

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Pediatric Postmarketing Adverse Event Review

Date: October 27, 2011

To: Lisa L. Mathis MD, Associate Director
Pediatric and Maternal Health Staff (PMHS)
Office of New Drugs (OND),
Center for Drug Evaluation and Research (CDER)

And
M. Dianne Murphy, MD, Director
Office of Pediatric Therapeutics (OPT),
Office of the Commissioner (OC)

Through: Adrienne Rothstein, Pharm.D., Team Leader
Division of Pharmacovigilance (DPV) I,
Office of Surveillance and Epidemiology (OSE)

Bindi Nikhar, M.D., F.A.A.P, Deputy Director
DPV II, OSE

From: Teresa Rubio, Pharm.D., Safety Evaluator
DPV I, OSE

Subject: BPCA Pediatric Postmarketing Adverse Event Review

Drug Name(s): Flomax (NDA 20579) (Tamsulosin HCl)

Pediatric Exclusivity
Approval Date: 9/17/2009¹ (Labeling date 12/22/2009)

Applicant/sponsor: Boehringer Ingelheim

OSE RCM #: 2011-2687

1

<http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/UCM163159.pdf> (accessed 7/18/2011)

CONTENTS

1	Introduction.....	2
1.1	Product Formulations and Indications	2
1.2	Pediatric Filing history.....	3
1.3	Pediatric labeling'	3
2	METHODS AND MATERIALS.....	3
2.1	AERS Search Strategy	4
3	RESULTS	4
3.1	Counts of AERS Reports	4
3.2	Case Characteristics From Pediatric Case Series.....	6
4	DISCUSSION Of SERious PEDIATRIC Case series	7
4.1	Summary of pediatric deaths (n=0 in AERS, N =1 in Clinical Trials).....	7
4.2	Summary of selected pediatric adverse events	8
4.2.1	Bradycardia/Hypertension (n=1)	9
4.2.2	Hypotension (Separate AERS analysis, n=163)	9
4.2.3	Attention problems as an aspect of cognition (N=0)	10
5	CONCLUSIONs	10
6	RECOMMENDATIONS	10
7	appendices.....	11
7.1	Appendix A: Standard AERS Searches	11
7.2	Appendix B: Adverse Event Reporting System (AERS) Database Description 11	
7.3	Appendix C: AERS Case Numbers/ISR Numbers and Manufacturer Control Numbers for Pediatric Case Series	12
7.4	Appendix D: AERS search strategy for Hypotension (Separate AERS analysis, n=163).....	12

EXECUTIVE SUMMARY

In accordance with Best Pharmaceuticals for Children Act (BPCA), the Division of Pharmacovigilance (DPV) was asked to summarize post-marketing reports of adverse events associated with the use of Flomax (tamsulosin) in pediatric patients (0-16 years of age). The main focus of this review is pediatric deaths and pediatric reports of serious unlabeled adverse events with Flomax. Flomax® (tamsulosin HCl) is an alpha 1A receptor antagonist approved in the U.S. for treatment of the signs and symptoms of benign prostatic hypertrophy (BPH). Oral tamsulosin HCl has been studied in pediatric patients to treat elevated detrusor leak point pressure associated with neurological disorders, however is not currently labeled for pediatric use.

The Adverse Event Reporting System (AERS) database was searched for all reports of adverse events (serious and non-serious) up to the "data lock" date of July 19, 2011. AERS contained 5264 reports for Flomax. There were 9 pediatric cases, which represent approximately 0.2% of the total number of reports in this AERS search. Four cases were serious; of these, 3 involved accidental exposures resulting in a labeled adverse event diarrhea (1), hypotension (1), or overdose (1). These cases of accidental exposure are being reviewed by DMEPA. The fourth serious case involving off-label use reported bradycardia and hypertension (both unlabeled); the adverse events started within 2 hours after administration, and resolved 5 hours after administration.

No fatal cases in pediatric patients were identified in AERS. One pediatric fatality was identified in clinical trials for NDA approval; however, cause of death was inconclusive due to lack of clinical details.

A separate AERS search for Flomax and hypotension, as requested by the Office of Pediatric Therapeutics did not identify further cases of hypotension in pediatric patients.

No safety issues in pediatric patients were identified in this review of Flomax. DPV will continue routine monitoring of adverse events with the use of Flomax in pediatric patients.

1 INTRODUCTION

1.1 PRODUCT FORMULATIONS AND INDICATIONS

- **Product Formulations:** Flomax 0.4 mg (capsule; oral).
- **Indications:** Flomax® (tamsulosin HCl) is an alpha 1A antagonist approved in the U.S. for treatment of the signs and symptoms of benign prostatic hypertrophy (BPH).

Alpha receptor antagonists are effective in voiding dysfunction because they relax the smooth muscle at the bladder neck and proximal urethra. Anticholinergic agents may also be effective for voiding dysfunction due to their ability to decrease the frequency of uninhibited detrusor muscle contractions during bladder filling and increase bladder capacity. They are thought to block muscarinic receptor subtypes M1 to M5, with M3

appearing to be the most functionally important and mediates direct contraction of the detrusor muscle.^{2 3}

1.2 PEDIATRIC FILING HISTORY

Information on pediatric use was added to the label on December 22, 2009 (Pediatric Change date). As noted below, Flomax capsules are not labeled for use in pediatric populations.

1.3 PEDIATRIC LABELING^{4,5}

Flomax U.S. label, Section 8.4 Pediatric Use

Efficacy and positive benefit/risk of tamsulosin hydrochloride was not demonstrated in two studies conducted in patients 2 years to 16 years of age with elevated detrusor leak point pressure (>40 cm H₂O) associated with known neurological disorder (e.g., spina bifida). Patients in both studies were treated on a weight-based mg/kg schema (0.025 mg, 0.05 mg, 0.1 mg, 0.2 mg, or 0.4 mg tamsulosin hydrochloride) for the reduction in detrusor leak point pressure below 40 cm H₂O. In a randomized, double-blind, placebo-controlled, 14-week pharmacokinetic, safety and efficacy study in 161 patients, no statistically significant difference in the proportion of responders was observed between groups receiving tamsulosin hydrochloride and placebo. In an open-label, 12-month safety study, 87 patients were treated with tamsulosin hydrochloride. The most frequently reported adverse events (≥5%) from the pooled data of both studies were urinary tract infection, vomiting, pyrexia, headache, nasopharyngitis, cough, pharyngitis, influenza, diarrhea, abdominal pain, and constipation.

Special Populations

Pediatric Use FLOMAX capsules are not indicated for use in pediatric populations

2 METHODS AND MATERIALS

² Nepple K, Cooper CS. Up-to-date: management of voiding dysfunction in children. Last Update: 4/20/11. Date of accession: 9/15/11.

³ Chapple C, Yamanishi T, Chess-Williams R. Muscarinic receptor subtypes and management of the overactive bladder. *Urology*. Volume 60, Issue 5, Supplement 1, November 2001, pages 82-6.

⁴ http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020579s026lbl.pdf, Date of accession: 7/19/2011

⁵

<http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/UCM163159.pdf> (accessed 7/18/2011)

2.1 AERS SEARCH STRATEGY

The Adverse Event Reporting System (AERS) database was searched with the strategy described in Table 1, Appendix A and Appendix D.

Table 1: AERS Search Strategy*	
Date	July 19, 2011
Time period	April 15, 1997 -- July 19, 2011
Drug Names	Flomax, NDA 020579
Additional criteria	Refer to Appendix A

* See Appendix B for description of the AERS database.

3 RESULTS

3.1 COUNTS OF AERS REPORTS

Table 2: Counts¹ of AERS Reports From April 15, 1997 to July 19, 2011			
	All reports (US) ²	Serious ³ (US)	Death (US)
Adults (≥ 17 yrs.)	2750 (1096)	1299 (291)	61 (9)
Pediatrics (0-16 yrs.)	13 (6)	8 (2)	0 (0)
Age unknown (Null values)	2501 (1037)	788 (173)	55 (12)
Total	5264 (2143)	1395 (466)	116 (21)
¹ May include duplicates ² US counts in parentheses ³ 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.			

In addition to reviewing pediatric reports with serious outcomes, we also reviewed all reports with the age unknown reporting an outcome of death to determine if the report concerned a pediatric patient. **Figure 1** below summarizes the specific selection of cases to be reviewed in **Section 3.2**.

Figure 1: Selection of Pediatric AERS cases

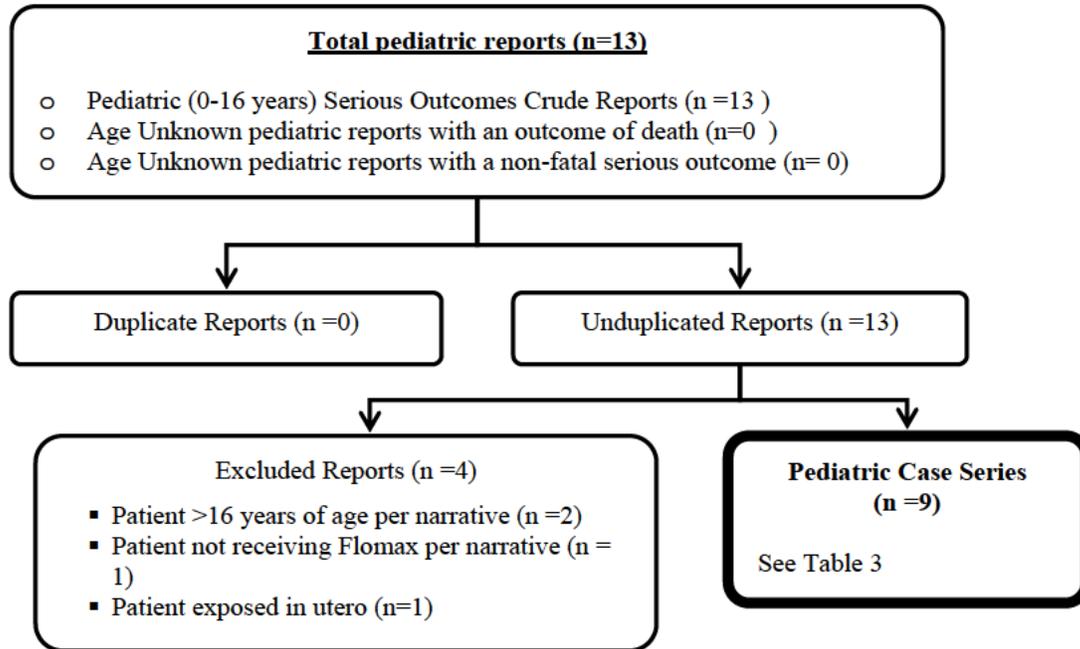
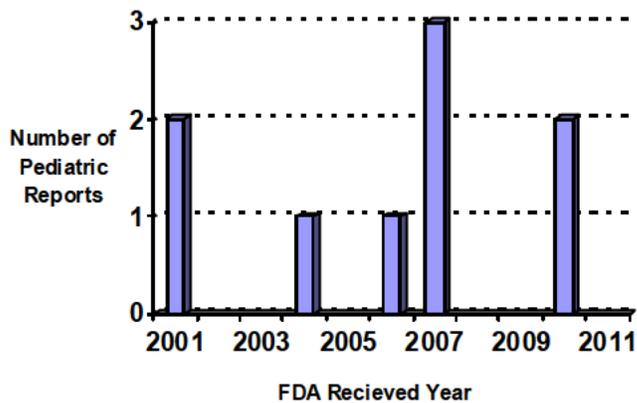


Figure 2 depicts pediatric reports in the case series for Flomax in AERS over time. These counts include data where age (0-16 years) is known. The number of reports received per year ranged between 0 to 3 reports.

Figure 2. Counts of AERS Pediatric Cases for Flomax by Year of FDA receipt (n=9)



3.2 CASE CHARACTERISTICS FROM PEDIATRIC CASE SERIES

There were nine pediatric cases evaluated, including 5 male and 4 female patients. The mean age was 7 years. Five cases were from the United States, 1 foreign and the other 3 not reported. Daily dose ranged from “½ Flomax capsule” to “10 or less capsules”. The mean duration of therapy was 5 days, with a range of one time to 2 weeks. Indications were for relaxing bladder/neurogenic bladder/spasms (3), accidental exposure (3), and unreported (3). The reported serious outcomes were “other” (2) and “hospitalization” (2). There were no pediatric cases with a fatal outcome in this AERS case series.

Table 3 summarizes the 9 AERS cases from the Pediatric Case Series with Flomax.

Table 3: Case characteristics of pediatric case series. [As of July 19, 2011] (N=9)		
Age (n=9)	0- <1 month (0) 2-5 years (5) 12-16 years (2)	1 month- <2 years (1) 6-11 years (1)
Gender	Male (5) Female (4)	Unknown (0)
Country of occurrence	United States (5) Foreign (1)	Not reported (3)
Event date	2000 (2), 2004 (1), 2006 (1), 2007 (3), 2010 (2)	
Daily dose	1.6 mg once (1), "10 or less capsules" (1), 0.2mg UNK (1), "½ Flomax capsule" (1), 200ug/day increased to 400ug/day (1) 0.4mg daily (3), 0.4mg - 0.8mg (1)	
Duration of therapy when reported (n=6) †	Mean: 5 days Median: 3 days	Range: one time to 2 weeks
Indications	Relax bladder/neurogenic bladder/bladder spasms (3), N/A- accidental exposure (3), Unreported (3)	
Outcome (when reported)*	Death (0) Hospitalized (2) Life-threatening (0) Other serious (2) Unknown (0)	Disability (0) Congenital anomaly (0)

† Reviewer interpretation of the narrative

*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. A report may have one or more (>1) outcome.

Appendix C contains AERS Case numbers / ISR numbers and Manufacturer Control Numbers for the Pediatric Case Series from the AERS database.

4 DISCUSSION OF SERIOUS PEDIATRIC CASE SERIES

4.1 SUMMARY OF PEDIATRIC DEATHS (N=0 IN AERS, N =1 IN CLINICAL TRIALS)

No pediatric deaths were reported for this case series in AERS.

There was one pediatric fatality that occurred during the pivotal pediatric Phase III study for NDA 020579. A 7-year-old male patient with a complex medical history including a past medical history of myelomeningocele at L3-L5, Arnold Chiari malformation, hydrocephalous, neurogenic bladder with urinary incontinence, bilateral congenital talipes equino varus (club feet), left nephrectomy for a nonfunctioning hydronephrotic kidney and a shunt for the chronic hydrocephalus received tamsulosin HCl at a dose of 0.05 mg daily. The patient expired approximately 2 weeks after starting tamsulosin. The FDA Medical Officer reviewing the case narrative concluded that this single report was

inconclusive due to a lack of information.⁶ The medical officer's complete synopsis follows below.

One death (Patient 6082) was reported in the pivotal Phase III study BI 527.51. The 7 year old male patient received the first dose of study medication (low dose group) on 16 October 2008 followed by an uneventful clinical evaluation on 24 October 2008 (Visit 3/Week 1) and on 30 October 2008 (Visit 4/Week 2). The patient regularly took the study medication after breakfast under parental guidance with the last dose reported on 31 October 2008. On [REDACTED] (b) (6) at 7 am, the patient's father called the trial coordinator and complained that the patient was sick. He reported that the patient was unresponsive since morning. The father was asked to bring the patient to the site immediately. The patient arrived at the site at 8:45 a.m., where he was found to be expired. Blood pressure and pulse were not recordable, heart sounds were absent, there were no respiratory movements and the pupils were dilated and non-reacting. The patient's parents did not agree to any kind of test or post mortem examination. They removed the dead patient from clinic against medical advice by 9:15 a.m. Hence, autopsy could not be performed. The parents did not respond to phone calls from the clinic. The patient had a past medical history of myelomeningocele at L3-L5, Arnold Chiari malformation, hydrocephalous, neurogenic bladder with urinary incontinence, and bilateral congenital talipes equino varus (club feet). The patient did not have surgical repair of the neural tube defect, nor did he have any intervention for accompanying malformations. The patient did have a left nephrectomy for a nonfunctioning hydronephrotic kidney and a shunt for the hydrocephalus. The primary investigator found the cause of death to be indeterminate and the BI clinical monitor judged that the death was unrelated to the study medication (tamsulosin HCl 0.05 mg).

Reviewer's Comment: The medical officer reviewing this information concluded that "the case narrative of the one death report was inconclusive due to lack of information".⁷

4.2 SUMMARY OF SELECTED PEDIATRIC ADVERSE EVENTS

Of the 9 pediatric cases evaluated, 4 had a serious outcome (2 hospitalizations, 2 categorized as medically significant). Three of these 4 cases involved accidental exposure at doses of 0.2 mg (3 year old child ingested ½ capsule of Flomax 0.4 mg), 1.6 mg (21 month old female ingested great-grandfather's Flomax), and "10 or less capsules" (2 year old female ingested unknown strength or quantity). Two of these cases resulted in

⁶ Clinical Review Chong M. Kim, June 25, 2009, NDA 20-579/S-026 Flomax (tamsulosin hydrochloride Flomax)

⁷ Chong M. Kim, Clinical Review NDA 20-579 tamsulosin hydrochloride (Flomax®), November 25, 2009

a labeled adverse event (diarrhea, hypotension) and one resulted in no harm (accidental dose of “10 or less capsules”). These cases of accidental exposure are being reviewed by DMEPA. In the remaining serious case, bradycardia and hypertension were reported (discussed in Section 4.2.1).

4.2.1 BRADYCARDIA/HYPERTENSION (N=1)

The unlabelled events bradycardia and hypertension were reported in one case involving off-label use of tamsulosin. A 4-year-old male with a history of suprapubic catheter insertion and urinary retention started to experience bradycardia, hypertension and lethargy while receiving treatment with tamsulosin (brand unknown). The reactions started 2 hours post administration and resolved within 5 hours post administration. The boy had been on treatment with tamsulosin (brand unknown) 200 ug for 1 day and with 400 ug for 1 week (dates unspecified). The patient experienced a short episode of hypertension, but the bradycardia was “significant”. During feeling lethargic, the patient was only rousable to being moved or shaken which prompted him to pull awake, but the patient was not alert. At the time of reporting the patient had recovered. Evaluator Comment: “Timelines are suspect. Dechallenge is positive for all events, rechallenge is positive for lethargy”.

Based on this one case report of bradycardia/hypertension with tamsulosin (brand name unknown), a signal with Flomax is not supported at this time.

4.2.2 HYPOTENSION (SEPARATE AERS ANALYSIS, N=163)

OPT requested that DPV conduct a separate AERS search of hypotension reports for Flomax to determine if there were further reports of hypotension in pediatrics. The Adverse Event Reporting System (AERS) database was searched with the strategy described in Appendix D.

As mentioned previously, hypotension is a labeled event for Flomax. An AERS search conducted on July 19, 2011 for serious events of hypotension with Flomax identified 163 reports, 1 of which was a pediatric patient already included in the original case series (ISR 6820454, 3 year old female ingested ½ of Flomax 0.4mg capsule). The child experienced hypotension and was taken to an emergency department. Upon arrival to the emergency department the child received 25 g of activated charcoal (AC) and was started on IV fluids. Within 2 hours of her ingestion, her BP dropped to 64/31 (99/66 = 50 percentile for age group) which responded to a 320 ml bolus of IV fluids. She remained normotensive thereafter and was discharged asymptomatic at 6 hours post ingestion. The Astellas medical reviewer assessed hypotension as serious due to medical significance. The reporting author assessed the causality as probably related to tamsulosin.

4.2.3 ATTENTION PROBLEMS AS AN ASPECT OF COGNITION (N=0)

OPT requested that DPV review the AERS pediatric case series for behavioral effects following Flomax, as this had been noted in the Medical Officer's Clinical Review.⁸ No behavioral issues were noted in the 9 pediatric cases evaluated in this AERS case series.

5 CONCLUSIONS

Overall, no safety issues in pediatric patients were identified in this review of Flomax. Off-label use in one patient resulted in bradycardia and hypertension; both adverse events are unlabeled. However, considering that this is a single case and that Flomax is known to cause hypotension, a signal for Flomax and bradycardia/hypertension is not supported at this time. We also acknowledge the single death from the pediatric clinical trial⁹ for NDA 020579, and agree with the reviewing FDA Medical Officer that the case narrative of the one death report was inconclusive due to lack of information about the cause of death.

Of the 9 pediatric cases reviewed, four cases were serious; of these, 3 involved accidental exposures resulting in a labeled adverse event diarrhea (1), hypotension (1), or overdose (1). These cases of accidental exposure are being reviewed by DMEPA.

6 RECOMMENDATIONS

DPV will continue routine monitoring of adverse events with the use of Flomax in pediatric patients.

⁸ Chong M. Kim, Clinical Review NDA 20-579 tamsulosin hydrochloride (Flomax®), November 25, 2009, page 44

⁹ Clinical Review Chong M. Kim, June 25, 2009, NDA 20-579/S-026 Flomax (tamsulosin hydrochloride Flomax)

7 APPENDICES

7.1 APPENDIX A: STANDARD AERS SEARCHES

- A. Adults (17 yrs and above)
 - 1. All outcomes from approval date (no set criteria)
 - 2. Serious outcomes from approval date
 - 3. Death as an outcome from approval date

- B. Ages 0-16 yrs ONLY
 - 1. Same as above 1-3

7.2 APPENDIX B: ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE DESCRIPTION

The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses AERS to monitor adverse events and medication errors that might occur with these marketed products. The structure of AERS complies with the international safety reporting guidance ([ICH E2B](#)) issued by the International Conference on Harmonization. Adverse events in AERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA).

AERS data do have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive all adverse event reports that occur with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

7.3 APPENDIX C: AERS CASE NUMBERS/ISR NUMBERS AND MANUFACTURER CONTROL NUMBERS FOR PEDIATRIC CASE SERIES

ISR Number	Case Number	Manufacturer Control Number
4427530	4195222	2004-BP-06338BP
5093249	6097287	CA-BOEHRINGER INGELHEIM GMBH, GERMANY-2006-CN-00382CN
6820454	7368139	US-B.I. PHARMACEUTICALS,INC./RIDGFIELD-2010-BP-04796YA
6543398	7250121	US-B.I. PHARMACEUTICALS,INC./RIDGFIELD-2010-BP-00600BP
5528451	6473494	GB-BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.-2007-BP-24758YA
5420169	6387045	US-BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.-2007-BP-07885BP
5426880	6392008	US-BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.-2007-BP-17623BP
3713986	3652240	2000-BP-01208
3714969	5955269	2000-BP-02270

7.4 APPENDIX D: AERS SEARCH STRATEGY FOR HYPOTENSION (SEPARATE AERS ANALYSIS, N=163)

Date	July 19, 2011
Time period	April 15, 1997 -- July 19, 2011
Drug Names	Flomax, NDA 020579
MedDRA** Preferred Terms	orthostatic hypotension, hypotension, diastolic hypotension

* See Appendix B for description of the AERS database.

** MedDRA = Medical Dictionary for Regulatory Activities

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TERESA M RUBIO
10/28/2011

ADRIENNE M ROTHSTEIN
10/28/2011

BINDI M NIKHAR
10/31/2011