One Year Post Exclusivity Adverse Event Review:

Salmeterol

Pediatric Advisory Committee Meeting
November 28, 2007

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Food and Drug Administration

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
Background Drug Information

• **Drug:** Serevent® (salmeterol xinafoate)
• **Therapeutic Category:** long-acting beta<sub>2</sub>-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

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
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 us study that compared the safety of salmeterol (SEREVENT® Inhalation Aerosol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176 patients treated for 28 weeks on salmeterol versus 3 deaths out of 13,176 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)

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 disorders
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

Patient Demographics

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Salmeterol</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 to 11</td>
<td>5 (&lt;1%)</td>
<td>3 (&lt;1%)</td>
</tr>
<tr>
<td>12 to 18</td>
<td>1648 (12.5%)</td>
<td>1619 (12.3%)</td>
</tr>
<tr>
<td>All</td>
<td>13,176</td>
<td>13,179</td>
</tr>
</tbody>
</table>
Summary of Pediatric Data from SMART study (12 to 18 years of age)

<table>
<thead>
<tr>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary: Combined respiratory-related death or life-threatening experience</td>
<td>2</td>
<td>2</td>
<td>0.9824</td>
<td>0.1386</td>
<td>6.9658</td>
</tr>
<tr>
<td>Secondary: Respiratory-related death</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All cause hospitalization</td>
<td>37</td>
<td>16</td>
<td>2.2718</td>
<td>1.2689</td>
<td>4.0674</td>
</tr>
</tbody>
</table>

[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

[Image of book cover]

http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm

(updated August 2007)
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)

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
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

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
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

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo (n=215)</th>
<th>Salmeterol Diskus (n=211)</th>
<th>Albuterol inhalation powder (n=115)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ear signs &amp; symptoms</td>
<td>3</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>3</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Headache</td>
<td>14</td>
<td>17</td>
<td>20</td>
</tr>
<tr>
<td>Asthma</td>
<td>2</td>
<td>4</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Skin rashes</td>
<td>3</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Urticaria</td>
<td>0</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>
**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-agonists\(^2\)
- Majority of use in adults and primarily as combination product\(^2\)
  - 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 Prescribers\(^2\)
  - salmeterol: pediatricians (<9%)
  - salmeterol/fluticasone: pediatricians (<3%)
- Most common diagnosis: asthma NOS (ICD-9 493.9)\(^4\)

\(^1\)IMS Health, IMS Nationals Sales Perspectives\(^\text{TM}\), Data extracted May 2007
\(^2\)Verispan, LLC, Vector One\(^\text{®}\) 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 xlsx, detail age.xlsx)
\(^4\)Verispan Physician Drug and Diagnosis Audit File 2007-745 PDDA combined Age-Diag.xlsx

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**Drug Use Trends: salmeterol**

- Dispensed prescriptions from April 2004/March 2005 vs. April 2006/March 2007\(^1\)
  - salmeterol declined by 49% in adults (1.9 million to 950,949) & 72% (40,000 to 21,000)\(^2\) 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

\(^1\)Verispan, LLC, Vector One\(^\text{®}\) National (VONA), Data extracted May 2007
\(^2\)Due to small sample size, Verispan recommends caution when trending values below 10,000
Salmeterol Pediatric Exclusivity Studies

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
**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)
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

Acknowledgements

OSE
Lanh Green
Ann Corkey-Mackey
Ann McMahon
David Moeny
Solomon Iyasu
Andrew Mosholder
PMHS
Lisa Mathis
Denise Pico-Branco

DPAP
Sally Seymour
Peter Starke
OPT
Judith Cope
BJ Gould
Dianne Murphy
Jean Temeck