

One Year Post Exclusivity Adverse Event Review: Salmeterol

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Salmeterol Outline

- **Background Drug Information**
- **Relevant Safety Labeling and History**
 - **Boxed Warning and SMART Study**
 - **Pulmonary-Allergy Drug Advisory Committee June 2005**
- **Asthma Treatment Guidelines**
- **Current Pediatric Labeling/Pediatric Studies**
- **Drug Use Trends**
- **Pediatric Exclusivity Studies and Labeling Changes**
- **Adverse Events (OSE)**
 - **Since approval**
 - **One-year post exclusivity**
 - **Perspectives from clinical trials**
- **Summary**

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Background Drug Information

- **Drug:** Serevent® (salmeterol xinafoate)
- **Therapeutic Category:** long-acting beta₂-adrenergic agonist
- **Sponsor:** GlaxoSmithKline
- **Original Market Approval:**
 - Metered dose inhaler (MDI): February 4, 1994 [discontinued as part of chlorofluorocarbon phase out]
 - Inhalation powder (diskus): September 19, 1997
 - Combination products: fluticasone/salmeterol
 - Advair Diskus: August 24, 2000
 - Advair HFA: June 8, 2006
- **Pediatric Exclusivity Granted for studies performed with MDI:** Mar 9, 2006

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Background Drug Information

- **Indication:**
 - Maintenance and prevention of asthma ≥ 4 years, including nocturnal asthma
 - “... should only be used as additional therapy for patients not adequately controlled on other asthma-controller medications (e.g., low to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with two maintenance therapies.”
 - Prevention of exercise-induced bronchospasm ≥ 4 years
 - Chronic Obstructive Pulmonary Disease (COPD) in adults
- **Dosage:**
 - Asthma and COPD: 1 inhalation (50 mcg) twice daily approximately 12 hours apart
 - Prevention of exercise induced bronchospasm: 1 inhalation 30 minutes before exercise

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Relevant Safety Labeling: Boxed Warning

WARNING

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

- Class labeling: similar boxed warning on other long acting beta₂ adrenergic agonists (e.g., formoterol)
- Medication Guide: required for each product (including combination products)

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Relevant Safety Labeling

- Contraindications: hypersensitivity to salmeterol or component
- Warning:
 - Watch for signs of worsening asthma
 - Not to treat acute or deteriorating asthma or substitute for corticosteroids
 - Increasing use of short-acting agent is marker of deteriorating asthma
 - Do not use with other long-acting beta-agonist
 - Do not exceed dose
 - Paradoxical bronchospasm
 - Immediate hypersensitivity (urticaria, angioedema, rash and bronchospasm)
 - Use with caution in patients with cardiovascular disorders₆

Salmeterol Multicenter Asthma Research Trial: SMART

Multicenter, randomized, double-blind, placebo controlled study of salmeterol 42 mcg BID (MDI)

Population: patients with asthma, n=26,355, 12 years and older

Duration: 28 weeks

Primary endpoint: combined respiratory related deaths and life-threatening experiences (intubation and/or mechanical ventilation)

Secondary endpoints: asthma-related deaths, life-threatening experiences and all-cause hospitalizations

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Salmeterol Multicenter Asthma Research Trial: SMART

Patient Demographics

Age (y)	Salmeterol	Placebo
1 to 11	5 (<1 %)	3 (<1%)
12 to 18	1648 (12.5%)	1619 (12.3%)
All	13,176	13,179

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Summary of Pediatric Data from SMART study (12 to 18 years of age)

Outcome[1]	Salmeterol (N=1648)	Placebo (N=1619)	Relative Risk[2]	95% LCI	95% UCI
Primary: Combined respiratory-related death or life- threatening experience	2	2	0.9824	0.1386	6.9658
Secondary: Respiratory-related death	1	0			
All cause hospitalization	37	16	2.2718	1.2689	4.0674

- [1] Respiratory-relatedness and relationship to asthma determined by the Mortality and Morbidity Review Committee (MMRC). Life-threatening experiences are defined by the protocol as the occurrence of endotracheal intubation and/or mechanical ventilation.
- [2] The relative risk represents the quotient obtained when the event rate for the salmeterol treatment group is divided by the event rate for the placebo group.

Pulmonary-Allergy Advisory Committee June 2005: Key Issues

- Convened to discuss safety of long-acting beta agonists (LABAs) and signal of severe asthma exacerbation and asthma related death
- Potential adverse event- severe asthma exacerbations
 - not seen during salmeterol clinical developmental program but identified during postmarketing and SMART study
- Results of SMART
 - Boxed warning already incorporated in salmeterol labeling
- Question of class labeling:
 - Although only 12 mcg dose of formoterol was approved for marketing, during phase 3 formoterol clinical trials, increased risk of severe asthma exacerbation (no deaths) with 24 mcg compared with 12 mcg dose
- Salmeterol and formoterol important treatment options and recommended by clinical guidelines

Pulmonary-Allergy Advisory Committee June 2005: Questions and Answers

Based on the currently available information

- Do you agree that salmeterol should be marketed in the United States?

YES: 13 NO: 0

- Should the labeling of formoterol containing product include warnings similar to those in salmeterol?

YES: 12 NO: 0 ABSTAIN: 1

- Do you agree that formoterol should be marketed in the United States?

YES: 13 NO: 0

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National Asthma Education and Prevention Program (NAEPP) Guidelines



<http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm>
(updated August 2007)

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NAEPP 2007 Asthma Treatment Guidelines: Key points re: LABAs

Long acting beta2 agonists or LABAs: salmeterol and formoterol (duration of bronchodilation 12 hours or more after one dose)

- NOT to be used as monotherapy for long-term control (Evidence A)
- Use with inhaled corticosteroids (ICS) for long-term control and prevention of symptoms moderate or severe persistent asthma
 - 12 years and older (Evidence A)
 - 5 to 11 years (Evidence B)

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Current Labeling: Adults and Adolescents (12 years and older)

- **Asthma**

2 randomized, double blind, studies, 50 mcg Diskus (n=149) vs. placebo (n=152) vs. albuterol (n=148) x 12 weeks

- Significant improvement in primary endpoint: pulmonary function (FEV1)
- Significant improvement secondary endpoints (mean AM expiratory flow, mean percent nights without awakening and decrease rescue inhalations)
- Trend towards increased mean % days without asthma symptoms
- Similar asthma exacerbations each group
- No tachyphylaxis

2 randomized, double blind, placebo control trial of 50 mcg Diskus, 42 mcg MDI vs. placebo BID x 12 weeks

- Significant improvement pulmonary function (FEV1) for both active treatments
- No statistical difference between MDI and Diskus

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Current Labeling: Adults and Adolescents (12 years and older)

Concomitant ICS Therapy

Two randomized, double blind, controlled, parallel group clinical trials (n=925, 12 to 78 years), 88 mcg BID fluticasone plus MDI vs. increase to 220 mcg fluticasone BID x 6 months

In salmeterol + fluticasone group

- Significantly greater improvement pulmonary function and asthma symptoms
- Significantly greater reduction in supplemental inhaler use
- Fewer patients experienced asthma exacerbations (8.8% vs. 13.8%)

Exercise Induced Bronchospasm (EIB)

Two randomized, single dose, crossover studies in adults and adolescents (n=53)

- Single 50 mcg dose 30 minutes before exercise prevented EIB
- Protection lasted up to 8.5 hours

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Current Labeling: Ages 4 to 11 years

Asthma

- Randomized, double blind, controlled study children 4 to 11 with asthma (n=449) using 50 mcg Diskus BID x 12 weeks
 - Peak expiratory flow: 36 to 39% post-dose increase from baseline
 - FEV1: 32 to 33% post-dose increase from baseline
- Randomized, double blind, placebo controlled trial (n=207) using MDI
- Two randomized, double blind, controlled clinical trial (n=211) using Diskus 50 mcg BID x 12 weeks with and without ICS
 - Efficacy demonstrated for PEF and FEV1

Exercise Induced Bronchospasm (EIB)

Two randomized studies in children ages 4 to 11 (n=50)

- single 50 mcg dose 30 minutes before exercise prevented EIB
- Protection lasted up to 11.5 hours

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Current Labeling: Safety- Ages 4 to 11 years

- **Safety base: 2,500 patients ages 4 to 11**
 - 346 treated for 1 year
 - includes patients treated during pivotal efficacy trials and 7 additional trials analyzed for safety
- **Pivotal efficacy trials:**
 - two 12-week, controlled studies of salmeterol (n=211) compared with placebo (n=215) and albuterol 200 mcg QID (n=115)
 - No specific safety signals identified; no deaths

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Current Labeling: Safety- Ages 4 to 11 years

Adverse events that occurred higher than placebo and greater than 3%

Adverse Event	Placebo (n=215)	Salmeterol Diskus (n=211)	Albuterol inhalation powder (n=115)
Ear signs & symptoms	3	4	9
Pharyngitis	3	6	3
Headache	14	17	20
Asthma	2	4	<1
Skin rashes	3	4	2
Urticaria	0	3	2

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Drug Use Trends: salmeterol

- Most of the distribution is outpatient (81% sales)¹
- Salmeterol accounted for <5% of the yearly retail prescription volume of inhaled beta-agonists²
- Majority of use in adults and primarily as combination product²
 - Salmeterol
 - Adults: 226,739 (~95%)
 - Children: 8, 658 patients
 - Children <4 years: 0.7% (60 patients)¹
 - Salmeterol/fluticasone
 - Adults: 5 million (~87%)
 - Children: 779,000 patients
 - Children <4 years: <0.5% (4,000 patients)³
- Primary Prescribers²
 - salmeterol: pediatricians (<9%)
 - salmeterol/fluticasone: pediatricians (<3%)
- Most common diagnosis: asthma NOS (ICD-9 493.9)⁴

¹IMS Health, IMS Nationals Sales Perspectives™, Data extracted May 2007

²Verispan, LLC, Vector One® National (VONA), Post Exclusivity Year, data extracted May 2007

³ Verispan Total Patient Tracker, Post Exclusivity Year (2007-745 TPT Serevent and Serevent-Advair age 0-16 xls, detail age.xls)

⁴Verispan Physician Drug and Diagnosis Audit File 2007-745 PDDA combined Age-Diag.xls

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Drug Use Trends: salmeterol

- Dispensed prescriptions from April 2004/March 2005 vs. April 2006/March 2007¹
 - salmeterol declined by 49% in adults (1.9 million to 950,949) & 72% (40,000 to 21,000²) in children
 - salmeterol/fluticasone increased by 9% overall (16.8 to 18.3 million prescriptions)

Dispensed prescriptions decreased pre- and post-exclusivity periods (April 2005/March 2006 to April 2006/March 2007)¹

- salmeterol: decreased in all pediatric age groups (ages 0 to 16 y by 48%)
- salmeterol/fluticasone: declined 21% in ages 0 to 16

¹Verispan, LLC, Vector One® National (VONA), Data extracted May 2007

²Due to small sample size, Verispan recommends caution when trending values below 10,000

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Salmeterol Pediatric Exclusivity Studies

Summaries of Medical and Clinical Pharmacology Reviews
of Pediatric Studies
as of February 22, 2007

Total Number of Drugs with Summaries Posted: 74

Summaries of Medical and Clinical Pharmacology Reviews

Drug	Sponsor	Review Summary	
Rosiglitazone - Avandia	GlaxoSmithKline	Medical	Clinical Pharmacology
Salmeterol - Serevent	GlaxoSmithKline	Medical	None*
Sertraline - Zoloft	Pfizer	Medical	None*

<http://www.fda.gov/cder/pediatric/Summaryreview.htm>

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Pediatric Exclusivity Studies:

Two dose ranging and two safety/efficacy studies

- Study 1: dose-ranging, crossover study of 3 doses salmeterol vs. placebo (n=21, 24 to 47 months)
- Study 2: dose ranging, crossover study of 3 doses salmeterol vs. placebo (n= 21, 6 to 23 months)
- Study 3: 4 week, randomized, double-blind, placebo-controlled safety and efficacy study (n= 338, 24 to 47 months)
- Study 4: 4 week, randomized, double blind, placebo controlled safety and efficacy (n= 167, 6 to 23 months)

All studies double-dummy, drug or placebo administered via holding chamber with facemask (“spacer”)

In addition, *in vitro* data required to confirm drug delivery via a spacer

Note: Studies performed with the MDI, which is no longer marketed

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Pediatric Exclusivity Studies: Efficacy Conclusions

In vitro data

- Not adequate to characterize delivery of salmeterol via valved holding chamber
- Unclear whether children received study medication
- Limited interpretation of clinical findings

Efficacy

- Efficacy data did not establish superiority over placebo
 - No difference between drug and placebo for change from baseline asthma-symptom score
 - No difference in secondary endpoints (peak expiratory flow, asthma symptom-free days, rescue medication use, treatment failures and discontinuations)

Labeling change: none

- Limited interpretation of clinical studies due to *in vitro* issue

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Pediatric Exclusivity Studies: Safety Conclusions

Limited interpretation of safety data due to *in vitro* issue

- No deaths
- AEs more common children 6 to 23 months (n=188) compared with 24 months to < 4 years (n= 359)
- AEs similar to those in adults and adolescents > 12 years
 - Fever most common
 - AEs more frequent in salmeterol group than placebo include infection, irritability, and psychomotor disorders
 - Although tremor noted more frequently in treated group during 1 of the 4 studies at week 4, tremor did not occur in majority of patients and was mild when occurred
 - Nasal findings shifted from normal to abnormal in more treated patients
 - No clinically significant differences in terms of vital signs, laboratory measurements and EKGs (including Holter monitors)

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Summary: salmeterol

- Salmeterol diskus is approved down to 4 years of age based on well-controlled efficacy and safety studies
- Pediatric Exclusivity Studies did not establish efficacy of MDI with valved spacer < 4 years of age
 - Cannot assure medication was delivered without adequate characterization of drug delivery via valved holding chamber, thus clinical relevance of efficacy and safety findings unclear
 - No labeling change based upon exclusivity studies
 - MDI no longer marketed due to CFC phase out
- SMART pediatric data suggests increase in hospitalization for pediatric patients
- Current labeling includes boxed warning for all patients regarding potential fatalities, description of SMART and warnings against use as a single agent or during exacerbations
- MedGuide required for all salmeterol containing products, including combination

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