



Pediatric Focused Safety Review: Dulera[®] (mometasone furoate and formoterol fumarate)

Pediatric Advisory Committee Meeting May 7, 2012

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Food and Drug Administration**

Outline

- Background Information
- Clinical Studies
- Relevant Labeling
- Drug Use Trends
- Adverse Events
 - Dulera[®] (mometasone furoate and formoterol fumarate)
 - Foradil[®] (formoterol fumarate)
- Summary

Background Drug Information

Dulera[®]

(mometasone furoate and formoterol fumarate)

- **Drug:** Dulera[®] (mometasone furoate and formoterol fumarate)
- **Sponsor:** Schering
- **Therapeutic Category:** combination product; corticosteroid and long-acting beta₂-adrenergic agonist
- **Formulation:** inhalational aerosol (100 mcg/5 mcg, 200 mcg/5 mcg)
- **Original Market Approval:** June 22, 2010

Background Drug Information (continued)

Dulera[®]

(mometasone furoate and formoterol fumarate)

- **Indication:** treatment of asthma in patients ≥ 12 years

(Important limitation: not indicated for the relief of acute bronchospasm)

- **Dosing:**

Previous Therapy	Recommended Dose	Maximum Recommended Daily Dose
Inhaled medium dose corticosteroids	DULERA 100 mcg/5 mcg, 2 inhalations twice daily	400 mcg/20 mcg
Inhaled high dose corticosteroids	DULERA 200 mcg/5 mcg, 2 inhalations twice daily	800 mcg/20 mcg

- **PREA Postmarketing Requirements:**

- Waived: 0-4 years
- Deferred: 5-11 years

Background Drug Information (continued)

Dulera[®]

(mometasone furoate and formoterol fumarate)

- **Risk Evaluation and Mitigation Strategy (REMS)**

Goal:

To inform healthcare providers and prescribers of the:

1. increased risk of asthma-related death and serious outcomes with the long-acting beta2-adrenergic agonists including Dulera[®].
2. appropriate use of long-acting beta2-adrenergic agonists including Dulera[®].

Elements

1. Communication Plan
2. Timetable for Submission of Assessments

Pivotal Studies

Dulera[®]

(mometasone furoate and formoterol fumarate)

Two randomized, double-blind, parallel group, multicenter clinical trials in 1509 patients ≥ 12 years with persistent asthma uncontrolled on medium or high dose inhaled corticosteroids

- Trial 1: 26-week, compared Dulera[®] to placebo and individual components (n=781)
- Trial 2: 12-week, compared two doses of Dulera[®] to mometasone (n=728)

Efficacy results in patients 12-17 years were similar to those observed in adults.

Clinical Studies-Safety

Dulera[®]

(mometasone furoate and formoterol fumarate)

Safety data from 3 clinical trials in patients ≥ 12 years with asthma (n=1913)

- Pooled data from two 12 to 26 week trials (n=679 exposed to Dulera[®])
 - Treatment-emergent reactions in Dulera[®] groups occurring at an incidence of $\geq 3\%$ and $>$ placebo: nasopharyngitis, sinusitis, headache
- Data from 52 week active comparator trial (n=271 exposed to Dulera[®])
 - Safety outcomes in general similar to the 12 to 26 week trials
 - Dysphonia observed at higher frequency

The type and frequency of adverse reactions in patients 12-17 years were similar to those in adults.

Relevant Labeling

Dulera[®]

(mometasone furoate and formoterol fumarate)

Boxed warning: Asthma-Related Death

WARNING: ASTHMA-RELATED DEATH

Long-acting beta₂-adrenergic agonists (LABA), such as formoterol, one of the active ingredients in DULERA, increase the risk of asthma-related death. Data from a large placebo-controlled U.S. study that compared the safety of another long-acting beta₂-adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of the LABA, including formoterol. 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, DULERA should only be used 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 LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue DULERA) 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 DULERA for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids. [See *Warnings and Precautions (5.1).*]

Relevant Labeling (continued)

Dulera[®]

(mometasone furoate and formoterol fumarate)

4 Contraindications:

- 4.1 Status asthmaticus
- 4.2 Hypersensitivity

5 Warnings and Precautions:

- 5.1 Asthma-Related Death
- 5.2 Deterioration of Disease and Acute Episodes
- 5.3 Excessive Use of Dulera[®] and Use with Other Long-Acting Beta₂-Agonists
- 5.4 Local Effects (oropharyngeal candidiasis)
- 5.5 Immunosuppression
- 5.6 Transferring Patients from Systemic Corticosteroid Therapy

Relevant Labeling (continued)

Dulera[®]

(mometasone furoate and formoterol fumarate)

5 Warnings and Precautions (continued)

- 5.7 Hypercorticism and Adrenal Suppression
- 5.8 Drug Interactions with Strong Cytochrome P450 3A4 Inhibitors
- 5.9 Paradoxical Bronchospasm and Upper Airway Symptoms
- 5.10 Immediate Hypersensitivity Reactions
- 5.11 Cardiovascular and Central Nervous System Effects
- 5.12 Reduction in Bone Mineral Density
- 5.13 Effect on Growth (monitor growth in children)
- 5.14 Glaucoma and Cataracts
- 5.15 Coexisting Conditions
- 5.16 Hypokalemia and Hyperglycemia

Relevant Labeling (continued)

Dulera[®]

(mometasone furoate and formoterol fumarate)

6 Adverse Reactions

6.1 Clinical Trials Experience

6.2 Postmarketing Experience: anaphylactic reaction

7 Drug Interactions

8 Use in Specific Populations

8.4 Pediatric Use

- Clinical study information:
 - 123 patients 12-17 years treated with Dulera[®]
 - Safety and efficacy similar to patients ≥ 18 years
- Safety and efficacy not established in patients <12 years
- Growth data and management

Relevant Labeling (continued)

Dulera[®]

(mometasone furoate and formoterol fumarate)

10 Overdosage

12 Clinical Pharmacology

12.2 Pharmacodynamics

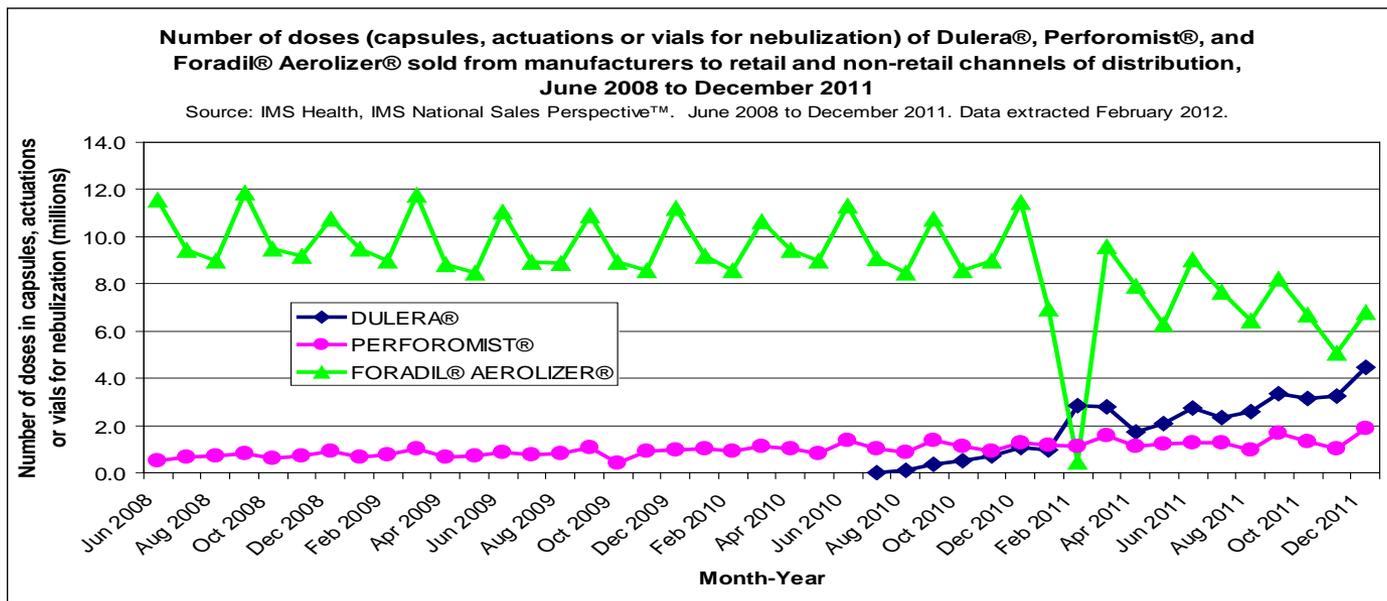
Summary of HPA axis effects provided

17 Patient Counseling Information

Medication Guide

Dulera[®] Drug Utilization

- Sales Distribution (from manufacturers):
 - Formoterol-containing products: Dulera[®], Perforomist[®], and Foradil[®] Aerolizer[®]:



- Approximately 34.9 million doses Dulera[®] sold from manufacturers (July 2010-December 2011, cumulative)

Dulera[®] Drug Utilization (continued)

July 1, 2010- December 31, 2011 (cumulative)

- Dulera[®] prescription and patient counts*:

Ages	All (Total Patients)	≥17 years	12-16 years	5-11 years	0-4 years
Prescriptions (Rx) Dispensed	374,515 (100%)	332,144 (88.7%)	21,103 (5.6%)	18,848 (5.0%)	2,395 (<1%)
Patients Receiving Rx	205,271 (100%)	183,015 (89.2%)	11,823 (5.8%)	9,882 (4.8%)	1,308 (<1%)

*Source: IMS Health, Vector One[®]: National (VONA) and Total Patient Tracker (TPT). July 2010 through December 2011. Data extracted March 2012. (Note, data provided in the March 21, 2012 Use Review were extracted January 2012).

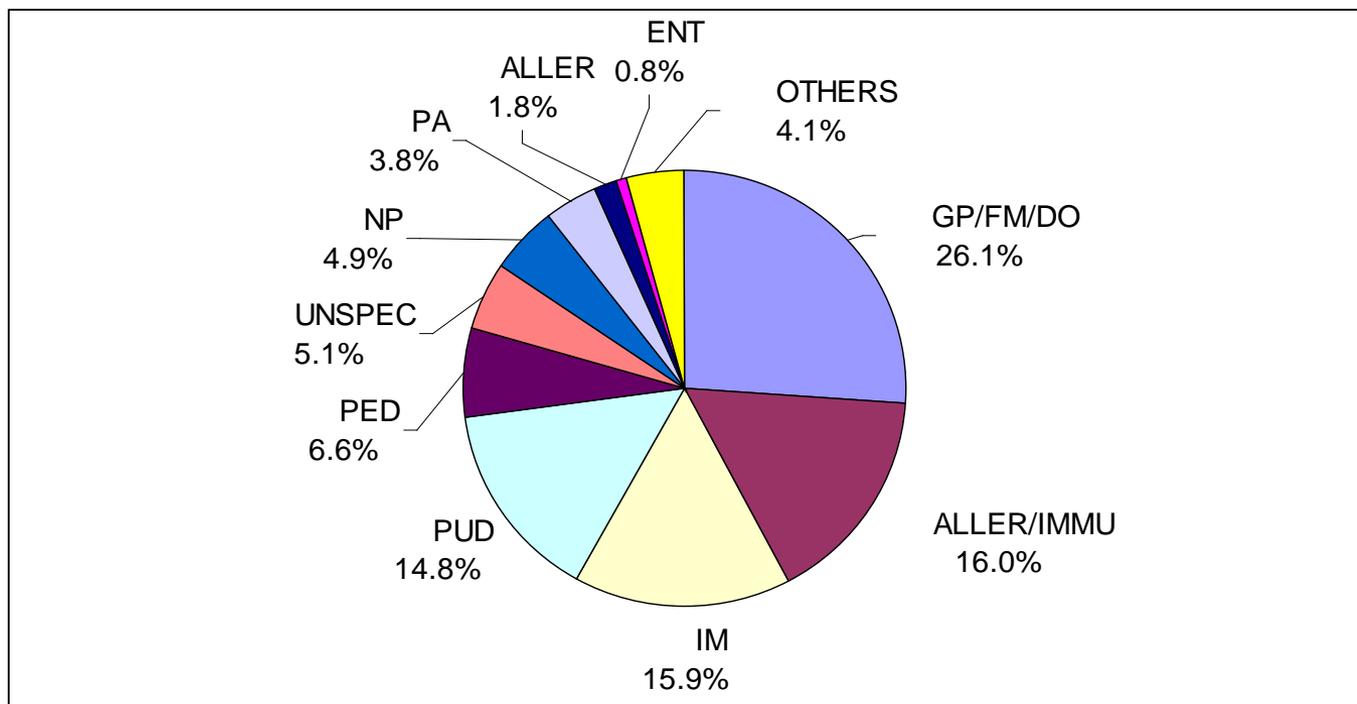
- “Asthma NOS” was the top diagnosis for all age groups**.

**Source: SDI, Physician Drug and Diagnosis Audit[™]. July 2010 through December 2011. Data Extracted March 2012.

Dulera[®] Drug Utilization (continued)

July 1, 2010- December 31, 2011

- Top Ten Prescribing Specialties



Source: IMS Health, Vector One[®]: National (VONA). July 2010 through December 2011. Data extracted January 2012.

Pediatric Safety Reviews

Dulera[®]

(mometasone furoate and formoterol fumarate)

Foradil[®]

(formoterol fumarate)

Total Number* of Dulera[®] Adverse Event Reports Since Product Approval (June 22, 2010 to December 31, 2011)

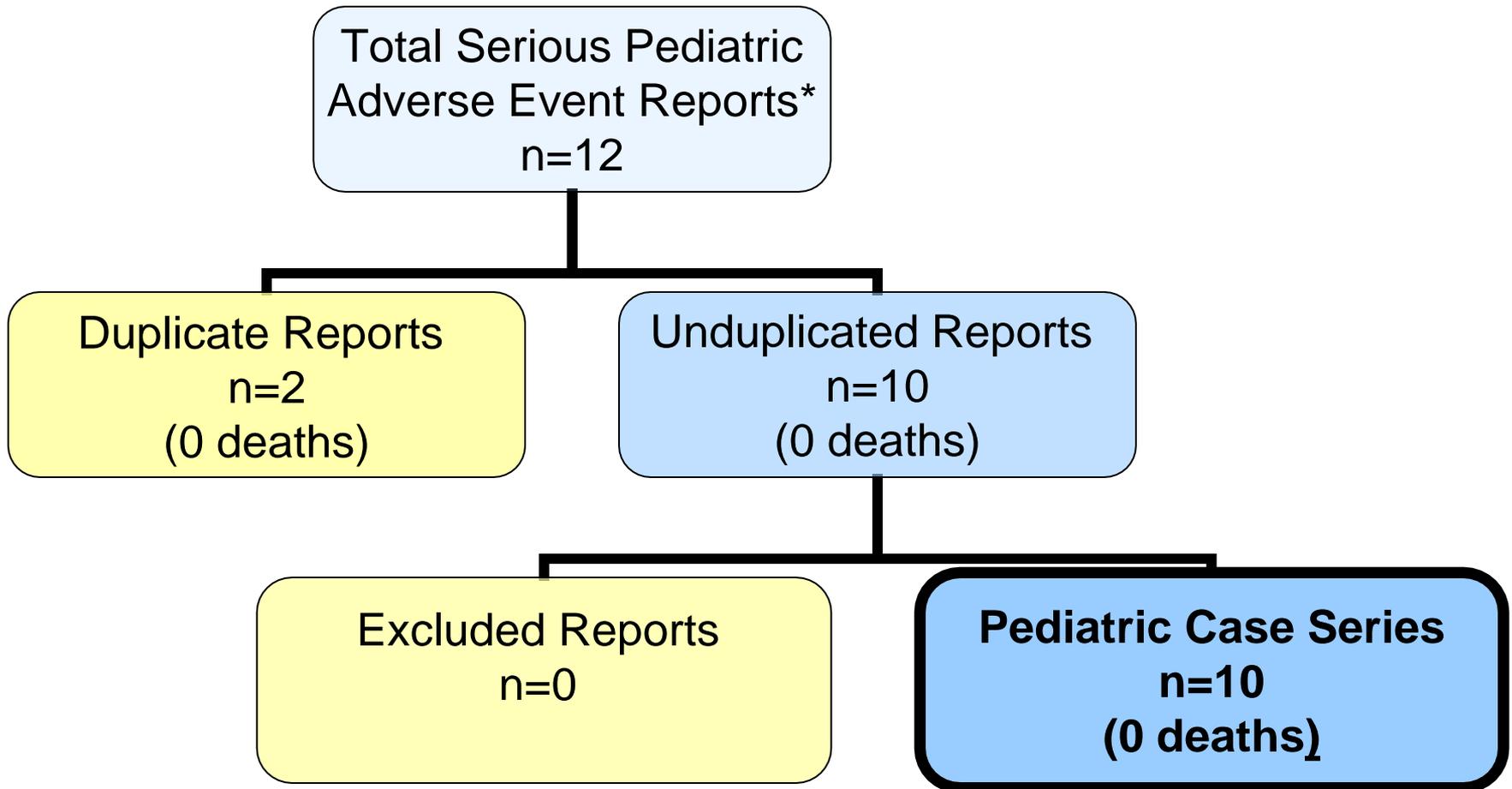
	All reports (US)	Serious**(US)	Death (US)
Adults (≥ 17 yrs.)	63 (63)	59 (59)	2 (2)
Pediatrics (0-16 yrs.)	13 (13)	12 (12)	0 (0)
Unknown Age (Null values)	61 (61)	59 (59)	4 (4)****
Total	137 (137)	130 (130)	6 (6)

* Not assessed for causality and may include duplicates

**Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening events, hospitalization (initial or prolonged), disability, congenital anomaly and other serious important medical events.

***No null cases in pediatrics found

Dulera[®] Adverse Event Reports Case Selection



*n=0: age unknown pediatric reports with an outcome of death

Characteristics of Serious Pediatric Cases Dulera[®] (n=10)

- Age (n=10)
 - 0-< 2 years* (n=0)
 - 2-5 years* (n=4)
 - 6-11 years* (n=2)
 - 12-16 years (n=4)

**Unapproved age group: <12 years*
- Dosing (n=7)
 - Mean: 314mcg/9 mcg
 - Range: 100mcg/5 mcg- 800mcg/20mcg
- Indications
 - Asthma (n=6)
 - Environmental allergies (n=1)
 - Unknown (n=3)

Serious Adverse Events

Dulera[®] (mometasone furoate and formoterol fumarate) (n=10)

- Fatal Serious Events (n=0)
- Serious Non-Fatal Adverse Events (n=10)
 - Neuropsychiatric Events (n=7)
 - Respiratory Events (n=2)
 - Other (n=1)

(Review did not identify other events of interest, i.e. infection, immunosuppression, impaired adrenal function, paradoxical bronchospasm, beta-adrenergic stimulation, decrease in bone mineral density, effects on growth, glaucoma and cataracts, hypokalemia and hyperglycemia)

Serious Adverse Events (continued)

Dulera[®] (mometasone furoate and formoterol fumarate)

Neuropsychiatric Events (n=7)

- Aggressive behavior (n=5)

- 2.5-year boy with aggression, changes in behavior and changes in sleeping pattern 1 week after starting Dulera[®] (200 mcg/5 mcg once daily). Dulera[®] discontinued. Patient recovered. Concomitant medications: as needed, mometasone furoate (intranasal) and albuterol.
- 2.3-year boy with “aggression, biting, weeping and overall behavior change” 1 week after starting Dulera[®] (100 mcg/5 mcg once daily). Dulera[®] discontinued. Patient recovered that day. Concomitant medication: as needed, albuterol.
- 4 year girl with mood changes, i.e. aggression, sleep disorder, nervousness, jitteriness and agitation after 1 year Dulera[®] (100 mcg/5 mcg treatment, frequency unknown). In past, similar symptoms with budesonide/formoterol fumarate resolved with lower dose. Dulera[®] continued. Ongoing symptoms at time of report.
- 4 year girl with “aggressive behaviors” after 1 week Dulera[®] (200 mcg/5 mcg 2 puffs, twice daily) treatment. Dulera[®] discontinued. Outcome unknown.
- 15-year boy with headache, aggressive behavior, and cough 4 days after initiating Dulera[®] (200mcg/5mcg 2 puffs, twice daily) for severe asthma. Dulera[®] discontinued and symptoms resolved in 4 days. History of “allergy” to fluticasone and salmeterol inhaler.

Serious Adverse Events (continued)

Dulera[®] (mometasone furoate and formoterol fumarate)

Neuropsychiatric Events (continued):

- Tremor (n=1):
 - 15-year female with tremor and “was jittery” x 1 day while on Dulera[®] (unknown dose and frequency). Dulera[®] discontinued and patient recovered; rechallenge negative. Concomitant medications: not reported.

- Motor and Phonic Tics (n=1):
 - 15-year female developed tics within a few minutes of first dose of Dulera[®] (200mcg/5mcg). Diagnosed with acute motor and phonic tics by child neurologist at Children’s Hospital of Philadelphia. Discharged without treatment. The day prior, patient took caffeine containing OTC products, i.e. 1 dose “Midol” and 2 doses of “Excedrin PMS”. Outcome unknown.

Serious Adverse Events (continued)

Dulera[®] (mometasone furoate and formoterol fumarate)

Respiratory Events (n=2):

- **Cyanosis:** 9 year girl with “feeling tired, vomiting, clammy, eyes glossy, lips turned blue and skin color was grey” 10 minutes after 2nd omalizumab injection. Event resolved with epinephrine, montelukast sodium, hydroxyzine, albuterol, and dexamethasone. Omalizumab therapy discontinued. Concomitant medications included Dulera[®], levocetirizine, montelukast sodium, levalbuterol, fluticasone furoate (nasal), fluticasone propionate (topical). Omalizumab considered “primary”, Dulera[®] considered “suspect”.

Dulera[®]: labeled for anaphylactic reaction; Omalizumab: boxed warning for anaphylaxis/hypersensitivity events.

- **Bronchospasm:** 10 year boy patient with bronchospasm after taking Dulera[®] 100mcg/5mcg. Treated with albuterol. Patient recovered. Dulera[®] was discontinued.

Other (n=1):

14 year girl with shortness of breath, shallow breathing, dizziness, sore throat, and chest pains one week after starting Dulera[®] (100mcg/5mcg, once daily). Two episodes resulted in treatment (and release) from the Emergency Department. Outcome unknown.

Adverse Events (AEs) formoterol fumarate

Background:

- Foradil[®], formoterol fumarate, is a powder inhalation for treatment of asthma (12 mcg every 12 hours), and prevention of bronchospasm in patients ≥ 5 years.
- Symbicort[®], budesonide and formoterol, is an inhalation aerosol for treatment of asthma in patients ≥ 12 years (formoterol dose 4.5 mcgx2, twice daily)
- Additional formoterol products are approved in adults for COPD

AERS Review:

- n=7: total number of formoterol fumarate AE reports (6/1/09 to 12/31/11)
- n=5: reports excluded secondary to concomitant medications

Two cases:

- 13 year girl hospitalized with "enlarged and painful" stomach. Foradil[®] discontinued. Patient recovered. Recurrence of events when Foradil[®] reintroduced. Foradil[®] use temporarily interrupted. Outcome: recovered.
- 1 day infant with transplacental exposure to formoterol diagnosed with craniosynostosis and congenital exophthalmos at birth.

Summary Pediatric Focused Safety Review

Dulera[®]

(mometasone furoate and formoterol fumarate)

- The pediatric safety review identified 5 reports of aggressive behavior, an unlabeled event.
- Four of the reports were in patients ≤ 4 years (product approved patients ≥ 12 years).
- Although FDA does not recommend labeling changes at this time, FDA intends to:
 - Continue routine postmarketing monitoring, including monitoring of pediatric neuropsychiatric events
 - Continue monitoring of the ongoing Dulera[®] clinical trials in pediatric patients 5-11 years
- Does the Committee concur?

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