

One Year Post Exclusivity Adverse Event Review: Budesonide & Fluticasone

**Pediatric Advisory Committee Meeting
September 15, 2004**

**Joyce Weaver, PharmD, BCPS
Postmarketing Safety Evaluator
Division of Drug Risk Evaluation
Center for Drug Evaluation and Research
Food and Drug Administration**



Budesonide

Drug Use Trends in Outpatient Settings: Budesonide

- The total number of prescriptions dispensed for all budesonide products increased from approximately 6.0 million in 2001 to 7.8 million in 2003.¹
- Pediatric patients (ages 1–16 years) accounted for approximately 29.1% of total U.S. prescriptions of budesonide products dispensed in 2003 (2.3 million).^{1,2*}
- In 2003, Rhinocort/Rhinocort Aqua was the fourth most commonly dispensed steroid nasal inhalant and the most commonly used budesonide product, accounting for 58.6% (~4.5 million) of budesonide prescriptions. Of these, 17.2% (~774,000) prescriptions were dispensed to pediatric patients.^{1,2*}

IMS Health, National Prescription Audit *Plus?* , On-Line, Dec 2000 – Nov 2003, Data Extracted Feb 2004

AdvancePCS? Dimension Rx, On-Line, Dec 2000 – Nov 2003, Data Extracted Feb 2004

*Calculation based on application of proportions of pediatric budesonide prescriptions in AdvancePCS? to IMS Health, National Prescription Audit *Plus?* to estimate number of budesonide prescriptions dispensed nationwide to pediatric population.

Drug Use Trends in Outpatient Settings: Budesonide

- Pulmicort represented 39.6% (~3.1 million) of budesonide prescriptions in 2003. Of these 3.1 million prescriptions, 58% were dispensed to pediatric patients. ^{1,2*}
- Entocort represented 1.8% (141,000) of budesonide prescriptions in 2003. Of these 141,000 prescriptions, 3.9% were dispensed to pediatric patients. ^{1,2*}

IMS Health, National Prescription Audit *Plus?*, On-Line, Dec 2000 – Nov 2003, Data Extracted Feb 2004

AdvancePCS? Dimension Rx, On-Line, Dec 2000 – Nov 2003, Data Extracted Feb 2004

*Calculation based on application of proportions of pediatric budesonide prescriptions in AdvancePCS? to IMS Health, National Prescription Audit *Plus?* to estimate number of budesonide prescriptions dispensed nationwide to pediatric population.

Adverse Event Reports: Budesonide

- From Marketing Approval (2/14/94 – 12/12/03):
 - Total number of reports, all ages:
 - 2845 reports (1284 US)
- From One-year Post Exclusivity (11/12/02 – 12/12/03):
 - Total number of reports, all ages:
 - 157 (68 US)
 - 100 serious (26 US)
 - Pediatric reports:
 - 38 (24 US)
 - 22 serious (7 US)
 - 1 death (US)

Pediatric Adverse Events: Budesonide

11/12/02 – 12/12/03

(n=38)

- Gender

– Female	13
– Male	22
– Unknown	3

- Age

– 0 - <1 mo.	2
– 1 mo. - <2 yrs	7
– 2 - 5 yrs	15
– 6 - 11 yrs	7
– 12 - 16 yrs	7

- Products*

– Pulmicort	27
– Rhinocort	5
– Entocort	1
– Unspecified product	5

*in some cases product used was non-US brand

Pediatric Adverse Events*: Budesonide (*n*=38)

- **Convulsions-6**
- **Asthma Nos-5**
- **Growth retardation-4**
- **Blood Cortisol Decreased-3**
- **Condition Aggravated-3**
- **Adrenal Suppression-2**
- **Anaphylactic Reaction-2**
- **Cataract Bilateral Nos-2**
- **Cushing's Syndrome-2**
- **Cushingoid-2**

*Each case can have an unlimited number of events

Pediatric Adverse Events: Budesonide

11/12/02 – 12/12/03

- Relationship of seizures (6) to budesonide not clear
 - 1 case confounded by use of theophylline
 - 2 cases not confirmed by health care professional; seizures not well described
 - 1 patient received CNS radiotherapy, stem cell transplantation, concomitant use of drug labeled for seizures
 - 1 case temporally related, no known confounding
 - 1 case of seizure a/w adrenal suppression

Pediatric Adverse Events: Budesonide

11/12/02 – 12/12/03

- Systemic steroid effects (*n=17*)
 - Growth retardation-4
 - Blood Cortisol Decreased-3
 - Adrenal Suppression-2
 - Cataract Bilateral Nos-2
 - Cushing's Syndrome-2
 - Cushingoid-2
 - Pituitary-Dependent Cushing's Syndrome-2
 - Diabetes, hyperglycemia, hypertension, pancreatitis
(1 case each)

Pediatric Adverse Events: Death

- *US case.* A 3-year-old girl who had received Pulmicort Respules for 3 months at an unknown dose for an unknown indication stopped breathing and was transported to an emergency room. The patient was receiving albuterol, cetirizine, cefdinir, and loratadine, and 2 other unknown medications concomitantly. The patient died in the emergency room. An autopsy showed mild pulmonary edema, congestion, and intra-alveolar hemorrhage, but the autopsy did not establish the cause of death.

Conclusions on Pediatric Adverse Events: Budesonide

11/12/02 – 12/12/03

- Most events, including systemic steroid effects, are included in labeling
- Convulsions not labeled, unclear relationship to budesonide

Fluticasone

Drug Use Trends in Outpatient Settings: Fluticasone Topical Ointment/Cream

- The total number of prescriptions dispensed for fluticasone topical ointment/cream in the U.S. have decreased by 17.5% in the past 2 years (3/02 to 2/04), from 1.2 million in 2002 to 990,000 in 2004.¹
- In the outpatient setting, children and adolescents have accounted for ~ 34% of all fluticasone topical ointment/cream prescriptions over the past two years (3/02-2/04)²

¹IMS Health, National Prescription Audit Plus? , On-Line, Mar 2001 – Feb 2004, Data Extracted Jul 2004

²AdvancePCS? Dimension Rx, On-Line, Mar 2001 – Feb 2004, Data Extracted Jul 2004

Drug Use Trends in Outpatient Settings: Fluticasone Nasal Spray

- The total number of prescriptions dispensed for fluticasone nasal spray in the U.S. have remained fairly consistent during the past 2 years (3/02 to 2/04), from 13.4 million in 2002 to 15.3 million in 2003.¹
- Top three prescribers in 2003 were: family practice, internal medicine, and osteopathic medicine.¹

Drug Use Trends in Outpatient Settings: Fluticasone Nasal Spray

- In the outpatient setting, children and adolescents have accounted for approximately 9% of all fluticasone nasal spray prescriptions over the past two years (3/02-2/04)²
 - 1.2 million prescriptions (9 %) (March 2002-February 2003) ^{1,2*}
 - 1.4 million prescriptions (9%) (March 2003-February 2004)^{1,2*}
- The most common diagnosis associated with the mention of fluticasone nasal spray was seasonal allergic rhinitis in patients 0-16 years.³

¹IMS Health, National Prescription Audit *Plus?* , On-Line, Mar 2001 – Feb 2004, Data Extracted May 2004

²AdvancePCS? Dimension Rx, On-Line, Mar 2001 – Feb 2004, Data Extracted May 2004

³IMS Health, National Disease and Therapeutic Index? , CD-Rom, Mar 2001- Feb 2004, Data Extracted May 2004

*Calculation based on application of proportions of pediatric fluticasone prescription claims in AdvancePCS? to total number of prescriptions dispensed in IMS Health, National Prescription Audit *Plus?* to estimate number of fluticasone prescriptions dispensed nationwide to pediatric population.

Drug Use Trends in Outpatient Settings: Fluticasone Oral Inhaler

- The total number of prescriptions dispensed for fluticasone oral inhaler in the U.S. have decreased during the past 2 years (3/02 to 2/04), from 7.9 million in 2002 to 6.9 million in 2003.¹
- Top three prescribers in 2003 were: internal medicine, family practice, and pediatrics.¹

¹IMS Health, National Prescription Audit *Plus?* , On-Line, Mar 2001 – Feb 2004, Data Extracted May 2004

Drug Use Trends in Outpatient Settings: Fluticasone Oral Inhaler

- In the outpatient setting, children and adolescents have accounted for over 24% of all fluticasone oral inhaler prescriptions over the past two years (3/02-2/04)²
 - 1.9 million prescriptions (24%) (March 2002-February 2003)^{1,2*}
 - 1.9 million prescriptions (28%) (March 2003-February 2004)^{1,2*}
- The most common diagnosis associated with the mention of fluticasone oral inhaler was bronchial asthma.³

¹IMS Health, National Prescription Audit *Plus?*, On-Line, Mar 2001 – Feb 2004, Data Extracted May 2004

²AdvancePCS? Dimension Rx, On-Line, Mar 2001 – Feb 2004, Data Extracted May 2004

³IMS Health, National Disease and Therapeutic Index?, CD-Rom, Mar 2001- Feb 2004, Data Extracted May 2004

*Calculation based on application of proportions of pediatric fluticasone prescription claims in AdvancePCS? to total number of prescriptions dispensed in IMS Health, National Prescription Audit *Plus?* to estimate number of fluticasone prescriptions dispensed nationwide to pediatric population.

Drug Use Trends in Outpatient Settings: Advair

(fluticasone & salmeterol combination)

- Prescriptions dispensed rose from 3.7 million in 2001 to 15.5 million in 2003¹
- Advair accounted for 17% of orally inhaled steroid Rx in 2001 and 54% in 2003¹
- Age 2-16 ~ 13% of total claims^{1,2*}

¹IMS Health, National Prescription Audit *Plus?*, On-Line, Mar 2001 – Feb 2004, Data Extracted May 2004

²AdvancePCS? Dimension Rx, On-Line, Mar 2001 – Feb 2004, Data Extracted May 2004

*Calculation based on application of proportions of pediatric desloratadine prescriptions in AdvancePCS? to IMS Health, National Prescription Audit *Plus?* to estimate number of desloratadine prescriptions dispensed nationwide to pediatric population

Adverse Event Reports: Fluticasone

- From Marketing Approval (10/19/94 – 3/25/04)
 - Total number of reports, all ages:
 - 4651 reports (3550 US)
- From One-Year Post Exclusivity (2/25/03 – 3/25/03)
 - Total number of reports, all ages:
 - 2093 reports (1904 US)
 - 1240 serious (331 US)
 - Pediatric Reports:
 - 128 reports (105 US)
 - 29 serious (16 US)
 - 5 death (4 US)

Pediatric Adverse Events: Fluticasone

2/25/03 – 3/25/04

(*n*=128)

- **Gender**

– Female	59
– Male	67
– Unknown	2

- **Age**

– 0 - <1 mo.	0
– 1 mo. - <2 yrs	1
– 2 - 5 yrs	26
– 6-11 yrs	68
– 12-16 yrs	32

- **Products**

– Inhaled fluticasone	22
– Nasal	24
– Inhaled fluticasone in combination /w salmeterol	82

Pediatric Adverse Events: Fluticasone (*n=128*)

- Asthma—15
- Vomiting—11
- Dyspnoea—9
- Drug Ineffective—8
- Pharmaceutical Product Complaint—8
- Condition aggravated—6
- Cough—6
- Pyrexia—6
- Nausea—5
- Cardiac Arrest—4
- Growth Retardation—4
- Headache—4
- Loss of Consciousness—4
- Rash—4
- Weight Increased—4

Issues from Pediatric Adverse Events: Fluticasone *2/25/03 – 3/25/04*

- Systemic steroid effects
 - 12 cases (1 death)
- Worsening asthma symptoms with Advair:
 - 22 cases (4 deaths)

Issues from Pediatric Adverse Events: Fluticasone *2/25/03 – 3/25/04*

- Systemic steroid effects
 - 12 cases (1 death)
- **Worsening asthma symptoms with Advair:**
 - 22 cases (4 deaths)

Pediatric Adverse Events: Fluticasone

- **Worsening asthma symptoms with Advair (n=22)**
 - Serious outcomes-10
 - Death-4
 - Age 5-14 years
 - Race not reported in most cases
 - Time to onset 0 days to 2 years (median 21 days)
 - Relative contribution of underlying disease & Advair not known

Pediatric Adverse Events: Deaths

1. *US case.* A 14-year-old black male was prescribed Advair after an episode of respiratory arrest. He had received Advair Diskus for 2 years when he experienced an acute asthma attack. He was transported to an emergency room; when he arrived he was in full cardiac arrest, and he died. No autopsy was performed.

Pediatric Adverse Events: Deaths

2. *US case.* A 13-year-old white male who had received Advair for about 6 months experienced an asthma attack, and he died. The treating physician stated the death was not due to Advair. An autopsy showed chronic bronchitis, hypertrophy of bronchial muscle, infiltrate of eos, mucous plugging of smaller bronchi/bronchioles, scattered microscopic foci of acute pneumonia, organizing pneumonia, and air trapping in the alveoli.

Pediatric Adverse Events: Deaths

3. *Non-US case.* A 14-year-old asthmatic girl was treated with salmeterol for an acute asthma attack. Apparently the patient refused treatment with a systemic corticosteroid. When she did not respond in the first day to treatment with salmeterol, treatment with a combined salmeterol and fluticasone product was started. Additionally, the patient was receiving albuterol. About 2 hours after her first dose of the combination product, the patient's condition worsened. She developed circulatory failure, and she died despite attempts to resuscitate her.

Pediatric Adverse Events: Deaths

4. *US case.* A 13-year-old boy experienced cardiac arrest and died after receiving Advair for an unknown period of time. While talking to a friend on the phone, the boy “just stopped talking.” An autopsy showed only lungs changes consistent with asthma.

Pediatric Adverse Events: Fluticasone

2/25/03 – 3/25/04

(*n*=128)

- **Gender**

– Female	59
– Male	67
– Unknown	2

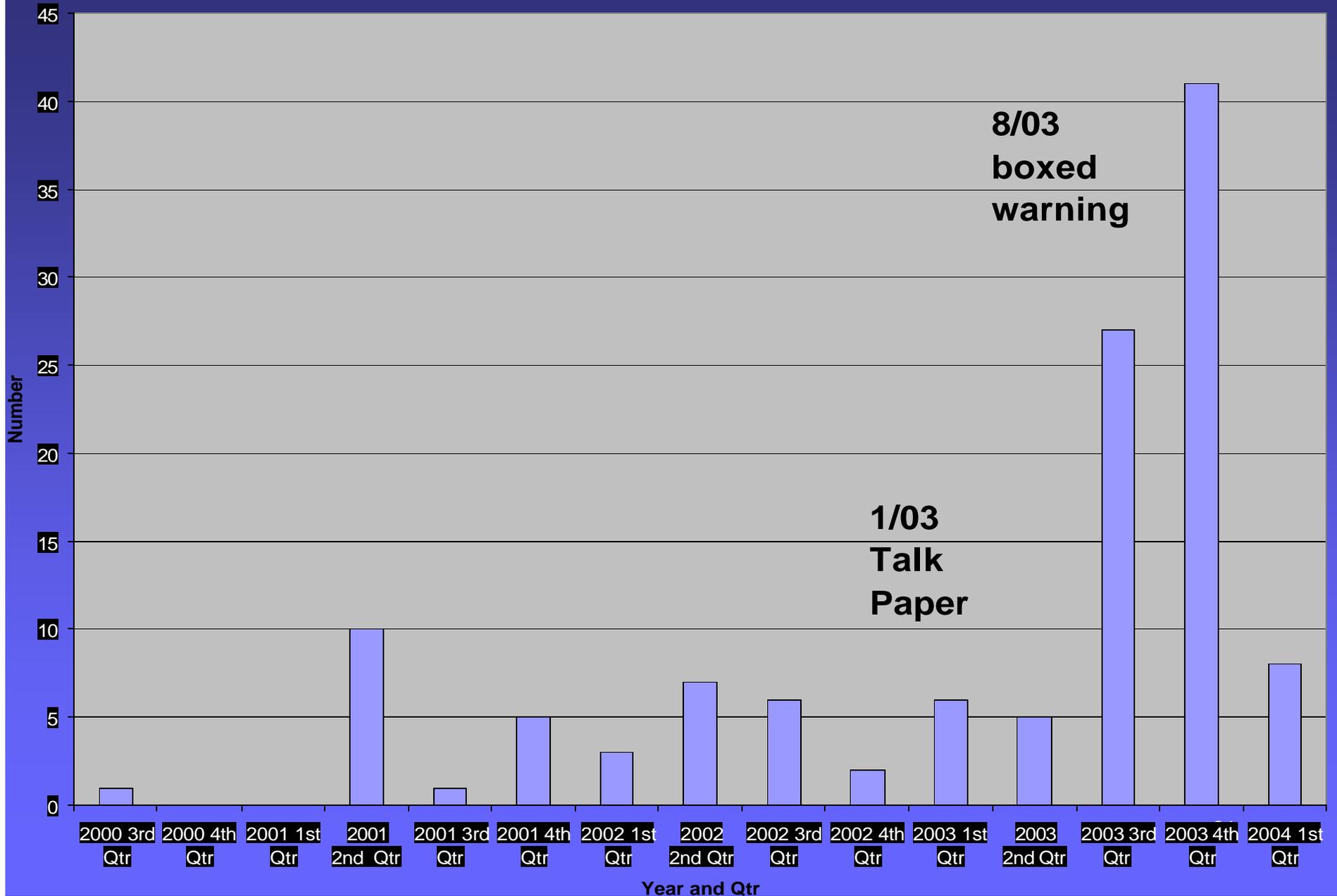
- **Age**

– 0 - <1 mo.	0
– 1 mo. - <2 yrs	1
– 2 - 5 yrs	26
– 6-11 yrs	68
– 12-16 yrs	32

- **Products**

– Inhaled fluticasone	22
– Nasal	24
– Inhaled fluticasone in combination /w salmeterol	82

Pediatric Advair AERS Reports 10/00 – 3/04



Relevant Safety Labeling

PRESCRIBING INFORMATION

ADVAIR DISKUS[®] 100/50

(fluticasone propionate 100 mcg and salmeterol* 50 mcg inhalation powder)

ADVAIR DISKUS[®] 250/50

(fluticasone propionate 250 mcg and salmeterol* 50 mcg inhalation powder)

ADVAIR DISKUS[®] 500/50

(fluticasone propionate 500 mcg and salmeterol* 50 mcg inhalation powder)

*As salmeterol xinafoate salt 72.5 mcg, equivalent to salmeterol base 50 mcg

For Oral Inhalation Only

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 13,174 patients treated for 28 weeks) versus those on placebo (4 of 13,179). Subgroup analyses suggest the risk may be greater in African American patients compared to Caucasians (see WARNINGS).

Issues from Pediatric Adverse Events: Fluticasone *2/25/03 – 3/25/04*

- **Systemic steroid effects**
 - 12 cases (1 death)
- **Worsening asthma symptoms with Advair:**
 - 22 cases (4 deaths)

Pediatric Adverse Events: Fluticasone

- **Systemic steroid effects ($n=12$)**
 - **Products/Doses**
 - Nasal product-2
 - Inhaled product-9
 - More than 1 source of steroids-6
 - Dose not reported in 4 cases
 - Only 1 case reported effect (GR) w/ Flonase w/i labeled dose

Pediatric Adverse Events: Deaths

1. *Non-US case.* An 8-year-old girl who used inhaled fluticasone for an unknown indication at an unknown dose for an unknown period of time developed adrenal crisis, and she died. Details regarding the case were not reported.

Conclusions on Pediatric Adverse Events: Fluticasone *2/25/03 – 3/25/04*

- Most events, including systemic steroid effects, are included in labeling
- Relative contribution of underlying disease & Advair in the AERS cases of asthma exacerbation not known
- Advair labeling contains warning about asthma outcomes with salmeterol