Pediatric Focused Safety Review: Advair HFA Inhalation Aerosol (fluticasone propionate/salmeterol xinafoate) Pediatric Advisory Committee Meeting March 24, 2015

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Outline

- Background Drug Information
- Relevant Labeling
- Drug Use Trends
- Adverse Events
- Summary and Conclusions
- Questions for Committee
Background Drug Information

- **Drug Name (active Ingredient):** Advair HFA (NDA 21,254; fluticasone propionate/salmeterol xinafoate)

- **Therapeutic Category:** Corticosteroid and Long-Acting Beta Agonist (LABA)

- **Original Market Approval:** June 8, 2006

- **Available Dosage Forms:** Inhalation Aerosol (HFA) and Diskus powder inhaler (NDA 21,077)

- **Sponsor:** GlaxoSmithKline

- **Approved Indications:** Treatment of asthma
  - HFA: 12 years and older
  - Diskus: 4 years and older

- Maintenance treatment in airflow obstruction and reducing exacerbations in adults with chronic obstructive pulmonary disease (COPD)

- **Limitation of Use:** Not indicated for the relief of acute bronchospasm
Required Pediatric Studies for Advair HFA

- Two studies were required in pediatric patients from 4 to 12 years of age:
  - To evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of Advair HFA 45/21 (Advair 45/21)
  - To evaluate for safety and tolerability of Advair 45/21 in this age group
- Outcome
  - No new safety signals were observed
  - Indication not extended to children younger than 12 years
- Pediatric labeling change: December 19, 2012
Pediatric Labeling Changes

8.4 Pediatric Use

- Safety and efficacy in pediatric patients 12 to 17 years was demonstrated in 38 patients. No difference in type or frequency of adverse event compared to adults.

- Efficacy not established in patients younger than 12 years. In a 12-week, active-control study of 350 pediatric patients, 4 to 11 years old, with persistent asthma on inhaled corticosteroids, safety was similar to adolescents and to adults.
LABA Safety Issue

- Serious asthma outcomes – hospitalizations, intubation, death
  - Serevent Nationwide Surveillance Study (SNS)
  - Salmeterol Multicenter Asthma Research Trial (SMART)
  - Meta-analysis
    - potential increased risk of asthma-related hospitalization in pediatric patients

- Long regulatory history spanning 20 years
  - Boxed Warning, REMS, multiple Advisory Committee meetings

- FDA required large safety trials to evaluate risk of LABA when added to ICS - ongoing
Ongoing Required Safety Trials
Adults and Adolescents

- Four randomized, double-blind, 26 week trials
  - Advair Diskus, Dulera, Foradil Aerolizer, Symbicort
- 11,700 patients 12 years and older with asthma per trial
  - 10% patients 12-17 years of age
- ICS/LABA vs. ICS
- Serious asthma outcomes
  - hospitalizations, intubation, death
- Non-inferiority design
  - 90% power to rule out 2 fold increase in event rate
- Required final report submission June 2017
  - projected submission date for Advair Diskus trial 1st quarter 2016
Ongoing Required Safety Trial
Pediatrics

• One randomized, double-blind, 26 week trial
  – Advair Diskus
• 6200 patients 4 to 11 years with asthma
• ICS/LABA vs. ICS
• Serious asthma outcomes
  – hospitalizations, intubation, death
• Non-inferiority design
  – 90% power to rule out 2.7 fold increase in event rate
• Required final report submission June 2017
  – projected submission date 1st quarter 2017
Relevant LABA Pediatric Class Labeling

• **Boxed Warning**
  - LABA increase the risk of asthma-related death
  - prescribe ICS/LABA for patients not adequately controlled on long term asthma control medications
  - available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients
  - for pediatric patients who require addition of a LABA to an ICS, a fixed dose combination product (ICS/LABA) should be used to ensure adherence with both drugs (single ingredient LABA product labels)

• **Contraindication**
  - use of LABA without concomitant asthma control medication (ICS) is contraindicated (single ingredient LABA product labels)
Relevant Safety Labeling
Boxed Warning

WARNING: ASTHMA-RELATED DEATH

Long-acting beta₂-adrenergic agonists (LABA), such as salmeterol, one of the active ingredients in ADVAIR® HFA Inhalation Aerosol, increase the risk of asthma-related death. Data from a large placebo-controlled US trial that compared the safety of salmeterol with placebo added to usual asthma therapy showed an increase in asthma-related deaths in subjects receiving salmeterol (13 deaths out of 13,176 subjects treated for 28 weeks on salmeterol versus 3 deaths out of 13,179 subjects on placebo). Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients.

Therefore, when treating patients with asthma, physicians should only prescribe ADVAIR HFA for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid, or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and a LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue ADVAIR HFA) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use ADVAIR HFA for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids [see Warnings and Precautions (5.1)].
Relevant Safety Labeling

5 Warnings and Precautions

5.1 Asthma-Related Death
5.2 Deterioration of disease and acute episodes
5.3 Excessive use of Advair HFA and use with other LABA’s
5.4 Local effects of ICS
5.5 Pneumonia
5.6 Immunosuppression
5.7 Transferring patients from systemic corticosteroid therapy
5.8 Hypercortisolism
5.9 Drug interactions with strong cytochrome P450 3A4 inhibitors (e.g., clarithromycin)
5.10 Paradoxical bronchospasm and upper airway symptoms
5.11 Immediate hypersensitivity reactions
5.12 Cardiovascular (CV) and central nervous system (CNS) effects
5.13 Reduction in bone mineral density (BMD)
5.14 Effect on growth
5.15 Glaucoma and cataracts
5.16 Eosinophilic conditions and Churg-Strauss syndrome
5.17 Coexisting conditions
5.18 Hypokalemia and hyperglycemia
# Pediatric Drug Utilization

National estimates of *patients* by age who received dispensed prescriptions for Advair® Diskus® and Advair® HFA from U.S. outpatient retail pharmacies

<table>
<thead>
<tr>
<th></th>
<th>Year 2013</th>
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<tbody>
<tr>
<td></td>
<td>Patients (N)</td>
<td>% Share</td>
<td>Patients (N)</td>
<td>% Share</td>
</tr>
<tr>
<td><strong>Advair® Diskus®</strong></td>
<td></td>
<td></td>
<td><strong>Advair® HFA</strong></td>
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<tr>
<td>0-16 years</td>
<td>215,519</td>
<td>5.88%</td>
<td>0-16 years</td>
<td>107,364</td>
</tr>
<tr>
<td>0-3 years</td>
<td>731</td>
<td>0.34%</td>
<td>0-3 years</td>
<td>6,842</td>
</tr>
<tr>
<td>4-11 years</td>
<td>92,710</td>
<td>43.02%</td>
<td>4-11 years</td>
<td>71,330</td>
</tr>
<tr>
<td>12-16 years</td>
<td>128,495</td>
<td>59.62%</td>
<td>12-16 years</td>
<td>33,032</td>
</tr>
<tr>
<td>17+ years</td>
<td>3,455,487</td>
<td>94.23%</td>
<td>17+ years</td>
<td>232,208</td>
</tr>
<tr>
<td>Unknown Age</td>
<td>954</td>
<td>0.03%</td>
<td>Unknown Age</td>
<td>106</td>
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*Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0 - 16 years includes patients aged 16 years and 11 months.*

**Summing patients across patient age bands is not advisable and will result in double counting and overestimates of patient counts.
Pediatric Drug Utilization

National estimates of *pediatric patients (0-16 years)* by age who received dispensed prescriptions for Advair® Diskus® and Advair® HFA

Top prescriber specialties

National estimates of prescriptions dispensed for Advair® Diskus® and Advair® HFA from U.S. outpatient retail pharmacies

Pediatric diagnoses associated with drug use

Diagnoses associated with the use of Advair® Diskus® and Advair® HFA, stratified by patient age, as reported from U.S. office-based physician surveys, January 2010 through June 2014 (cumulative)

- Asthma (ICD-9 493.9) was the top diagnosis across all pediatric ages
  - Advair® Diskus®
    - 0-3 years*: 100% of drug uses
    - 4-11 years*: 89% of drug uses
    - 12-16 years*: 86% of drug uses
  - Advair® HFA
    - 0-3 years*: 100% of drug uses
    - 4-11 years*: 88% of drug uses
    - 12-16 years*: 95% of drug uses

*Drug use mentions <100,000 are small for reliable national estimates of use by diagnoses. These mentions indicate that a given drug was mentioned during an office visit, but do not necessarily result in a prescription being generated.

### Total Adult and Pediatric FAERS Reports* with Advair (January 1, 2010 through June 30, 2014)

<table>
<thead>
<tr>
<th></th>
<th>All reports (US)</th>
<th>Serious† (US)</th>
<th>Death (US)</th>
</tr>
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<tbody>
<tr>
<td><strong>Adults (≥ 17 yrs.)</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>January 1, 2010 – June 30, 2014</td>
<td>7378 (6838)</td>
<td>4206 (3671)</td>
<td>578 (555)</td>
</tr>
<tr>
<td><strong>Pediatrics (0- &lt; 17 yrs.)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>January 1, 2010 – June 30, 2014</td>
<td>245 (203)</td>
<td>143 (101)</td>
<td>11 (9) §</td>
</tr>
</tbody>
</table>

* May include duplicates and transplacental exposures, and have not been assessed for causality
† Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events.
§ No additional cases of pediatric deaths were identified among cases not reporting an age.
Serious Pediatric Cases with Advair

- Pediatric reports with a serious outcome (n=143)
  - Pediatric reports with the outcome of death (n=11)

Excluded Reports (n=15) (Including 1 death)
- Duplicates (n=11)
- Transplacental exposure (n = 4)

Pediatric Case Series (n=128) (Including 10 deaths)
Safety Report Overview

- Serious adverse event reports: 128
- Deaths: 10
- Non-fatal unlabeled: 20
- Non-fatal labeled: 98
Pediatric Reports Associated with Death (n=10)

- Labeled (n=9)
  - Asthma related (n=8)
  - Adrenal crisis (n=1)
- Closely Related to Labeling (n=1)
  - Pulmonary mycosis (n=1)

Related terms in labeling: pneumonia (5.5), candida albicans (5.4), immuno suppression and potential worsening of infections (5.6) (e.g., existing tuberculosis; fungal, bacterial, viral, or parasitic infection; ocular herpes simplex).
Asthma-related death reports (n=8)

- Patient ages: 9 to 13 years of age (4 male/4 female)
- All patients experienced sudden onset of severe asthma which directly contributed to the death.
- One case in a 10-year old female was associated with medication overuse of up to 11 doses of fluticasone propionate/salmeterol xinafoate/day.
- Three cases confounded by concomitant use of both montelukast and albuterol. One additional case was confounded by use of albuterol.
Non-asthma-related death reports (n=2)

- **Adrenal crisis (1):** A 7-year-old female with asthma received fluticasone propionate/salmeterol xinafoate (25/125mcg HFA, two puffs) twice daily; the dose was reduced from 25/250 mcg HFA, BID, two weeks earlier. Two weeks later she developed gastroenteritis with electrolyte decompensation and died from brain edema with herniation and grand mal status. “The acute course of disease could be explained by adrenal crisis (Addison crisis)”, triggered by acute gastrointestinal infection.

- **Pulmonary mycosis (1):** A 10-year-old male received fluticasone propionate/salmeterol xinafoate (Advair) (unknown inhaler device, start date, dosing, and indication), experienced pulmonary mycosis and died. No additional information was reported.
Reports with Non-fatal Unlabeled Serious Outcomes (n = 20)

- Suicidal ideation (n=2)
- Tourette disorder (TD) (n=2)
- Circulatory collapse (n=2)*
- Papilledema (n=1)
- Benign intracranial hypertension (BIH) (n=1)
- Cheilitis granulomatosa (CG) (n=1)

*Possible relationship to labeled events
Suicidal/homicidal ideation (n=2)

- An 11-year-old female treated with montelukast and fluticasone propionate/salmeterol xinafoate (100/50mcg, one puff two times a day) experienced suicidal and homicidal ideation, and “mental disorder”. Montelukast is labeled for suicidal ideation.

- An 11-year-old male with asthma took fluticasone propionate/salmeterol xinafoate (250/50 mcg) inhaler for 4 months. Sometime during treatment he experienced multiple symptoms including suicidal ideation and attempt. Other reported symptoms included anger, ‘hypersensibility’, nightmares, depression, irritability, tic, disruptive behavior, moodiness, and mental deterioration. Fluticasone propionate/salmeterol xinafoate was discontinued and the outcome is unknown. Insufficient clinical information to assess causality.
Tourette Disorder (TD) (n=2)

- A 6-year-old male experienced TD “immediately” after starting fluticasone propionate/salmeterol xinafoate 45/21 mcg (inhaled) at 2 puffs BID. He also experienced brain disorder, repeating words, cardiac pain, increased tics, change in behavior, head and arm tremors, and “off-label use” (younger than 12 years). The events resolved when drug was discontinued and reappeared on re-exposure. The events resolved at a later date.
Tourette Disorder (TD) (n=2) (continued)

- A 9-year-old male with asthma, upper respiratory tract infection, and an “ill-defined disorder” (not otherwise specified) received fluticasone propionate/salmeterol xinafoate, montelukast, cromolyn, mometasone furoate, cetirizine hydrochloride, azithromycin, and caffeine experienced TD, obsessive-compulsive disorder, sensation of foreign body, hallucination, gastroesophageal reflux disease, panic attack, dysphagia, insomnia, tic, throat tightness, tachycardia, pruritus, postnasal drip, upper respiratory tract infection, nightmare, anxiety, fear, dyspnea, depressed mood, and aptyalism. Additional clinical information is unavailable.

  - Both cases suggest possible exacerbation of pre-existing disorder with inadequate data to establish causal link to fluticasone propionate/salmeterol xinafoate.

  - Tics, possibly related to TD, are labeled. (Warnings and Precautions, 5.12).
Circulatory Collapse (n=2)

- A 16-year-old female received fluticasone propionate/salmeterol xinafoate (Advair) for an unreported condition, and experienced “collapse with unknown cause” with drug maladministration (dose ‘doubled’ x 1 day for ‘a cold’). Other symptoms included laryngitis, hoarseness, headache, nausea, cough, throat irritation, stomach pain, and upper respiratory infection. She was treated with antibiotics and fluticasone propionate/salmeterol xinafoate was discontinued. The outcome is unknown.
  - Cardiovascular events are labeled (Overdose, section 10).
Circulatory Collapse (n=2) (continued)

- A 16-year-old female received fluticasone propionate/salmeterol xinafoate inhaler over a period of 2 weeks for exercise induced asthma. Approximately 2 days later, she experienced collapse, dizziness, vomiting, pallor, nausea, skin cold to touch, weakness, and later developed chest palpitations, fatigue and leg muscle tightness. Concurrent medical conditions included ferritin low and low iron level. Concurrent medications included levosalbutamol and co-trimoxazole*. The events persisted when fluticasone propionate/salmeterol xinafoate was discontinued.

  - Sulfamethoxazole (a component of co-trimoxazole) is a cytochrome P450 inhibitor which increases risk of cardiovascular effects of fluticasone propionate/salmeterol xinafoate (Warnings and Precautions, section 5.9).
Papilledema (n=1) and BIH (n=1)

- A 12-year-old female received fluticasone propionate/salmeterol xinafoate 100/50 mcg and albuterol for asthma, and on an unknown date she experienced progressive decreased vision because of papilledema. Fluticasone propionate/salmeterol xinafoate was continued and the events were unresolved (papilledema) and worsening (decrease of vision) at the time of report. Temporal relationship was not reported.
  - Visual disturbance, glaucoma, increased intraocular pressure, and cataracts are labeled with long term administration of inhaled corticosteroids.
Papilledema (n=1) and BIH (n=1) (continued)

- A 13-year-old male started fluticasone propionate/salmeterol xinafoate (125/25 mcg BID) for asthma. Concurrent medications included methylphenidate hydrochloride. At an unreported date, he developed pseudotumor cerebri, headache, and vision disturbance. He was hospitalized and the events were unresolved at the time of the report. Additional clinical information was not provided.

  - Systemic corticosteroids (e.g., methylprednisolone) are labeled for BIH (aka: pseudotumor cerebri). A PubMed literature review performed for this presentation using the terms BIH, pseudo tumor cerebri, and papilledema found 1 citation (only) of BIH reported on withdrawal of ICS in a patient with recent head trauma.*

Cheilitis granulomatosa (CG) (n=1)

- An 11-year-old male received fluticasone propionate/salmeterol xinafoate HFA inhaler (25/125 mcg, 1 to 2 times daily) for 5 years for ‘postinfectious’ asthma and ‘endocrine disorder’ when he developed CG under his lip. His medical history includes clotting disorder, dwarfism, food intolerances, and possible food allergy. Treatment with fluticasone propionate/salmeterol xinafoate was discontinued and he was treated with Fucicort (fusidic acid/betamethasone valerate). The events were unresolved at the time of the report.

  CG is an idiopathic, non-caseating granulomatous inflammation of the lips, unrelated to systemic granulomatous disease.* Treatment may not be necessary but may include dietary modification (elimination of topical allergens), antibiotics, systemic or intra-lesional-steroid injection. Since perioral disease may herald systemic disease, a comprehensive assessment for systemic disease is required to exclude other diagnoses.

- There is insufficient data to establish a causal link CG to fluticasone propionate/salmeterol xinafoate in this patient.

Reports with Non-fatal Unlabeled Serious Outcomes (n = 20, continued)

- **Streptococcal pharyngitis (SP) (n=2)**
  - Pharyngitis and bacterial infections are labeled
  - SP is a common pediatric infection
  - Uncontrolled data from postmarket reports cannot be used to assess occurrence or causality of common events

- **Stevens-Johnson Syndrome (SJS) (n=1)**
  - Confounded by co-administration of paracetamol and montelukast which are labeled for SJS

- **Pulmonary veno-occlusive disorder (PVOD) (n=1)**
  - Patient had pre-existing PVOD for which fluticasone propionate/salmeterol xinafoate was prescribed

- **General crisis, NOS (n=1)**
  - Insufficient clinical information

- **Product quality issue, NOS (n=1)**
  - Insufficient clinical information

- **Gait disturbance (n=1)**
  - Insufficient clinical information

- **Esophageal burn, NOS (n=1)**
  - Insufficient clinical information

- **Intentional misuse (n=1)**
  - Insufficient clinical information

- **Drug ineffective (n=2)**
  - Insufficient clinical information

NOS: Not otherwise specified
Reports with Non-fatal Outcomes
Labeled/Closely Related* to Labeled Terms (n=98)
{2 or more reports received}

- Box Warning /5.1 Asthma-Related Death /5.2 Deterioration of Disease and Acute Episodes
  - Asthma/bronchospasm/choking/dyspnea/stridor/wheezing/acute respiratory failure*/asphyxia*/respiratory distress* (n=36)
- 5.7 Transferring Patients from Systemic Corticosteroid Therapy /5.8 Hypercorticism and Adrenal Suppression
  - Adrenal gland disorder (n=13)
- Immune system disorders (n=13)
  - Hypersensitivity (n=8)/Angioedema (n=1)/Eyelid edema (n=1)/Hives (n=1)/Lip swelling(n=1)/Urticaria (n=1)

No trend toward increased frequency or severity of labeled events.
Reports with Non-fatal Outcomes
Labeled/Closely Related* to Labeled Terms (n=98)
{2 or more reports received, continued}

- 5.5 Pneumonia/6 Adverse Reactions/6.2 Postmarketing Experience
  - Pneumonia/Upper respiratory tract infection (n=9)
- 5.12 Cardiovascular and Central Nervous System Effects
  - Seizure/convulsion (n=5)
  - Cardiac disorders (n=4)
- 5.15 Glaucoma and Cataracts
  - Cataract (n=2)
- 6.2 Postmarketing experience
  - Aggression (n=3)
- Overdose/Overdosage (n=5)

No trend toward increased frequency or severity of labeled events.
Summary

All 10 death reports are associated with terms that are labeled or closely related to labeled terms.

No new safety signals were identified

Pediatric studies are underway to investigate LABA safety issue include LABA-ICS products, including Advair

FDA recommends continued routine postmarket monitoring.

Does the Committee agree?
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