE OUTSIDE OF THE FDA WITHOUT APPROPRIATE CLEARANCES

INTRODUCTION/ EXECUTIVE SUMMARY

An advisory committee meeting will be held on July 13, 2005 to consider the safety of the long-acting β_2-adrenergic agonists, formoterol and salmeterol. Although the primary focus of the meeting will be the randomized controlled trials on this issue, we are providing an AERS case review of domestic deaths involving the use of long-acting β_2-adrenergic agonists.

An estimated 20 million Americans have asthma. The prevalence of asthma has been increasing over the past 20 years across all age, sex and racial groups. There are more than 5000 deaths due to asthma each year. Since 1980 asthma death rates overall have

increased more than 50%. Women account for nearly 65% of asthma deaths overall. African Americans are three times more likely to die from asthma.[57]

We reviewed 201 cases of death reported for salmeterol (received by the FDA 5/1994-2/2005), and four deaths for formoterol (11/2003-5/2005). The four deaths reported for formoterol were poorly described. Two of the formoterol deaths were attributed to myocardial infarction, and no formoterol death was attributed to asthma. These four reports do not contribute significantly to our knowledge regarding the safety of formoterol.

Through 2004, the FDA received reports of 196 domestic deaths for salmeterol and one domestic death for formoterol. Three of the four formoterol deaths and five of the 201 salmeterol deaths were received in 2005. The total US sales of salmeterol-containing products are 45-fold higher than the total formoterol sales.[58]

Data from Salmeterol Multi-center Asthma Research Trial (SMART) suggest that African Americans may be at increased risk compared to other patients with the use of salmeterol. This information was incorporated into the labeling of the salmeterol-containing products in January 2003. We note that the inclusion of this information in the labeling does not appear to have changed prescribing to African American patients.[59]

Most (137/201, 68.2%) of the patients in the salmeterol-associated death cases had used the drug for asthma. Sixty-six percent (133/201) of the patients were receiving an inhaled or a systemic corticosteroid concomitantly. Fifty-eight percent (116/201) of the patients were receiving a short-acting β_2-adrenergic agonist (e.g., albuterol) concomitantly. Sixty-five cases contained one or more apparent contributing factors to the event (e.g., higher-than-recommended dose of salmeterol, exposure to an asthma trigger shortly before event, use of salmeterol for immediate relief, non-compliance with therapy, recent exacerbation of asthma, or decompensating asthma at the time of the salmeterol prescription).

Ninety-one cases described asthma-related deaths, and ten other cases described *possible* asthma-related deaths. In 25 of the 91 asthma-related deaths, the patients experienced short-interval fatal asthma attacks; that is, the patients died quickly after the onset of symptoms, with no reported recent exacerbation prior to the event. An additional 18 patients succumbed quickly after the onset of the acute attack, but the patients had experienced recent exacerbations of asthma, perhaps foretelling the final fatal event.

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[57] Data from the Asthma and Allergy Foundation of America (AAFA); available at URL http://aafa.org. Accessed 6/15/2005.

[58] Salmeterol: 196 deaths & 90,868,000 prescriptions through 2004; formoterol: 1 death & 2,003,000 prescriptions through 2004

[59] Total sales of salmeterol-containing products increased in both 2003 and 2004, and the percentage of prescriptions for African Americans remained constant (2002-10.7%, 2003-11.3%, and 2004-10.8%). See Attachment 5 for more detailed information.

Fifteen of the asthma-related deaths occurred in patients whose asthma was described as mild, moderate, or stable. Thirty-four of the asthma-related deaths occurred in patients whose asthma was described as severe. The severity of the underlying asthmatic condition was not reported in 42 of 91 cases.

Twenty-five cases described cardiac deaths. Fifteen of the 25 cardiac deaths occurred suddenly. Autopsy was reported in only three of the cases in which the deaths were described as cardiac-related, and the medical basis for determining that a death was cardiac-related was not described in many of the cases. It is possible that there was a misclassification of the cause of death by the reporter in some of the cases that were categorized as cardiac deaths.

The cause of death was not clear in the remainder of the cases, but it is likely that many of the deaths were asthma-related.

It is clear from some of the cases that the reporting physician was puzzled by the death outcome, perhaps because the physician did not expect a patient with well-controlled asthma to experience a sudden fatal asthma attack. However, it is noteworthy that more than 1,250 such deaths occur in the US each year and 25% of more than 5,000 yearly asthma deaths are of the short-interval type.[60]

It is difficult to draw conclusions from the AERS reports of death with the long-acting β_2-adrenergic agonists. Some patients with asthma will experience exacerbations of asthma even when receiving appropriate therapy. The relevant question with salmeterol and formoterol is whether the events occur more frequently and/or some patients are at increased risk when receiving a long-acting β_2-adrenergic agonist. Data from randomized controlled trials rather than AERS may be a better source to address this issue.

[60] Wobig EK, Rosen P. Death from asthma: rare but real. J Emerg Med. 1996 Mar-Apr;14(2): 233-40.

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Attachment #2: Salmeterol: Clinical and Demographic Characteristics of Pediatric Deaths as Reported to AERS from Initiation of Marketing to April 9, 2007 (n=23)

	FDA Case #	Source	Reporter Source	Age	Year	Sex	Dose *Dosage Form*	Time to Onset	Circumstances at Death	Cause of Death	Med history *Indication for Use*	Concomitant Medication	Description
1	6097972	Domestic	Consumer	13	2007	M	Unk *Diskus*	Unk	Unk	Unk	Not stated *Exercise-induced asthma (EIA)*	Not stated	Parents suspected leaking inhaler, but did not return product for QA testing
2	5999790	Foreign	Physician (Coroner)	7	2006	M	Unk *Unk*	Unk	Possible overdose-pt received 9 inhalations before death (time-frame not specified)	Viral pneumonia (autopsy results not available)	Not stated *Not stated*	Not stated	Rpt suspects **possible misuse (overdose)** may be related to pt death; additional information not available due to pending litigation
3	6191982	Domestic	Attorney	10	2007	M	Unk *Unk*	Unk	Unk	Unk	Not stated *Not stated*	Not stated	Per rpt, at time of death, pt using either Serevent or Advair
4	6035218	Foreign	Attorney	11	2006	F	25 mcg, unk freq *Unk*	1 day	Two weeks prior, pt complained of difficulty breathing; pt collapsed and died at medical center	Asthma (per post mortum)	Asthma *Asthma*	Albuterol	Per autopsy, partially digested food material found in bronchi; sponsor QA determined that 9% of inhaler contents had been expelled (**Reviewer note**: unable to determine if this is an overdose)

5	5933585	Domestic	Attorney	10	2006	M	Unk *Unk*	Unk	Pt taken from home to hospital where he died	Respiratory arrest following asthma attack	Asthma, systolic mumur, ventricular septal defect, ADHD, exzema, allergic to oats and eggs *Not stated*	Fluticasone and salmeterol combination, methylphenidate, pimecrolimus cream, albuterol, desloratidine, amoxicillin and clavulanate combination	Serevent and Advair both listed in formal legal complaint
6	6288948	Foreign	Consumer	9	2007	F	Unk *Unk*	Unk	None stated	Sudden death during asthma attack	Not stated *Asthma*	Fluticasone, montelukast	**Possible misuse (patient used salmeterol inhaler before death [acute asthma attack] because fluticasone ran out)**
7	3657776	Domestic	Attorney	16	1999	M	1 to 2 puffs BID *Unk*	Unk	Pt on camping trip--experienced difficulty breathing in early morning hours; pt used albuterol immediately before death; pt had hiked above the tree line during trip	Bronchial asthma (per autopsy)	Asthma, numerous allergies *EIA*	Albuterol, metaproterenol, cromolyn sodium, fluticasone nasal inhaler, "allergy shots"	Attending MD from camp stated that event appeared more likely an allergy attack or acute altitude sickness; possible pt using salmeterol and albuterol too often, not using 'breathing attachment" **Possible noncompliance**
8	3848699	Domestic	Consumer	13	2002	M	1 puff before exercise *Diskus*	3 years	Pt took 1 puff immed before football practice	Natural causes (per autopsy report), per rpt, one lung weighed more than the other	Lung disorder, ragweed allergy *EIA*	Albuterol	

9	5744503	Domestic	Attorney	9	2002	M	2 puffs BID *Metered-dose inhaler (MDI)*	3 years	Pt had acute asthma attack, ambulance took intubated pt to hospital where he died; pt had been staying at friend's house with cat (cats and possibly dogs listed as triggers)	Respiratory failure due to acute asthma attack (per autopsy)	Asthma triggers include dust, virsus, dogs/cats; pt had 4 acute asthma attacks over past yr--seen in MD office *Asthma*	Fluticasone, albuterol, past use of prednisone	
10	5153922	Domestic	Physician	16	1994	F	2 puffs BID *Unk*	27 days	Pt on vacation sitting near pool and developed sudden onset of SOB; no relief from albuterol or pirbuterol, brief effect from epinephrine autoinjector; pt tried to administer salmeterol, CPR performed, but pt died in hospital	Per MD, possible anaphylaxis due to food allergy because events were unusual for asthma exacerbation	Moderate asthma (no prior hospital-izations) *Asthma*	Theophylline, flunisolide nasal inhaler, albuterol, pirbuterol,"oral steroids" prescribed 2 to 3 weeks previously	In unspecified period before death, pt's asthma had improved such that she didn't need "use of additional B-agonists" and had increased physical exercise
11	5186181	Domestic	Consumer	12	1994	M	2 puffs BID *Unk*	29 days	Pt had asthma exacerbation after gym class; attempted to use metaproterenol inhaler; resuscitation unsuccessful	Acute asthma attack (per autopsy)	Asthma since age 2, several prior hospitaliza-tions due to asthma (no intubations) *Asthma*	Cromoglycate, theophylline, albuterol, beclomethasone dipropionate, triamcinolone acetonide, orciprenaline	

12	5186366	Domestic	Physician	16	1994	M	Unk *Unk*	35 days	Pt found dead at home one morning clutching unidentified inhaler; pt had been vomiting on previous day	Per MD, possible aspiration, viral gastro-enteritis, or overuse of inhaled medications	Mild to moderate asthma w EIA *Asthma and EIA*	Albuterol, cromoglycate	Pt used salmeterol for 5 weeks without difficulty; **per MD, possible misuse (possible overuse)**
13	5197735	Domestic	Physician	13	1994	F	Unk *Unk*	Unk	Pt at sports practice and began feeling sick; driven home by coach; parents drove her to MD office were she went into cardiac arrest	Acute asthma attack	Moderate to severe asthma, father asthmatic, *Asthma*	Albuterol	**Pt "horribly" noncompliant** with medications
14	5209198	Domestic	Physician	15	1995	F	Unk *Unk*	Unk	Pt found gagging at home and clutching an albuterol inhaler; pt to ER in full respiratory arrest, resuscitation unsuccessful	Not stated	Asthma *Asthma*	Albuterol	African American
15	5212796	Domestic	Physician	11	1995	M	2 puffs BID *Unk*	Approx-imately one month	Sudden asthma exacerbation during night; pt taken to ER where attempcts to resuscitate were unsuccessful	Asthma (per autopsy)	Severe asthma since age 5, unspecified allergies *Asthma*	Triamcinolone, cromoglycate, prednisone, cromolyn	African American

16	1607984	Domestic	Physician	15	1995	M	BID (dose unspeci-fied) *Unk*	22 days	Pt had difficulty breathing at home and died (per rpt, pt may have been using inhaler every hour on day of death)	Not stated	Asthma *Asthma*	None	Caucasian; **possible misuse (possible overdose--pt using inhaler ever hour on day of death)**
17	1680201	Domestic	Physician	16	1995	F	2 puffs BID *Unk*	379 days	Pt experienced sudden onset of vomiting, LOC, and died while getting ready for school	Cardiorespira-tory arrest secondary to asthma	Severe asthma w hx of asthma exacerabations requiring hospitalization and parenteral steroid bursts, dermatitis, allergic rhinitis, allergy to mold spores *Asthma*	Triamcinolone acetonide, cromoglycate, pirbuterol acetate	Caucasian
18	1682770	Domestic	Physician	16	1995	F	Unk *Unk*	1 year	Pt experienced asthma exacerbation; intubated in ER and died (pt had asthma exacerbation with trip to ER, 5days previously)	Acute asthma	Severe asthma *Asthma*	Unspecified corticosteroid, albuterol	Hispanic; **pt had poor compliance per MD**; pt had history of frequent exaverations and hospitalization

19	1741494	Domestic	Physician	14	1995	F	2 puffs BID *Unk*	385 days	Pt experienced asthma exacerbation at home (had been in "usual" state of health); transported to hospital where she died after complicated treatment and several episodes of cardiopulmonary resuscitation	Per pathologist, most likely that severe hypoxia led to severe CNS damage and fatal arrhythmias	Moderate asthma since age 1 with asthma exacerbation requiring hospitalization 4 to 5 times per year and frequent steroid bursts, collapsed lung at birth, two episodes of theophylline toxicity, epilepsy in early life, numerous allergies *Asthma*	Theophylline, triamcinolone acetonide, nedocromil, albuterol, orciprenalin	Caucasian; **long history of noncompliance**
20	1727400	Domestic	Physician	12	1995	M	Two "sprays" BID *Unk*	330 days	Pt experienced short-interval asthma attack at home; resuscitation unsuccessful (declared brain dead)	Acute asthma attack	"Very labile" asthma *Asthma*	Theophylline, albuterol, flunisolide, prednisone, prednisolone, unspec allergy medicine	Caucasian; pt reported as having "systemic steroid dependence"
21	1810642	Domestic	Physician	16	1996	M	Unk *Unk*	Unk	Not reported	Not stated	Asthma *Unk*	Albuterol	Very little information provided
22	1903522	Domestic	Physician	16	1996	M	Unk *Unk*	Unk	Pt experienced exacerbation of asthma while playing football; pt treated his asthma with salmeterol	Not stated	Asthma *Asthma*	Not reported	African American; **possible misuse (pt used salmeterol to treat an acute attack)**

23	2060807	Domestic	Physician	12	1997	M	2 puffs BID *Unk*	270 days	Pt experienced asthma exacerbation (treated with albuterol) and respiratory arrest at home; paramedic unable to revive pt; pt suffered pneumothorax, cardiac arrest and became brain death	Asthma, respiratory arrest, brain death due to anoxia	Severe asthma *Asthma*	Flunisolide (nasal inhaler), albuterol, zafirlukast, prednisone	Pt required recent monthly steroid bursts for asthma exacerbations, but no previous hospitalizations for asthma

Attachment #3: All Pediatric Fatalities Associated with Fluticasone and Salmeterol Combination Use as Reported to AERS from Initiation of Marketing up to July 30, 2007 (n=15)

	FDA Case #	Source	Reporter Source	Age	Year	Sex	Dose Strength*Dosage Form*	Time to Onset	Circumstances at Death	Cause of Death	Med history *Indication for Use*	Concomitant Medication	Description
1	6119806	Domestic	Physician	6	1999	M	1 puff BID, 500/50 mcg, *Diskus*	Unk	Not stated	Acute bronchial asthma	Long-term, severe asthma; GERD, atopic dermatitis, allergic rhinitis, *Asthma*	Montelukast, budesonide, certirizine, omeprazole, pimecrolimus	
2	6020753	Domestic	Nurse practit-ioner	12	2006	F	Unk, 100/50 mcg, *Diskus*	Unk	Pt died in ER	Per rpt, exact cause not known, possibly exacerbation of asthma	Not stated *Asthma*	Not stated	
3	5778687	Domestic	Attorney	11	2005	F	Unk, 100/50 mcg, *Diskus*	Unk	Pt used Diskus in pm and had a "strange re-sponse;" next am pt could not breath and was brain dead when ambulance arrived	Unk	Asthma since infancy with frequent trips to ER for exacerbation, *Asthma*	Not stated	

4	6150548	Domestic	Attorney	10	2005	F	1 puff BID, 100/50 mcg, *Metered-dose inhaler (MDI)* (per report)	50 months	Pt had difficulty breathing and was transported to hospital where she died	Asthma (per autopsy)	Asthma for 10 yrs with numerous hospitalizations for asthma flares, polycystic kidney, family history of asthma, numerous allergies/triggers including egg, dust, dander, weather chgs, peanut butter, exercise *Asthma*	Albuterol, montelukast, prednisone	Pt reported as "back to normal" following hospitalization one month before death; pt dose had been increased from 100/50 mcg to 500/50 mcg 16 months before death
5	6148247	Domestic	Attorney	13	2006	M	1 puff BID 250/50 mcg, *Diskus*	32 months	Pt awoke about midnight with chest tightness, unable to breath; he collapsed and was transported to ER in full arrest; pt given CPR and meds; had metabolic acidosis, seizures, cerebral edema, in coma, other complications; paralyzed with mechanical ventilation	Severe asthma exacerbation, anoxic cerebral injury, cerebral edema	Asthma since 3 years of age with intermittent asthma-related complaints (e.g., wheeze, chest pain, cough, congestion), unspec allergies, family hx of asthma, *Asthma*	Albuterol, montelukast	
6	3958621	Domestic	Physician	13	2003	M	Unk, 100/50 mcg, *Diskus*	Unk	Pt experienced cardiac arrest and died while talking on phone	Per sutopsy, changes in lungs consistent with asthma	Not stated *Asthma*	None	Pt had no history or family history of cardiac problems

7	6100611	Domestic	Attorney	14	2003	F	1 puff BID 100/50 mcg, *Diskus*		Not reported, per autopsy report, evidence of defib pads, catheters, NG tube, endotrach tube	Asthma (per autopsy)	Few mild exacerbations (triggers were chg in weather and colds), one year had a "lot" of attacks in middle of night with one possible hospitization, *Asthma*	Albuterol, cephalexin, prednisone	Pt had several occasions were she ran out of asthma medications, **possible noncompliant pt**
8	6332095	Domestic	Attorney	14	2005	M	Unk, 100/50 mcg, *Diskus*	Unk	Pt "suddenly collapsed, falling to the ground;" given CPR and pronounced dead at hospital	Not stated	Not stated *Asthma*	Not stated	
9	3998847	Domestic	Physician	14	2003	M	Unk, 100/50 mcg, *Diskus*	Approx 2 years	Pt had acute asthma attack; at hospital progressed to full cardiac arrest	Not stated	Pt had full respiratory arrest 2 yrs ago, father died of asthma attack, *Asthma*	Not stated	African American
10	6123273	Domestic	Attorney	14	2005	M	1 puff BID, 100/50 mcg, *Diskus*	3 years	Pt had SOB and wheezing and collapsed after playing baseball, taken to ER where he was unresponsive; given CPR and meds, but died due to cardiac/respir arrest	Bronchial asthma (per autopsy)	Mild asthma, iron-deficiency anemia, couple of trips to ER due to asthma, *Asthma*	Albuterol, montelukast	

11	5693969	Domestic	Physician	15	2004	M	1 puff BID, 100/50 mcg, *Diskus*	Approx 40 months	While playing basketball, pt collapsed and was pulseless (no report of respiratory difficulty)	Cardiac arrest (per autopsy)	Not reported, *Asthma*	Montelukast, triamcinolone acetonide, omalizumab	African American, **poor compliance with medication and medical appts**
12	6064859	Domestic	Physician	16	2006	F	1 puff BID, 100/50 mcg, *Diskus*	5 years	Pt awoke at 4 am with dyspnea, cyanosis, and then collapsed; pt died before EMS arrived, resuscitation unsuccessful	Acute asthma exacerbation	None reported, *Asthma*	Budesonide, albuterol, loratadine, Midrin	Pt reported to MD that condition had been worsening
13	4126280	Domestic	Attorney	14	2004	M	Not stated, 100/50 mcg, *Not stated*	13.5 months	Pt had asthma attack and next day had wheezing episode, vomited blood and collapsed; EMT arrived to find pt unresponsive with no pulse; after CPR, pt pronounced dead in hospital	Acute bronchial asthma (per autopsy)	Obese, multiple hospitalizations for asthma, *Asthma*	Albuterol, amoxicillin and clavulanic acid combo, Ocuflox	African American, pt switched from 100/50 to 500/50 strength and back to 100/50, 17 days before death; **poor compliance with Advair**
14	3998849	Domestic	Physician	13	2003	M	1 puff BID, 250/50 mcg, *Not stated*	5 months, 9 days	Pt stayed home from school not feeling well, found in his room unresponsive, pronounced dead by coroner	Asthma (per autopsy);albut-erol level=13 ng/mL (reference: 0.6 to 1.4 ng/mL) 3-5 hours post single inhaler dose	Multiple hospitalizations for asthma exacerbation; *Asthma*	Montelukast, albuterol	Caucasion; **possible overdose of albuterol**

15	6294252	Foreign	Physician	5	2007	F	1 puff BID, 500/50 mcg, *Not stated*	7 months	Pt developed abd pain, vomiting, headache, and imparied consciousness; had seizure upon admission to hospital, pt found to be hyponatremic with cerebral edema	Brain swelling, adrenal glands underweight, no features of asthma in lungs (per autopsy)	Asthma since 18 months, eczema, *Asthma*	Fluticasone propionate (750 mcg BID), sodium cromogycate, theophylline, monmontelukast	Literature report; pt's receiving high daily doses of fluticasone; reporter suspects hyponatremia and cerebral edema related to cortisol deficiency leading to impaired water excretion, pt's brother also affected, but did not die, **fluticasone overdose**

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/s/

Andy Mosholder
10/24/2007 01:37:43 PM
DRUG SAFETY OFFICE REVIEWER

Ann Corken
10/24/2007 01:59:26 PM
DRUG SAFETY OFFICE REVIEWER

Lanh Green
10/24/2007 02:07:44 PM
DRUG SAFETY OFFICE REVIEWER

Ann W McMahon
10/25/2007 09:30:01 AM
DRUG SAFETY OFFICE REVIEWER