Pediatric Focused Safety Review: Flomax® (tamsulosin hydrochloride)

Pediatric Advisory Committee Meeting
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Center for Drug Evaluation and Research
Food and Drug Administration

Outline

- Background Information
- Pediatric Studies
- Pediatric Labeling Changes
- Relevant Safety Labeling
- Drug Use Trends
- Adverse Events
- Summary

Background Drug Information
Flomax® (tamsulosin hydrochloride)

- **Drug:** Flomax® (tamsulosin hydrochloride)
- **Formulation:** Capsules
- **Adult Indication**: Treatment of the signs and symptoms of benign prostatic hyperplasia
- **Pediatric Indication**: None
- **Therapeutic Category:** $Alpha_1$ adrenoceptor antagonist
- **Sponsor:** Boehringer Ingelheim

Background Drug Information (continued)
Flomax® (tamsulosin hydrochloride)

- **Original market approval:**
  April 15, 1997

- **Pediatric exclusivity granted:**
  September 17, 2009

- **BPCA labeling changes:**
  December 22, 2009

Two Pediatric Exclusivity Studies Flomax® (tamsulosin hydrochloride)

- Pediatric Patients
  - 2 years to 16 years of age
  - Elevated detrusor leak point pressure (>40 cm H_20) associated with known neurological disorder

Two Pediatric Exclusivity Studies, continued Flomax® (tamsulosin hydrochloride)

- 14-week, randomized, double-blind, placebo-controlled, PK, safety and efficacy study (n=161)
  - Endpoint: reduction in detrusor leak point pressure below 40 cm H_20
  - No statistically significant difference in the proportion of responders was observed between groups receiving tamsulosin hydrochloride and placebo
- 12-month, open-label, safety study (n=87)
  - Patients were treated with tamsulosin hydrochloride

Two Pediatric Studies: Safety Results Flomax® (tamsulosin hydrochloride)

Most frequently reported adverse events (≥ 5%) from the pooled data of both studies:

- Urinary tract infection
- Vomiting
- Pyrexia
- Headache
- Nasopharyngitis
- Cough
- Pharyngitis
- Influenza
- Diarrhea
- Abdominal pain
- Constipation

Two Pediatric Studies: Safety Results Flomax® (tamsulosin hydrochloride), Fatality (n=1)

- 7 year old male with a complex medical history, found unresponsive 15 days after beginning tamsulosin hydrochloride
- Medical history included:
  - Myelomeningocele at L3-L5 without surgical repair
  - Arnold Chiari malformation
  - Hydrocephalus with a shunt
  - Neurogenic bladder with urinary incontinence
  - Status-post nephrectomy for a nonfunctioning hydronephrotic kidney
  - Bilateral congenital talipes equinovarus

Two Pediatric Studies: Safety Results Flomax® (tamsulosin hydrochloride) Fatality (n=1), continued

- Uneventful clinical evaluations 8 and 14 days after 1st dose
- Parents declined post-mortem evaluations
- Primary investigator concluded cause of death to be indeterminate

Pediatric Labeling Changes
Flomax® (tamsulosin hydrochloride)

- (8.4) Use in Specific Populations, Pediatric Use
  - Flomax® capsules are not indicated for use in pediatric populations
  - Describes the two pediatric studies

Pediatric Labeling Changes, continued Flomax® (tamsulosin hydrochloride)

- (12) Clinical Pharmacology
  - (12.2) Pharmacodynamics: Urologic pharmacodynamic effects have been evaluated in neurologically impaired pediatric patients and in adults with benign prostatic hyperplasia
  - (12.3) Pharmacokinetics, Specific Populations, Pediatric Use: Flomax® capsules are not indicated for use in pediatric populations

Relevant Safety Labeling: Contraindications Flomax® (tamsulosin hydrochloride)

- Contraindicated if known to be hypersensitive to tamsulosin hydrochloride or any component of Flomax® capsules.
- Reactions have included: skin rash, urticaria, pruritis, angioedema, and respiratory symptoms.

Relevant Safety Labeling: Warnings and Precautions Flomax® (tamsulosin hydrochloride)

- (5.1) Orthostasis
  - potential for syncope
- (5.3) Priapism
  - tamsulosin, like other alpha$_1$ antagonists, has been associated with priapism

(Flomax® and generic)
January 2002 – June 2011
Dispensed Prescriptions

Time Frame	Number of dispensed prescriptions
2002	~6.5 million
2010	~12.6 million
January 2002 – June 2011	~92.1 million

[1] Source: IMS, Vector One®: National (VONA). January 2002 through June 2011. Data Extracted 8/2011.

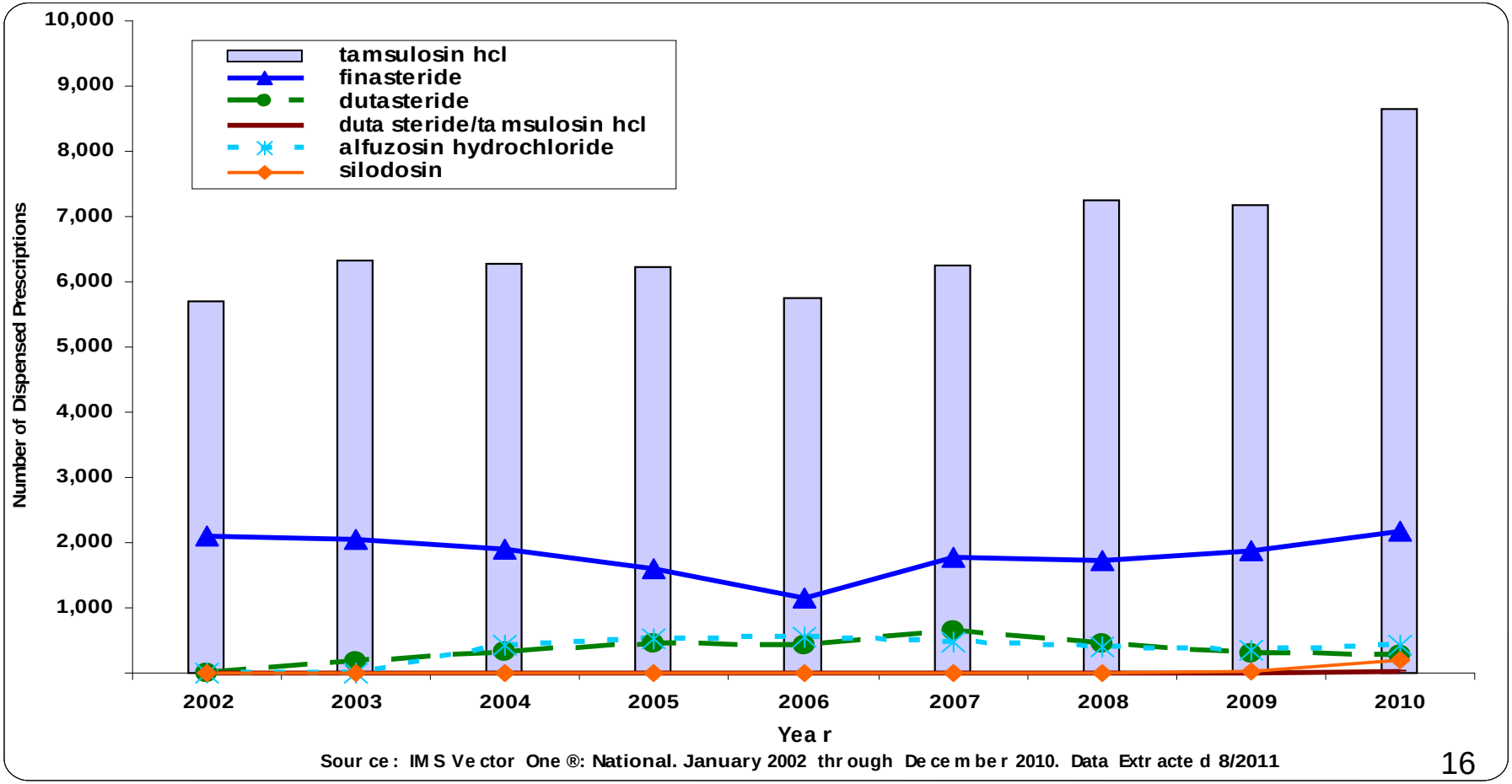
Tamsulosin Hydrochloride Use[1]
(Flomax® and generic)
January 2002 – June 2011 (cumulative)
U.S. Outpatient Retail Setting Projected Unique Patients

Patient age (years)	Patient Count	Share
0 – 16	24,252	0.2%
17+	11,277,987	99.8%
Unspecified age	4,886	0%

[1] Source: IMS, Vector One®: Total Patient Tracker. January 2002 through June 2011. Data Extracted 8/2011.

Tamsulosin Hydrochloride (Flomax® and generic) Pediatric Use[1]

Nationally estimated number of prescriptions dispensed for benign prostatic hyperplasia agents (USC 24200) to pediatrics (0-16 years) through U.S. outpatient retail pharmacies



Sour ce : IM S Ve ctor One ®: National. January 2002 thr ough De ce m be r 2010. Data Extr acte d 8/2011

Associated Diagnosis for Pediatric Outpatient Use[1] tamsulosin hydrochloride, (Flomax® and generic) January 2002 – June 2011 (cumulative)

Diagnosis	Share of pediatric patients
Calculus of Kidney	36.4%
Incontinence of Urine	18.9%
Urination Abnormality Not Elsewhere Classified	17.5%
Urethral Stricture Not Otherwise Specified	16.8%
Calculus of Ureter	10.4%

[1]Source: SDI Physician Drug and Diagnosis Audit®. January 2002 through June 2011. Data Extracted 8/2011.

Tamsulosin Hydrochloride Use[1]
(Flomax® and generic)
U.S. Outpatient Retail Setting
January 2002 – June 2011 (cumulative)

- Gender
  - Overall, males accounted for majority of use
  - Among pediatric patients, nearly 40% of use was among females

[1] Source: IMS, Vector One®: Total Patient Tracker. January 2002 through June 2011. Data Extracted 8/2011.

Tamsulosin Hydrochloride Use[1]
(Flomax® and generic)
U.S. Outpatient Retail Setting
January 2002 – June 2011 (cumulative)

- Prescribing specialty
  - Most common, Urology (30.9%)
  - Pediatrics (<1%)

[1]Source: IMS, Vector One®: National VONA. January 2002 through June 2011. Data Extracted 8/2011.

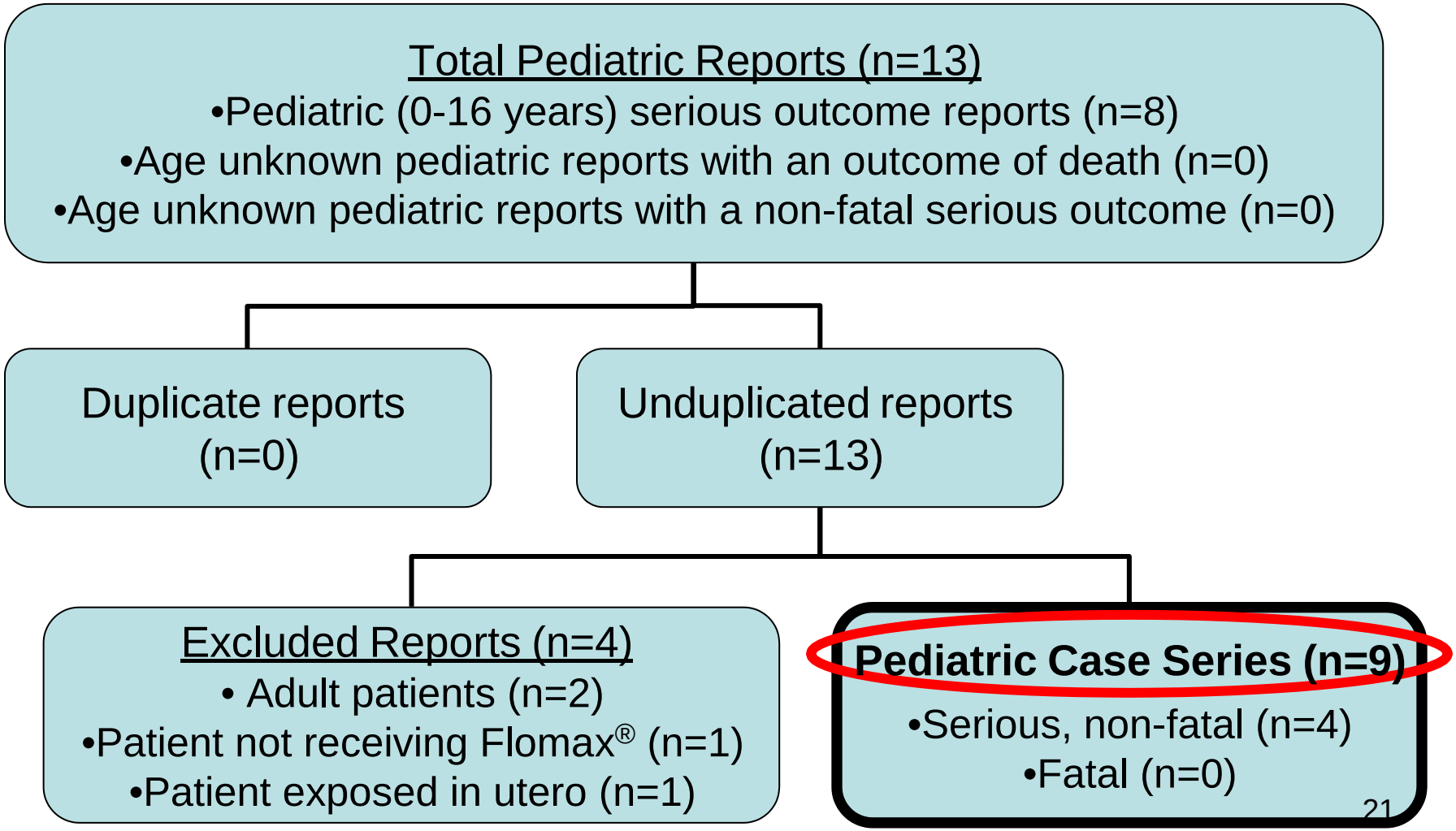
Total Number* of Flomax®
Adverse Event Reports Since Adult Approval
(April 15, 1997 – July 19, 2011)

	All reports (US)	Serious** (US)	Death (US)
Adults (≥ 17 yrs.)	2750 (1100)	1299 (291)	61 (9)
Pediatrics (0-16 yrs.)	13 (6)	8 (2)	0 (0)
Unknown Age (Null values)	2501 (1042)	788 (173)	55 (12)
All Ages	5264 (2148)	2095 (466)	116 (21)

*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.

Selection of Pediatric AERS Cases: Flomax®



Serious Nonfatal Pediatric Cases Flomax® (n=4)

- Accidental Exposure (n=3)
- Bradycardia, Hypertension and Lethargy (n=1)

Characteristics of Serious Pediatric Cases Flomax® (n=4)

- Accidental Exposure (n=3)

Age and gender of person exposed	~Amount of Flomax® received	Additional information	Outcome
21 month old female	1.6 mg	Child ingested great-grandfather's Flomax®	Diarrhea*, decreased urine output
2 year old female	Unknown strength and quantity	"10 or less capsules"	No harm
3 year old female	0.2mg	Child ingested ~½ of a 0.4 mg capsule	Hypotension*

*Labeled Adverse Event

Characteristics of Serious Pediatric Cases, continued. Flomax® (n=4)

- Bradycardia, Hypertension and Lethargy (n=1)
  - 4 year old male with history of suprapubic catheter insertion and urinary retention
  - Tamsulosin dose (brand not specified): 200 µg for 1 day and then 400 µg for 1 week
  - Experienced bradycardia, hypertension, and lethargy beginning 2 hours post-administration. Patient rousable to being moved.
  - Symptoms resolved 5 hours post-administration.
  - Per reporter, “Timelines are suspect. Dechallenge is positive for all events, rechallenge is positive for lethargy.”

AERS Analysis: Hypotension

- Labeled adverse event
- 163 AERS reports identified
  - 1 pediatric report
- 3 year old female who ingested ~half of a 0.4mg Flomax® capsule (previously discussed)
  - Received activated charcoal and IV fluids in Emergency Room (ER)
  - BP 64/31, which responded to IV fluids
  - Discharged from ER asymptomatic 6 hours post-ingestion

Medication Errors Post Marketing Review tamsulosin hydrochloride (April 15 1997 – November 1, 2011)

- Accidental Pediatric Exposure Cases (n=6)
  - 3 cases identified in safety review (previously discussed)
  - 3 additional cases identified

Medication Errors Post Marketing Review tamsulosin hydrochloride (n=6)

- Accidental Pediatric Exposure, additional cases (n=3)

Age and gender of person exposed	Amount of tamsulosin received	Additional information	Outcome
2 year old male	~1 capsule of tamsulosin (brand not specified)	Patient also ingested metoprolol, benazepril/ hydrochlorothiazide	No symptoms during first 10 minutes but no further information provided
2 year old male	~1 Flomax® capsule	Patient found chewing Flomax®	No additional information provided
Unknown age, female	~1 Flomax® capsule	Man reported he dropped medication and granddaughter chewed it	Treatment was not reported

Medication Errors Post Marketing Review
tamsulosin hydrochloride Accidental Exposures (April 15 1997 – November 1, 2011)

- How tamsulosin was obtained by child was only described in 1/6 cases (reporter dropped it)
- Packaging: high-density polyethylene bottles with child-resistant closures
- Division of Medication Errors and Prevention Analysis does not recommend changes to packaging or labeling

Summary Pediatric Focused Safety Review Flomax® (tamsulosin hydrochloride)

- This concludes the pediatric focused safety review.
- No new pediatric safety signals were identified.
- FDA recommends returning to routine monitoring.
- Does the Committee concur?

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