CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
21287s016

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	sNDA/SE-8
Application Number(s)	21-287/S016
Priority or Standard	Priority
Submit Date(s)	June 16, 2010
Received Date(s)	June 16, 2010
PDUFA Goal Date	December 16, 2010
Division / Office	Division of Reproductive and Urologic Products (DRUP)
Reviewer Name(s)	Christine P. Nguyen
Review Completion Date	December 13, 2010
Established Name	Alfuzosin
(Proposed) Trade Name	Uroxatral
Therapeutic Class	Alpha adrenergic antagonist
Applicant	Sanofi-aventis U.S., Inc.
Formulation(s)	Oral solution or tablet
Dosing Regimen	0.1 or 0.2 mg/kg/day
Indication(s)	Reduction in detrusor leak point pressure
Intended Population(s)	Pediatric patients 2-16 years with neurogenic bladder and elevated detrusor leak point pressure

Template Version: March 6, 2009

Table of Contents

1 RECOMMENDATIONS/RISK BENEFIT ASSESSMENT 7

1.1 Recommendation on Regulatory Action 7
1.2 Risk Benefit Assessment 7
1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies 8
1.4 Recommendations for Postmarket Requirements and Commitments 8

2 INTRODUCTION AND REGULATORY BACKGROUND 8

2.1 Product Information 8
2.2 Tables of Currently Available Treatments for Proposed Indications 9
2.3 Availability of Proposed Active Ingredient in the United States 9
2.4 Important Safety Issues With Consideration to Related Drugs 9
2.5 Summary of Presubmission Regulatory Activity Related to Submission 10

3 ETHICS AND GOOD CLINICAL PRACTICES 10

3.1 Submission Quality and Integrity 10
3.2 Compliance with Good Clinical Practices 10
3.3 Financial Disclosures 10

4 SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES 11

4.1 Chemistry Manufacturing and Controls 11
4.3 Preclinical Pharmacology/Toxicology 11
4.4 Clinical Pharmacology 11
4.4.1 Mechanism of Action 11
4.4.3 Pharmacokinetics 13

5 SOURCES OF CLINICAL DATA 16

5.1 Tables of Studies/Clinical Trials 16
5.2 Review Strategy 18
5.3 Discussion of Individual Studies/Clinical Trials 18

6 REVIEW OF EFFICACY 20

Efficacy Summary 20
6.1 Indication 20
6.1.1 Methods 20
6.1.2 Demographics 20
6.1.3 Subject Disposition 22
6.1.4 Analysis of Primary Endpoint(s) 23
6.1.5 Analysis of Secondary Endpoints(s) 29
6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations 30

7 REVIEW OF SAFETY 31

Safety Summary 31
7.1 Methods 31
7.1.1 Studies/Clinical Trials Used to Evaluate Safety 31
7.1.2 Categorization of Adverse Events 31
7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence 31
7.2 Adequacy of Safety Assessments 31
7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations 31
7.2.2 Explorations for Dose Response 32
7.2.3 Special Animal and/or In Vitro Testing 32
7.2.4 Routine Clinical Testing 33
7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class 33
7.3 Major Safety Results 33
7.3.1 Deaths 33
7.3.2 Nonfatal Serious Adverse Events 33
7.3.3 Dropouts and/or Discontinuations 34
7.3.4 Significant Adverse Events 35
7.3.5 Submission Specific Primary Safety Concerns 35
7.4 Supportive Safety Results 36
7.4.1 Common Adverse Events 36
7.4.2 Laboratory Findings 38
7.4.3 Vital Signs 39
7.4.4 Electrocardiograms (ECGs) 40
7.4.5 Special Safety Studies/Clinical Trials 41
7.5 Other Safety Explorations 41
7.5.1 Dose Dependency for Adverse Events 41
7.6 Additional Safety Evaluations 41
7.6.2 Human Reproduction and Pregnancy Data 41
7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound 41

8 POSTMARKET EXPERIENCE 41

9 APPENDICES 42

9.2 Labeling Recommendations 42

Table of Tables

Table 1: Plasma pharmacokinetic parameters of alfuzosin solution in children 2-7 years old (TID regimen) 14
Table 2: Plasma pharmacokinetic parameters of alfuzosin tablet in children 8-16 years old (BID regimen) 14
Table 3: Formulation effect (estimates formulation ratios with 90% CIs) 16
Table 4: Summary of Clinical Trials 16
Table 5: Demographics and baseline characteristics (EFC5722, ITT) 20
Table 6: Baseline disease characteristics (EFC5722, ITT) 21
Table 7: Baseline mean (SD) detrusor LPP (cm H_2O) by treatment and age group (EFC5722, ITT) 21
Table 8: Detrusor leak point pressure by treatment group (EFC5722, ITT) 23
Table 9: Proportion of patients with detrusor leak point pressure < 40 cm H_2O by age, anticholinergic, and treatment (EFC5722, ITT) 24
Table 10: Summary of complete and partial response rates at Week 12 (ITT, EFC6269) 27
Table 11: Descriptive statistics on grade of hydronephrosis at baseline and Week 12 (ITT, EFC6269) 28
Table 12: Absolute and relative change from baseline detrusor LPP at Week 12 (EFC5722, ITT) 29
Table 13: Common AEs reported by at least 5 subjects by Preferred Term (Safety, EFC5722) 37
Table 14: Common AEs reported by at least 5 patients by Preferred Term (Safety, EFC5722) 38
Table 15: Vital sign changes during the double-blind period (Safety, EFC5722) 39
Table 16: QTc changes from baseline exceeding thresholds in patients with normal QTc at baseline (Safety, EFC5722) 40

Table of Figures

Figure 1: Subgroup analyses of detrusor leak point pressure (ITT, EFC5722) 25

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From a clinical perspective, this supplement NDA should be approved to include new pediatric data, but not a new pediatric indication, in the prescribing information of Uroxatral (alfuzosin). Results of the primary trial EFC5722 did not demonstrate efficacy of alfuzosin treatment for the reduction of detrusor leak point pressure in pediatric patients 2-16 years old with elevated detrusor leak point pressure due to a neurological condition. No new or unexpected safety findings were observed in the target pediatric population.

1.2 Risk Benefit Assessment

Trial EFC5722 was an international, multicenter, randomized, 12-week, double-blind, placebo-controlled, parallel group study to assess the efficacy and safety of oral alfuzosin in the reduction of detrusor leak point pressure (LPP) in children 2-16 years old with elevated detrusor LPP of neurogenic origin. Study patients were randomized in a 1:1:1 fashion to alfuzosin 0.1 mg/kg/day, alfuzosin 0.2 mg/kg/day, or matching placebo and were stratified by age group (2-7 years old, 8-16 years old) and anticholinergic use (yes/no). The double-blind study was followed by a 40-week open-label safety extension. Overall, 172 patients were randomized and treated; 57 patients were in the placebo group, 57 patients in the alfuzosin 0.1 mg group, and 58 patients in the alfuzosin 0.2 mg group. One hundred-sixty seven (167) completed the 12-week double-blind period, and 163 entered the open-label period. The treatment groups were balanced with respect to baseline demographics and disease characteristics.

The primary endpoint was response to treatment defined as the proportion of subjects with a detrusor LPP < 40 cm H_2O at Week 12 (end of treatment). A total of 172 patients were included in the ITT population. The response rates for placebo, alfuzosin 0.1 mg/kg/day, alfuzosin 0.2 mg/kg/day were 40%, 40% (p=1.0), and 48% (p=0.9), respectively. Adjusting for age and anticholinergic use did not change the results of the primary analysis. Results of analyses of the secondary efficacy endpoints were similar to that of the primary endpoint, with no statistical differences observed between drug and placebo groups.

Safety assessments included collection of all adverse events, physical examination, vital signs (including orthostatic), safety ECGs, vision and cognitive testing, and monitoring of laboratory tests (hematology, chemistry, hormones, urine). Of the 172 subjects who received at least one dose of study drug in the double-blind period, 65%, 50%, and 61% of patients in placebo, alfuzosin 0.1 mg, and alfuzosin 0.2 mg groups, respectively, reported at least one adverse event. No deaths occurred in the entire

pediatric program. One placebo patient (weight decreased) and 2 alfuzosin patients (shunt malformation, epilepsy) experienced a serious adverse event, none of which were considered treatment-related. One placebo patient (dizziness) and 3 alfuzosin patients (pruritic rash, diarrhea x 2) discontinued due to adverse events. The most common adverse events were nasopharyngitis (13%), pharyngitis (11%), and cystitis (10%). Common adverse events reported at a higher incidence in both alfuzosin dose groups than placebo included respiratory tract infection (placebo at 2% vs. alfuzosin 0.1 mg at 3% and alfuzosin 0.2 mg at 3%), pyrexia (1% vs. 2% and 5%), diarrhea (1% vs. 3% and 2%), and headache (1% vs. 2% and 3%). The safety findings in the open-label period were similar to those in the placebo-controlled period. Dizziness was reported at a similar rate between placebo and any active treatment (1.8%); no drug-related syncope or orthostatic hypotension occurred in the entire pediatric program.

Because the pediatric data did not demonstrate efficacy, no risk/benefit assessment for a new indication was necessary.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No postmarket risk evaluation and management stragtegies are recommended.

1.4 Recommendations for Postmarket Requirements and Commitments

No postmarket requirements and commitments are recommended other than the routine postmarket surveillance required by law.

2 Introduction and Regulatory Background

2.1 Product Information

Alfuzosin, an alpha adrenergic antagonist, is approved and marketed worldwide for the treatment of benign prostatic hyperplasia (BPH). It has been registered in the European Union since 1987 as an immediate-release 2.5 mg tablet for a three times daily administration, since 1994 as an extended-release 5 mg tablet for a twice daily treatment, and since 1999 as an oral 10 mg extended-release tablet (OD formulation). The OD formulation of alfuzosin was registered in 2002 in Canada and in 2003 in the United States under the trade name Uroxatral under NDA 21-287.

Two oral formulations (extended-release tablet and immediate-release solution) were developed and used in the pediatric trials.

- Tablet film-coated extended-release tablets contain 1.5 mg of alfuzosin hydrochloride and the following excipients:

- (b) (4)
- (b) (4)
- Matching placebo tablets contained the same excipients

- Solution: supplied for oral administration as a 0.2 mg/mL solution. Excipients included (b) (4) The matching placebo solution contained the same excipients.

2.2 Tables of Currently Available Treatments for Proposed Indications

No pharmacotherapy is currently approved for the treatment of elevated detrusor leak point pressure (LPP) in pediatric patients with neurogenic bladder.

Reviewer's comment*: Another alpha-adrenergic antagonist, tamsulosin, was recently evaluated in the same pediatric population* (b) (4)

2.3 Availability of Proposed Active Ingredient in the United States

Alfuzosin is currently approved under NDA 21-287 for the treatment of symptomatic BPH. The approved dose and formulation is alfuzosin 10 mg tablet, once daily (OD formulation). No pediatric formulation is approved worldwide.

2.4 Important Safety Issues With Consideration to Related Drugs

Alfuzosin belongs to the pharmacologic class of alpha-adrenergic antagonist. Safety issues associated with this drug class include:

- Postural hypotension/syncope: Alpha-adrenergic antagonists cause peripheral adrenergic blockade, leading to peripheral vasodilatation and subsequent fall in blood pressure. Clinically significant outcomes are orthostatic hypotension and syncope. The hypotensive effects can be potentiated by the concomitant use of other alpha-adrenergic antagonists, antihypertensives, or nitrates.
- Rare but potentially serious adverse effects of alpha-adrenergic antagonist treatment include Intraoperative Floppy Iris Syndrome (IFIS) and priapism.
- Common adverse reactions observed in BPH trials include dizziness, upper respiratory infection, headache, fatigue, and nasal congestion.
- Alfuzosin should be use with caution in patients with severe renal impairment or a history of QT prolongation, or those taking medications which prolong the QT interval. A thorough QT study conducted in healthy adults demonstrated that, at the approved dose of 10 mg, no QTc prolongation was observed using various methods to correct

for effect of heart rate changes. At alfuzosin 40 mg, the upper bound of the 95% confidence interval around the mean QTc interval using the Fridericia method (but not other methods) exceeded the regulatory threshold of 10 ms (13.5 ms), but was still lower than that observed with the positive control moxifloxacin. The clinical impact of this finding is unknown.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Alfuzosin, 10 mg OD tablet, was approved for the treatment of symptomatic BPH under NDA 21-287 in 2003.

(b) (4)

On February 21, 2006, the Agency issued a pediatric Written Request (WR) outlining 3 pediatric studies in children with neurogenic bladder (one pharmacokinetic study, one pivotal pharmacodynamic/efficacy study, and one supportive exploratory efficacy and safety study in children with hydronephrosis). A relative bioavailability study was also conducted in response to the WR under Drug Information section, which stated that, when appropriate, "a relative bioavailability study comparing the approved drug to the age-appropriate formulation may be conducted in adults." The objective of the WR was to evaluate the safety and efficacy of alfuzosin in pediatric patients ages 2 – 16 years with elevated detrusor leak point pressure (LPP) with or without hydronephrosis of neurologic etiology. Two amendments to the WR were issued: Amendment 1 (June 15, 2006) modified the date of final study report submissions to June 16, 2010; Amendment 2 (October 17, 2008) allowed for the inclusion of pediatric patients with Grade 3 hydronephrosis in the exploratory safety and efficacy study.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

No DSI audit was necessary because no new indication was granted.

3.2 Compliance with Good Clinical Practices

Per the Applicant, all studies were conducted in accordance with FDA guidelines on "Good Clinical Practice" and the principles of the Declaration of Helsinki.

3.3 Financial Disclosures

Financial disclosure information was provided for the 4 studies submitted in this sNDA (PKM6270, EFC5722, EFC6269, and BDR10380). One investigator in study PKM6270 (b) (6) and another in study EFC5722 (b) (6) had

disclosable financial interest. These investigators, however, did not have proprietary interest in the tested product. Financial disclosure information from one investigator in Study EFC5722 (b) (6) was missing due to the investigator leaving the clinical trial site and unsuccessful attempts to reach the investigator. Per the Applicant, the investigator did not perform any patient assessment. The remaining 84 investigators had no disclosable financial interests.

Reviewer's comment*: Adequate financial disclosure information was submitted to demonstrate compliance with financial disclosure requirements.*

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

CMC recommends approval of this supplement. No CMC information was submitted in the submission. There were no changes proposed for the CMC information in the product label.

4.3 Preclinical Pharmacology/Toxicology

The toxicology team recommends approval of this supplement. In discussions that preceded the Written Request, the Applicant agreed to conduct a juvenile rat study to assess any new potential risks in a juvenile animal model. This study did not show any new safety signals in the juvenile model. The reader is referred to the pharmacology/toxicologist's review.

4.4 Clinical Pharmacology

The clinical pharmacology team recommends the approval of this pediatric supplement.

4.4.1 Mechanism of Action

In children, the primary cause of neurogenic voiding disorders is congential myelodysplasia and similar congenital malformations; other causes include spinal cord tumor or injury and perinatal cerebral palsy. Voiding disorders can be due to either the inability to store urine and/or poor bladder emptying due to an inability to relax the bladder neck, sphincter, and/or the pelvic floor musculature during voiding. Poor bladder emptying due to lack of coordination between the detrusor contractions and urethral sphincter relaxation from a neurologic cause is termed neuropathic detrusor-sphincter dyssynergia. Consequently, a high pressure/low compliant bladder develops with

possible complications of vesicoureteral reflux, hydronephrosis, and chronic renal disease; urinary tract infections are also common in children with neurogenic bladder.

Management of children with neurogenic bladder includes intermittent clean catherization (CIC) and anticholinergic therapy in children with detrusor overactivity (storage dysfunction). Currently, no pharmacotherapy has been approved for the treatment of emptying voiding dysfunction. One of the aims of treatment of children and adolescents with poor bladder emptying is to relax the bladder outlet, which may improve the coordination of detrusor contraction and sphincter relaxation, and preserving upper urinary tract function. Improved bladder emptying has been shown to reduce voiding bladder pressures, improve hydronephrosis and decrease risk of renal damage, and decrease the frequency of urinary tract infections (UTIs).

The presence of alpha-1-adrenergic receptors has been documented at the bladder outlet and in the proximal urethra (1). Increased α-receptor activity has been demonstrated in the setting of bladder instability secondary to bladder outlet obstruction (2). Alpha-blockade therapy, such as alfuzosin, is hypothesized to reverse these effects and facilitate relaxation of the bladder base, proximal urethra and external sphincter.

According to the Applicant, alfuzosin acts selectively antagonizes postsynaptic alpha 1-adrenoreceptors located in the urogenital organs. Studies with alfuzosin have demonstrated improvement in urodynamic parameters with decreases in peak urethral pressure, increases in vesicourethral diameter, or decreases in residual urine volume in adult patients with neuropathic bladder (3). One study conducted with alfuzosin in 17 children with neurogenic bladder treated for at least 3 weeks showed improvement in urodynamic parameters, including detrusor LPP (4).

McGuire et al (5) first suggested that detrusor LPP above 40 cm H_2O in a low compliant bladder was associated with an increased risk of upper urinary tract deterioration in children with neurogenic bladder; if detrusor LPP exceeded 40 cm H_2O during cystometry, ureterovesical reflux and dilated ureters was found in 68% and 81% of patients, respectively. Detrusor LPP has been used most frequently to predict upper tract problems in neurological patients with reduced bladder compliance. The initial care of newborns with spina bifida focuses on preventing bladder and upper urinary tract damage from detrusor LPP > 40 cm H_2O.

1 De Voogt HJ, van der Sluis C. Preliminary evaluation of alpha-adrenergic blocking agents in children with neurogenic bladder due to myelomeningocele. Dev Med Child Neurol Suppl. 1976; (37): 82-8.
2 Mingin GC, Nguyen, HT, Mathias RS, et al. Growth and metabolic consequences of bladder augmentation in children with myelomeningocele and bladder exstrophy. Pediatrics. 2002;110:1193-8.
3 Park JM, McGuire EJ, Koo HP, et al. External urethral sphincter dilation for the management of high risk myelomingocele: 15-year experience. J Urol. 2001;165:2383-8.
4 Schulte-Baukloh H, Michael T, Miller K, et al. Alfuzosin in the treatment of high leak point pressure in children with neurogenic bladder. BJU Int. 2002;90:716-20.
5 McGuire E, Woodside J, Borden T et al. Prognostic value of urodynamic tstng in myelodysplastic patients. J Urol. 1981;126:205-9.

4.4.3 Pharmacokinetics

Pharmacokinetics of the 2 pediatric formulations was evaluated in study PKM6270. In addition, a population pharmacokinetic (PopPK) analysis was conducted using the pooled PK data from the 3 pediatric studies and a comparative bioavailability study was conducted evaluating the PK of the approved adult formulation to the pediatric formulations. Results are summarized below; refer to the clinical pharmacologist's review for detailed analyses.

Study PKM6270:
This study was an international, multicenter, randomized, open-label, parallel-group, PK study of two fixed oral doses of alfuzosin (0.1 and 0.2 mg/kg/day) in children and adolescents of both genders with elevated detrusor LPP of neuropathic etiology and LPP ≥ 40 cm H_2O. After a screening period of up to 4 weeks, patients were randomized and received study treatment for 4 weeks. The treatment period was followed by a 1-week follow up period. The primary objective of this study was to investigate the PK of two doses of alfuzosin (0.1 or 0.2 mg/kg/day) given as a solution (alfuzosin 0.2 mg/mL) three times daily (TID) in children (2 to 7 years) or given as tablets (alfuzosin 1.5 mg per tablet) twice daily (BID) regimen in children or adolescents (8-16 years). Blood samples were obtained in Day 1 and Day 7. A total of 29 subjects were enrolled (15 patients randomized to the 0.1mg/kg/day group; 14 patients randomized to the 0.2 mg/kg/day group); 15 patients were in the 2-7 year old group and 14 were in the 8-16 year old group. Results are shown in Tables 1 and 2.

Table 1: Plasma pharmacokinetic parameters of alfuzosin solution in children 2-7 years old (TID regimen)

	C_{max} [1] (ng/mL)	t_{max} [1] (h)	C_{max} [2] (ng/mL)	t_{max} [2] (h)	AUC_{0-4} [1] (ng.h/mL)	AUC_{4-8} [2] (ng.h/mL)	AUC_{0-8} (ng.h/mL)
				0.1 mg/kg/day			
Day 1 N=7	6.41±3.99 (62) [5.59] N=6	1.50 (1.00-2.02) N=6	6.68±1.52 (23) [6.51]	0.75 (0.75-1.88)	13.9±5.93 (43) [12.9]	19.1±4.89 (26) [18.6]	33.0±6.55 (20) [32.5]
Day 7 N=7 Rac	6.89±3.40 (49) [6.17]	1.00 (0.97-2.05)	6.45±2.75 (43) [5.99]	0.83 (0.71-1.82)	16.9±6.69 (40) [15.8] [1.22]	18.4±6.58 (36) [17.4] [0.94]	35.2±13.1 (37) [33.3] [1.02]
				0.2 mg/kg/day			
Day 1 N=8	17.1±10.1 (59) [14.6]	1.00 (1.00-2.00)	18.7±10.7 (57) [16.2]	0.89 (0.75-3.97)	42.9±22.1 (52) [38]	50.8±30.6 (60) [43.1]	93.7±49.3 (53) [83.1]
Day 7 N=8 Rac	22.3±13.8 (62) [18.8]	1.01 (1.00-2.00)	24.6±13.5 (55) [20.7]	1.25 (0.71-1.80)	55.9±33.9 (61) [46.3] [1.22]	67.0±35.7 (53) [57.1] [1.33]	123±69.3 (56) [104] [1.25]

Tabulated values are Mean ± SD (CV%) [Geometric Mean] except for t_{max} where values are Median (Min, Max)

[1] PK parameters after the fist drug intake of the day

[2] PK parameters after the second drug intake of the day

Source: NDA 21-287/S016, Module 2.5, Clinical Overview, p. 14, Table 3

Table 2: Plasma pharmacokinetic parameters of alfuzosin tablet in children 8-16 years old (BID regimen)

	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-12} (ng.h/mL)
		0.1 mg/kg/day	
Day 1 N=7	3.41±2.20 (65) [2.86]	3.43 (2.95-8.00)	24.2±9.92 (41) [22.3] N=6
Day 7 N=7 Rac	5.85±2.91 (50) [4.91]	3.00 (0.00-7.88)	56.5±11.4 (20) [55.5] N=5 [2.49]
		0.2 mg/kg/day	
Day 1 N=7	7.26±1.76 (24) [7.07]	3.93 (2.98-4.03)	50.0±15.4 (31) [48.0]
Day 7 N=7 Rac	12.4±2.85 (23) [12.1]	3.17 (2.98-4.02)	82.5±19.9 (24) [80.1] [1.67]

Tabulated values are Mean ± SD (CV%) [Geometric Mean] except for tmax where values are Median (Min, Max)

Source: NDA 21-287/S016, Module 2.5, Clinical Overview, p. 14, Table 4

For the same daily dose (mg/kg/day), the solution formulation resulted in higher exposure (Cmax, AUC) than tablet formulation. For the solution formulation, exposure was greater than dose proportional (~ 3X increase in AUC from 0.1 mg/kg/day to 0.2 mg/kg/day on Day 7). For the tablet formulation, exposure was less than dose proportional (~1.4X increase in AUC from 0.1 mg/kg/day to 0.2 mg/kg/day on Day 7).

Reviewer's comment*: Study PKM6270 provided PK data for the new pediatric formulations (solution, tablet). These data showed that the 2 pediatric formulations are not equivalent in terms of Cmax and AUC and therefore are not interchangeable (i.e. given the same dose, exposure with solution [Cmax] is expected to be higher than that observed with tablet for the 8-16 year-olds).*

Study POH0209 (Population PK):
The objective of study POH0209 was to develop and qualify a PopPK model for alfuzosin based on PK data obtained from the 3 pediatric studies [PKM6270, EFC5722, and EFC6269]) to assess alfuzosin PK variability and the influence of key demographic factors (body weight, age, sex, and race), renal function, and formulation (solution, tablet) on alfuzosin PK parameters. Overall, 209 patients exposed to alfuzosin (841 concentrations), with 134 administered with solution (572 samples) and 75 administered with tablet (269 samples) were included in the analysis. Gender, age, race, creatinine clearance, and dose did not have any statistically significant influence on alfuzosin PK. Drug formulation and body weight were significant covariates affecting alfuzosin PK variability. The absorption rate constant of alfuzosin was ~3-fold higher in the solution compared to the tablet. The apparent clearance of alfuzosin was 1.7-fold higher for a 45 kg child compared to a 20.7 kg child (45.0 kg and 20.7 kg were the mean body weight for tablet and solution formulations, respectively).

Relative bioavailability study (BDR10380):
This was a phase 1, single center, open-label, randomized, repeated-dose (3 days), 3-period with 3-sequence crossover study. Each treatment period was separated by a 4-day (± 1 day) wash-out period. The primary objective of this study was to determine the relative bioavailability of each of the 2 pediatric formulations of alfuzosin (0.2 mg/mL solution administered TID and 1.5 mg tablet administered BID) compared to the approved alfuzosin 10 mg OD tablet reference formulation. The study enrolled 15 healthy male subjects; all completed the study. Results are shown in Table 3.

Table 3: Formulation effect (estimates formulation ratios with 90% CIs)

Parameter	Comparison	Estimate	90% CI
AUC_{0-24} normalized to 10 mg (ng.h/mL)	A vs. C	1.42	(1.28 to 1.57)
	B vs. C	1.27	(1.15 to 1.40)
AUC_{0-24} (ng.h/mL)	A vs. C	1.06	(0.96 to 1.17)
	B vs. C	1.14	(1.03 to 1.26)
C_{max} (ng/mL)	A vs. C	1.00	(0.88 to 1.15)
	B vs. C	0.97	(0.91 to 1.04)

Treatment A = alfuzosin 7.5 mg (12.5 mL pediatric solution TID)
Treatment B = alfuzosin 9 mg (3 x 1.5 mg pediatric ER tablets BID)
Treatment C = alfuzosin 10 mg (1 x 10 mg adult ER tablet OD)
PGM=SL77049910/BDR10380/CSR/BS/PGM_RPT/PK_BDR10380_KRM.sas OUT=OUTPUT/pk_FORM_k_t_2_i.rtf (02SEP2008 - 14:01)
Source: NDA 21-287/S016, Module 2.5, Clinical Overview, p. 11, Table 1

When normalized to the same dose of 10 mg, the bioavailability of the pediatric solution and pediatric tablet were 42% and 27% higher, respectively, than that of the marketed OD tablet. The Cmax values of the 3 formulations, however, were similar for the doses tested. The pediatric solution dose of 7.5 mg and pediatric tablet dose of 9 mg provided similar bioavailability to that of OD tablet dose of 10 mg.

***Reviewer's comment**: According to the pharmacometric reviewer, the approved adult dose of alfuzosin 10 mg OD (once daily) provided for a systemic exposure similar to alfuzosin 0.11-0.14 mg/kg/day using the pediatric formulations. Therefore, the pediatric doses of 0.1 and 0.2 mg/kg/day used in the phase 3 pediatric trials provided systemic exposure similar to the therapeutic exposure in adults.*

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 4 summarizes the clinical studies conducted with the pediatric formulations of alfuzosin. The study population for the 3 pediatric studies included children and adolescents 2 – 16 years old with elevated detrusor leak point pressure (LPP) of neurologic etiology. The pediatric patients were stratified into 2 age groups: 2-7 years old ("younger" age group) and 8-16 years old ("older" age group).

Table 4: Summary of Clinical Trials

Study Name/ Study Design	Objective Population Endpoint	Test Product	Study outcomes
PKM6270/ 4-week,	Characterize the PK for 2 doses of alfuzosin in	0.1 or 0.2 mg/kg/day with:	Total: 29

multicenter, open-label, randomized, parallel group (6 centers)	children and adolescents 2 – 16 years of age stratified into 2 age groups (2-7 years, 8-16 years) Pediatric patients with elevated detrusor leak point pressure (LPP) of neuropathic etiology PK parameters	(a) solution (2-7 years) or (b) tablet (8-16 years)	Gender: 11M/18F Age: 7.6 ± 3.9 years Treatment groups: 0.1 mg/kg/day (N=14) 0.2 mg/kg/day (N=15)
EFC5722/ Multicenter, double-blind, randomized, placebo-controlled, parallel group (12 weeks controlled, 40 weeks open-label) (49 centers)	Efficacy of alfuzosin compared to placebo on detrusor LPP Pediatric patients 2-16 years old with elevated detrusor leak point pressure (LPP) of neuropathic etiology Change from baseline LPP	0.1 or 0.2 mg/kg/day with: (a) solution (2-7 years, 8-16 years) or matching placebo (b) tablet (8-16 years) or matching placebo	Total: 172 (placebo-controlled)/153 (open-label) Gender: 87M/85F Age: 8.3 ± 4.0 years Treatment groups: 0.1 mg/kg/day (N=57) 0.2 mg/kg/day (N=58) Placebo (N=57)
EFC6269/ Multicenter, open-label, stratified (age group, formulation), non-comparative (12 weeks initial phase, 40-weeks safety extension) (13 centers)	Efficacy of alfuzosin on hydronephrosis Pediatric patients 2-16 years old with elevated detrusor leak point pressure (LPP) of neuropathic etiology and newly diagnosed or progressive hydronephrosis Change from baseline in grade of hydronephrosis	0.2 mg/kg/day with: (a) solution or (b) tablet	Total: 25 (initial 12 weeks)/22 (open-label) Gender: 9M/16F Age: 7.9 ± 4.0 years Treatment groups: 0.2 mg/kg/day (N=25)
BDR10380/ Single-center, open-label, randomized, multi-dose (3 days), 3-period, 3-sequence crossover	Relative bioavailability of alfuzosin pediatric formulations (solution, table) compared to adult tablet formulation (once-daily tablet) Healthy adult males PK parameters	Solution: 7.5 mg/day (split 3 times daily) Pediatric tablet: 9 mg/day (split 2 times daily) OD tablet: 10 mg once daily	Total: 15 Gender: 15M Age: 26.6 ± 7.4 years Treatment groups: Solution (N=15), pediatric tablet (N=15), OD tablet (N=15)

Source: NDA 21-287/S016, Module 5.2, Tabular Listing of Clinical Studies

5.2 Review Strategy

The focus of the clinical review is on study EFC5722 with supportive information from EFC6269 and PKM6270. The relative BA study (BDR10380) in healthy adult males will not be further discussed in this clinical review; the reader is referred to the clinical pharmacologist's review.

5.3 Discussion of Individual Studies/Clinical Trials

Study PKM6270 (study period: 7/10/06 to 2/23/07) This was an international, multicenter, 4-week, randomized, open-label, parallel-group PK study of 2 doses of alfuzosin (0.1 mg/kg/day or 0.2 mg/kg/day) in children and adolescents of both genders with elevated detrusor LPP (≥ 40 cm H_2O) of neurologic etiology. Patients were randomized to either dose group and received treatment for 4 weeks, followed by a 1-week off-treatment period. The primary objective was to characterize the PK of 2 doses of alfuzosin given as a solution TID in children 2-7 years old and given as tablets BID in children 8-16 years old. A total of 29 patients were enrolled and received treatment.

Study EFC5722 (study period: 10/24/07 to 12/9/09): This was an international, multicenter, 12-week, double-blind, placebo-controlled study to investigate the efficacy, pharmacodynamics, and safety of 2 oral doses of alfuzosin (0.1 and 0.2 mg/kg/day) in pediatric patients 2-16 years of age with elevated LPP associated with neurological disorder, followed by a 40-week open label extension phase. The primary objective was to evaluate the efficacy of alfuzosin compared to placebo on detrusor LPP in the target population. The study consisted of a 4-week screening period, a 12-week double-blind period, followed by a 40-week open label safety extension. This was conducted at 49 sites in 15 countries; 7 sites were in the United States. The number of patients randomized per site ranged from 1 to 18. One hundred seventy-two (172) patients were enrolled and treated, 153 of who completed the entire study. The study employed an Independent Data Monitoring Committee (DMC).

Key inclusion criteria: Pediatric patients age 2 – 16 years old with elevated detrusor LPP (≥ 40 cm H_2O and < 100 cm H_2O) due to a neurological etiology

Study treatment: Daily dose was adjusted to body weight on an mg/kg basis.

- *Oral Solution* (containing 0.2 mg/mL alfuzosin or 0.2mg/mL placebo): 0.1 mg/kg/day or 0.2 mg/kg/day divided into 3 doses given at breakfast, lunch, and dinner. The maximum total daily dose was 7.5 mg, which corresponded to the maximum daily dose in adults. Patients in the age group 2-7 years received the solution formulation.
- *Oral Tablet* (containing 1.5 mg alfuzosin or 1.5 mg placebo): 0.1 mg/kg/day or 0.2 mg/kg/day divided into 2 doses given at breakfast and dinner. The maximum total daily dose was 10 mg. Patients in the age group 8-16 years received tablet or solution formulation.

Primary Endpoint: proportion of patients with LPP < 40 cm H_2O at the end of the double-blind period (Week 12). Responders were defined as patients with LPP < 40 cm H_2O at Week 12.

Secondary Endpoints: absolute and relative change in detrusor LPP, relative change in detrusor compliance, and the number of urinary tract infections (UTI)

The primary efficacy population was the Intent-to-Treat (ITT) population, which comprised of randomized and treated patients who had ≥ 1 post-baseline value and, whenever appropriate, a baseline value. The per-protocol (PP) population included all patients in the ITT population with no major efficacy-related protocol deviation. Efficacy analyses were performed on the PP population only if the difference in the number of patients in the ITT and PP populations was ≥ 5%. The primary analysis of the primary efficacy endpoint was the comparison between each alfuzosin dose and placebo on the ITT population, conducted with a Fisher's exact test. A two-sided 95% confidence interval (CI) for pairwise differences alfuzosin versus placebo in success rates (detrusor LPP <40 cm H_2O at Week 12) was built based on the Wilson's score method without continuity correction. A Fisher's exact test at the 2-sided 2.5% significance level was used to account for multiplicity of doses (0.1 mg and 0.2 mg/kg/day) (Hochberg correction).

The safety population included all randomized patients exposed to study medication. In case of switch of study treatment during the course of the trial, patients were analyzed in the lowest dose of alfuzosin actually received. Analyses of safety variables for 12-week double-blind period and for the entire 52-week study period (12 weeks double-blind period + 40 weeks open-label extension) were performed using the safety population. The safety data were presented by descriptive statistics.

Study EFC6269 (study period: 3/6/08 to 10/9/09): This was an international, multicenter, 12-week, open-label, non-comparative study investigating the efficacy, pharmacodynamics, and safety of alfuzosin 0.2 mg/kg/day in children and adolescents 2-16 years of age with newly diagnosed or progressive hydronephrosis associated with elevated detrusor LPP of neurologic etiology, followed by a 40-week open label extension phase. The primary objective of the study was to determine efficacy of alfuzosin in the treatment of children and adolescents 2-16 years of age presenting with a detrusor LPP ≥ 40 cm H_2O and with newly diagnosed or progressive hydronephrosis. The study was conducted at 13 sites in 8 countries (India, Maylasia, Poland, Russia, Singapore, Slovakia, Taiwan, and Turkey). The number of patients randomized per site ranged from 1 to 6. A total of 25 patients were enrolled and treated, 22 of who completed the entire study. The study employed an independent Data Monitoring Committee.

Amendment: One protocol amendment dated May 5, 2008, was submitted to the original protocol and was implemented prior to the completion of the study. The change

allowed the enrollment of patients with Grade 3 hydronephrosis. The change to the inclusion criteria did not affect the integrity of the efficacy or safety analyses.

6 Review of Efficacy

Efficacy Summary

Alfuzosin at 0.1 or 0.2 mg/kg/day was not superior to placebo in reducing detrusor leak point pressure in pediatric patients with elevated detrusor LPP ≥ 40 cm H_2O of neurologic etiology.

6.1 Indication

The treatment of pediatric patients, age 2 to 16 years, with elevated detrusor leak point pressure associated with a known neurological disorder.

6.1.1 Methods

Efficacy data and analyses were not pooled. The efficacy review focuses on the findings of study EFC5722. Primary efficacy analyses of study EFC6269 will also be presented.

6.1.2 Demographics

EFC5722:
Baseline demographic characteristics were similar across the 3 treatment groups. Of the 172 randomized patients, 87 were males and 85 females, and 84 were in the 2-7 year-old age group and 88 in the 8-16 year-old age group. A majority of patients were Caucasians (80%). By Tanner staging, 56/87 (65%) males and 51/85 females (60%) were pre-adolescent. The mean age and weight were 8.3 years and 29.9 kg, respectively. See Table 5.

Table 5: Demographics and baseline characteristics (EFC5722, ITT)

Mean values	Placebo N=57	Alfuzosin 0.1 mg N=57	Alfuzosin 0.2 mg N=58	Total N=172
Age (years)	8.3	7.9	8.7	8.3
Gender-% Male/female	51/49	53/47	48/52	51/49
Weight (kg)	30	29	31	30
Puberty stage in girls (% pre-adolescent)	57	67	57	60
Puberty stage in boys (% pre-adolescent)	62	67	75	64

Source: NDA 21-287/S016, Module 5.3.5.1, Study Report, p. 54, Table 10

Baseline disease characteristics were balanced across the treatment groups and are presented in Table 6. Overall, 91 of 172 patients (53%) were concomitantly treated with

anticholinergic therapy (range: 49% [placebo] to 55% [alfuzosin 0.2 mg]). Ninety-four of 172 patients (55%) were using clean intermittent catherization (CIC) at randomization (range: 49% [alfuzosin 0.1 mg] to 61% [placebo]).

Table 6: Baseline disease characteristics (EFC5722, ITT)

	Placebo N=57 n (%)	Alfuzosin 0.1 mg N=57 n (%)	Alfuzosin 0.2 mg N=58 n (%)	Total N=172 n (%)
Spina bifida	25 (44)	31 (54)	29 (50)	85 (50)
Meningomyelocele	20 (35)	19 (33)	17 (29)	56 (33)
Neural tube defect	20 (35)	20 (35)	23 (40)	63 (37)
Detrusor sphincter dyssynergia	1 (2)	0	2 (3)	3 (2)
Hydronephrosis	0	1 (2)	0	1 (1)
Any UTI history	9 (16)	7 (12)	18 (31)	34 (20)
Anticholinergic use at randomization	28 (49)	31 (54)	32 (55)	91 (53)
Clean intermittent catherization at randomization	35 (61)	28 (49)	31 (53)	94 (55)

Source: NDA 21-287/S016, Module 5.3.5.1, Study Report, p. 55-60, adapted from Tables 11-14

Reviewer's comment: *The study population does not appear to be severely impaired from a urological standpoint, given that only approximately half of the subjects were using clean intermittent catherization or being treated with an anticholinergic agent, and that only 20% had any history of UTI.*

Baseline values for the primary efficacy variable are presented in Table 7. The mean baseline detrusor LPP ranged from 50 to 54 cm H_2O across treatment and age groups, with the exception of the 8-16 year old patients randomized to placebo, where the mean baseline detrusor LPP was higher at 65 cm H_2O.

Table 7: Baseline mean (SD) detrusor LPP (cm H_2O) by treatment and age group (EFC5722, ITT)

	Placebo	Alfuzosin 0.1 mg	Alfuzosin 0.2 mg
2-7 years old	N=25	N=26	N=28
Baseline LPP (SD) (cm H_2O)	52 (12)	54 (15)	50 (8)
8-16 years old	N=29	N=27	N=28
Baseline LPP (SD) (cm H2O)	65 (13)	52 (12)	51 (12)

Source: NDA 21-287/S016, Module 5.3.5.1.25, adeffic.xpt, Medical Officer's analysis

EFC6269:
Of the 25 enrolled and treated patients, 16 (64%) were female and a majority were Caucasians (72%). The mean age and weight were 7.9 years and 27.0 kg, respectively. Twelve (12) patients were in the 2-7 years old age group and 13 in the 8-16 year old age group. By Tanner scoring, 63% of females and 78% of males were pre-

adolescent. Approximately 50% of the study population was treated with anticholinergic therapy and/or CIC at randomization. Eleven (11) of 12 patients in the younger group and 9 of 13 in the older group had bilateral hydronephrosis at baseline. The mean duration of diagnosis for hydronephrosis was 1.8 years and 4.3 years in the younger and older age groups, respectively.

6.1.3 Subject Disposition

EFC5722:
Overall, 172 patients were enrolled and randomized in a 1:1:1 manner to alfuzosin 0.2 mg/kg/day, 0.1 mg/kg/day, or matching placebo. Patients were stratified by age group (2-7 years old or 8-16 years old) and anticholinergic medication use (yes/no). Fifty-seven (57) patients were randomized to placebo, 57 to alfuzosin 0.1 mg dose group, and 58 to 0.2 mg dose group. Eighty-four (84) patients were in the younger group and 88 were in the older group. All subjects in the younger group received solution; among the older group, 27 of 88 patients (31%) received solution and 61 of 88 (69%) received the tablet formulation of the test product. Of the 172 patients, 167 (97%) completed the 12-week double-blind period. Five patients (3%) discontinued the study prematurely (1 placebo due to an AE, 3 alfuzosin due to AEs, and 1 alfuzosin due to too much blood draw/child not improving).

Overall, 163 patients entered the 40-week open-label extension. Eighty (80) patients were treated with alfuzosin 0.1 mg/kg/day and 83 were treated with alfuzosin 0.2 mg/kg/day. Eighty (80) patients were in the younger group and 83 were in the older group. Of the 153 patients who completed the safety extension, 73 (48%) were in the 2-7 years age group and 80 (52%) were in the 8-16 years age group. Ten patients (5 patients in each dose group) discontinued the safety extension (4 due to AEs, 4 to "other reasons," 1 due to lack of efficacy, and 1 due to poor compliance to protocol).

Protocol Violations: Overall, 23 of 172 patients (13%) had a major protocol violation and were excluded from the Per Protocol population. The incidence of subjects with a major protocol violation was balanced across the 3 treatment groups (7/57 in placebo, 8/57 in the alfuzosin 0.1 mg group, 8/58 in the alfuzosin 0.2 mg group). The most common major protocol violations were "LPP measured beyond Cmax" reported for 10 patients, and "LPP missing or without leakage" reported for 8 patients (3 in placebo, 4 in 0.1 mg group, 1 in 0.2 mg group).

EFC6269:
Overall, 25 patients were enrolled and treated with 0.2 mg/kg/day alfuzosin. Twelve (12) of 25 patients were in the 2-7 year old age group and 13 were in the 8-16 year old age group. Twenty-four (24) patients completed the initial 12-week treatment phase. Of the 23 patients who continued into the 40-week open-label safety extension, 22 completed the study. One patient (2-7 year age group) discontinued during the first 12

weeks because of conflict in schedule and another patient, also in the 2-7 year age group, discontinued during the open-label extension because of lack of efficacy.

6.1.4 Analysis of Primary Endpoint(s)

EFC5722:
The primary efficacy variable was detrusor leak point pressure (LPP). The primary comparison of interest was alfuzosin, at either dose, compared to placebo for the *proportion of patients with detrusor LPP < 40 cm H_2O at Week 12* (responder analysis). Multiplicity of statistical testing was addressed using the Hochberg procedure. Detrusor LPP is an acceptable endpoint for the indication based on its use in clinical practice and published literature supporting its clinical relevance.

At Week 12, the proportion of responders was 40% for placebo and alfuzosin 0.1 mg groups, and 48% for alfuzosin 0.2 mg group. The differences in response between drug and placebo groups were not statistically significant (p > 0.9). See Table 8.

Table 8: Detrusor leak point pressure by treatment group (EFC5722, ITT)

		Alfuzosin (mg/kg/day)	
	Placebo (N=57)	0.1 (N=57)	0.2 (N=58)
LPP			
< 40 cmH_2O	23 (40.4%)	23 (40.4%)	28 (48.3%)
≥ 40 cmH_2O or missing	34 (59.6%)	34 (59.6%)	30 (51.7%)
Diff in response vs Placebo	-	0.0%	7.9%
95% CI diff vs Placebo [a]	-	0.0 (-17.5; 17.5)	7.9 (-10.0; 25.1)
p-values vs Placebo [b]	-	1.0000	0.4545
Adjusted p-values vs Placebo [c]		1.0000	0.9090

Note : [a] CI is 2-sided and built based on Wilson's score method without continuity correction
Note : [b] p-values come from Fisher's exact test
Source: NDA 21-287/S016, Module 2.5, Clinical Overview, Table 7, p. 21 (verified by Medical Officer)

Similarly, no statistically significant between-group differences were observed when the primary endpoint was analyzed using the Per-Protocol population.

Sub-group analyses of the primary endpoint were provided for age and anticholinergic use, as these characteristics were considered clinically relevant baseline factors that may impact treatment effect. All 95%CIs for the respective odds ratio included 1.0, indicating no statistical significant difference between drug and placebo. See Table 9.

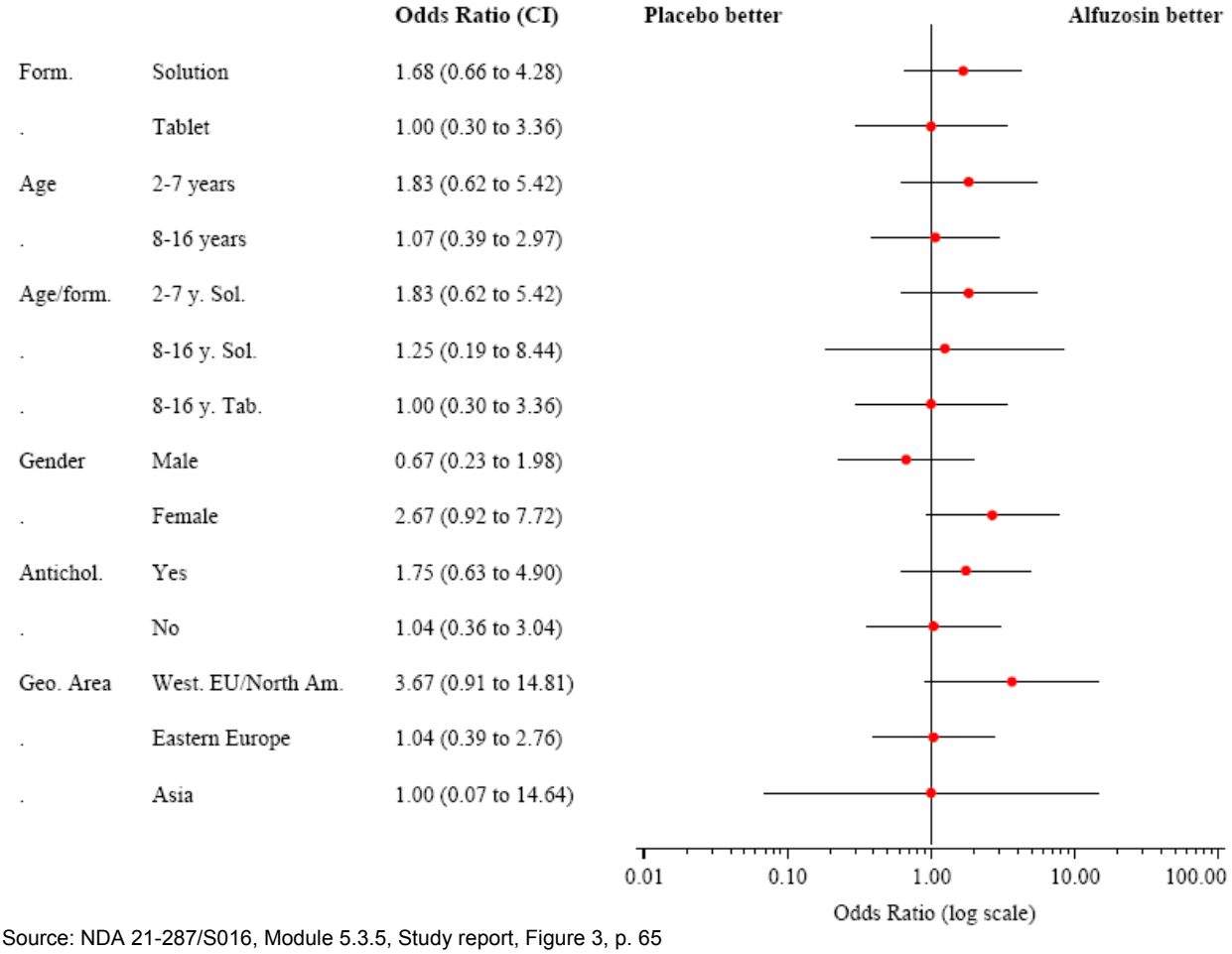
Table 9: Proportion of patients with detrusor leak point pressure < 40 cm H_2O by age, anticholinergic, and treatment (EFC5722, ITT)

Stratum	Anticholinergic Use	Treatment	DLPP < 40 cm	Odds ratio estimate (95% CI)
2-7 y/o Solution	Yes	Placebo (N=14) 0.1 mg (N=15) 0.2 mg (N=15)	4 (29) 9 (60) 6 (40)	- 3.8 (0.8, 17.7) 1.7 (0.4, 7.9)
2-7 y/o Solution	No	Placebo (N=14) 0.1 mg (N=13) 0.2 mg (N=13)	5 (36) 6 (46) 7 (54)	- 1.5 (0.3, 7.2) 2.1 (0.5, 9.8)
8-16 y/o Solution	Yes	Placebo (N=4) 0.1 mg (N=6) 0.2 mg (N=5)	3 (75) 2 (33) 4 (80)	- 0.2 (0.01, 2.8) 1.3 (0.1, 31.1)
8-16 y/o Solution	No	Placebo (N=4) 0.1 mg (N=4) 0.2 mg (N=4)	1 (25) 0 1 (25)	- NC 1.0 (0.04, 24.6)
8-16 y/o Tablet	Yes	Placebo (N=10) 0.1 mg (N=10) 0.2 mg (N=12)	4 (40) 2 (20) 7 (58)	- 0.4 (0.1, 2.8) 2.1 (0.4, 11.6)
8-16 y/o Tablet	No	Placebo (N=11) 0.1 mg (N=9) 0.2 mg (N=9)	6 (55) 4 (44) 3 (33)	- 0.7 (0.1, 3.9) 0.4 (0.1, 2.6)

Source: NDA 21-287/S016, Module 5.3.5, Study report, Table 49, p. 134-135

Sub-analyses of the primary endpoint were also provided for formulation, age, gender and geographic areas shown in Figure 1. The 95% CI for all odds ratio estimates included 1.0 for all variables analyzed.

Figure 1: Subgroup analyses of detrusor leak point pressure (ITT, EFC5722)



Source: NDA 21-287/S016, Module 5.3.5, Study report, Figure 3, p. 65

Reviewer's comment: *The statistical reviewer confirmed to the negative efficacy findings of the primary and sub-group analyses of the primary endpoint. Refer to the statistical review for details.*

EFC6269:
The primary efficacy variable was the change in grade of hydronephrosis. Two renal ultrasounds were done during each time point, one with a full bladder and one with an empty bladder. All ultrasound images were reviewed by a central pediatric radiologist. Grading of hydronephrosis was based on the Society for Fetal Urology classification shown below:

Ref.: Fernbach, S.K., Maizels, M., Conway, J.J. Ultrasound grading of hydronephrosis: introduction to the system used by the Society for Fetal Urology. Pediatr Radiol 1993; 23:478-480

"Positive" clinical response was defined as a grade decrease (improvement) ≥1 in hydronephrosis from baseline to Week 12. The primary analysis was the analysis of the complete response (see definition below). Complete response was assessed in patients with bilateral or unilateral hydronephrosis at baseline as follows:

Complete Response
- For patients with bilateral hydronephrosis at baseline, complete response was defined as "positive" clinical response for both kidneys.
- For patients with unilateral hydronephrosis at baseline, complete response was defined as "positive" clinical response for the affected kidney without worsening of the other kidney.

Partial response was assessed for patients with bilateral hydronephrosis and was defined as follows:

Partial Response
For patients with bilateral hydronephrosis at baseline, partial response was defined as positive clinical response for the one kidney without worsening of the other kidney.

Results:
At baseline, 20 children had bilateral hydronephrosis (11 in the younger group, 9 in the older group) and 5 had unilateral hydronephrosis (1 in the younger group, 4 in the older group).

***Reviewer's comment**: By hydronephrosis grading (the patient was assigned the grade that was the worst of the two grades if he/she had bilateral hydronephrosis), 7 patients had grade 1, 10 had grade 2, and 8 had grade 3 hydronephrosis.*

At Week 12, 10/25 patients (40%) had a complete response and 6/20 (30%) had a partial response. Among the complete responders, 2 (2/12 or 17%) were in the younger age group and 8 (8/13 or 62%) were in the older age group. Of the 20 patients with bilateral hydronephrosis at baseline, 5 had a complete response and 6 had a partial response. All 5 subjects with unilateral hydronephrosis at baseline had a complete response. See Table 10.

Table 10: Summary of complete and partial response rates at Week 12 (ITT, EFC6269)

	Alfuzosin 0.2 mg/kg/day				
		8-16 years			
Complete response	2-7 years Solution (N=12)	Solution (N=6)	Tablets (N=7)	Overall (N=13)	Total (N=25)
Bilateral hydronephrosis at baseline	11	4	5	9	20
Response in both kidneys	1/11 (9.1%)	3/4 (75.0%)	1/5 (20.0%)	4/9 (44.4%)	5/20 (25.0%)
Response in one kidney w/o worsening in other kidney	3/11 (27.3%)	0/4	3/5 (60.0%)	3/9 (33.3%)	6/20 (30.0%)
Unilateral hydronephrosis at baseline	1	2	2	4	5
Response w/o worsening in other kidney	1/1 (100%)	2/2 (100%)	2/2 (100%)	4/4 (100%)	5/5 (100%)

Source: NDA 21-287/S016, Module 5.3.5.2.1, CSR, p. 60, Table 16

The mean change from baseline to Week 12 in the grade of hydronephrosis for both kidneys was -0.60 (±1.01) for the entire study population, -0.09 (±0.80) for the 2-7 year old age group, and -1.04 (±0.80) for the 8-16 year old age group. See Table 11.

Table 11: Descriptive statistics on grade of hydronephrosis at baseline and Week 12 (ITT, EFC6269)

	Alfuzosin 0.2 mg/kg/day				
		8-16 years			
	2-7 years Solution (N=12)	Solution (N=6)	Tablets (N=7)	Overall (N=13)	Total (N=25)
Baseline					
Number	12	6	7	13	25
Mean (SD)	1.79 (0.72)	1.67 (0.82)	1.57 (0.93)	1.62 (0.85)	1.70 (0.78)
Median	1.50	1.50	2.00	1.50	1.50
Min : Max	1.0 : 3.0	0.5 : 3.0	0.5 : 3.0	0.5 : 3.0	0.5 : 3.0
Endpoint					
Number	10	6	7	13	23
Mean (SD)	1.65 (1.16)	0.25 (0.27)	0.86 (0.99)	0.58 (0.79)	1.04 (1.09)
Median	1.75	0.25	0.50	0.50	0.50
Min : Max	0.0 : 3.5	0.0 : 0.5	0.0 : 2.5	0.0 : 2.5	0.0 : 3.5
Change from baseline at endpoint					
Number	10	6	7	13	23
Mean (SD)	-0.10 (1.07)	-1.42 (0.92)	-0.71 (0.57)	-1.04 (0.80)	-0.63 (1.02)
Median	-0.25	-1.00	-0.50	-0.50	-0.50
Min : Max	-2.0 : 1.5	-3.0 : -0.5	-2.0 : -0.5	-3.0 : -0.5	-3.0 : 1.5

Source: NDA 21-287/S016, Module 5.3.5.2.1, Clinical Study, p. 100, Table 33

***Reviewer's comment**:*
At Week 12, four of 20 patients (20%) with bilateral hydronephrosis reported Grade 0 hydronephrosis in both the left and right kidneys (1 patient in the younger group and 3 patients in the older group). At baseline, the hydronephrosis grading (left kidney, right kidney) for these 4 patients were (1,3), (3,3), (2,2), (3,1). The efficacy results in this small, exploratory study appear promising but inconclusive. The study design (open-label, single-dose, non-comparative) and small sample size limit one's ability to draw any meaningful conclusion regarding drug effect on treatment of hydronephrosis.

In a retrospective study by Anderson PA et al (1993), 209 children with spina bifida were assessed for predictive factors for the development of hydronephrosis. Hydronephrosis was diagnosed in 100 children; 21 of these 100 children (21%) had an improvement in the grade of hydronephrosis without intervention.
(Anderson PA, Travers AH. Development of hydronephrosis in spina bifida patients: predictive factors and management. Br J Urol. 1993 Dec; 72(6): 958-61)

6.1.5 Analysis of Secondary Endpoints(s)

Results of secondary endpoints are presented only for study **EFC5722**

6.1.5.1 Absolute and relative change in detrusor LPP at Week 12

At Week 12, a numerically larger absolute and relative decrease from baseline in detrusor LPP was observed for both alfuzosin dose groups compared to placebo. The differences between drug and placebo, however, were not statistically significant (p>0.5). See Table 12.

Table 12: Absolute and relative change from baseline detrusor LPP at Week 12 (EFC5722, ITT)

	Placebo	Alfuzosin 0.1 mg	Alfuzosin 0.2 mg
	Absolute change from baseline (cm H_2O)		
Mean detrusor LPP (SD) Baseline Week 12	 54 (13) 48 (23)	 53 (13) 42 (18)	 51 (10) 39 (20)
Change from baseline LSMean (SE) LSMean difference vs. placebo (SE) p-value vs. placebo	 -5 (3) - -	 -12 (3) -6 (4) 0.1	 -13 (3) -7 (4) 0.06
	Relative change from baseline (%)		
LSMean (SE) LSMean difference vs. placebo (SE) p-value vs. placebo	-9 (6) - -	-21 (6) -11 (8) 0.14	-24 (6) -14 (7) 0.057

Source: NDA 21-287/S016, Module 5.3.5.1, Study report, Table 17, p. 66

***Reviewer's comment**: Although the absolute and relative change from baseline in LPP was greater for drug than placebo, the clinical relevance of the numerical differences between placebo and drug is unknown. Previous studies have indicated a "threshold" effect of detrusor leak point pressure in that LPP > 40 cm* H_2O *is associated with risk of upper urinary tract deterioration.*

The differences between placebo and drug for the change from baseline detrusor LPP were more pronounced in the younger age group than the older age group. In patients in the 2-7 year old age group, the mean change from baseline detrusor LPP was +1.6 cm H_2O for placebo, -14.0 cm H_2O for alfuzosin 0.1 mg, and -10.9 cm H_2O for alfuzosin 0.2 mg. In patients 8–16 years of age, mean change from baseline LPP was comparable between the alfuzosin treatment groups and the placebo group (placebo: -11.9 cm H_2O, alfuzosin 0.1 mg: -8.3 cm H_2O; and alfuzosin 0.2 mg: -13.9 cm H_2O).

***Reviewer's comment**: According to the pharmacometric reviewer, the exposure-response regression curve for the efficacy endpoints (primary and secondary) and PK parameters (AUC and Cmax) did not indicate a meaningful exposure-response relationship.*

6.1.5.2 Absolute and relative change in detrusor compliance at Week 12

At week 12, similar change from baseline in mean detrusor compliance was observed across the 3 treatment groups: placebo: 1.5 mL/cm H_2O; alfuzosin 0.1 mg: 2.0 mL/cm H_2O; alfuzosin 0.2 mg: 2.5 mL/cm H_2O. Similar results were observed with respect to relative change in detrusor compliance. No notable differences in the number of patients with detrusor compliance < 9 mL/cm H_2O were observed between drug and placebo groups.

6.1.5.3 Number of urinary tract infections during the treatment period

No differences in the proportion of patients experiencing symptomatic UTIs were noted between drug and placebo. However, in the 3 months prior to the study, more patients in the alfuzosin 0.2 mg group reported a symptomatic UTI (31%) than those in the alfuzosin 0.1 mg group (12%) or placebo (16%).

Number of symptomatic UTI	Placebo N=57	Alfuzosin 0.1 mg N=57	Alfuzosin 0.2 mg N=58
0	50	53	51
1	5	3	6
2	2	1	1

Source: NDA 21-287/S016, Module 5.3.5, Study Report, Table 22, p. 70

Subgroup analyses: Secondary endpoints were analyzed by age group (2-7 year old vs. 8-16 year-old) and anticholinergic use (yes/no), and the combination of age and anticholinergic use. The only notable finding was a statistically significant difference in the change from baseline detrusor LPP between placebo and drug groups in the 2-7 year old subgroup. The mean difference between alfuzosin 0.1 mg and placebo was -15.5 cm H_2O and that between alfuzosin 0.2 mg and placebo was -12.4 cm H_20. However, these findings are exploratory given that they are subgroup analyses and that statistical testing was not adjusted for multiplicity.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The alfuzosin doses administered in the pediatric studies (0.1 mg/kg/day or 0.2 mg/kg/day) were selected based on the efficacious doses of alfuzosin in adults. The approved daily doses of alfuzosin in adults 7.5 mg/day (2.5 mg TID) or 10 mg (5 mg BID) are equivalent to 0.11 mg/kg/day to 0.14 mg/kg/day based on an estimated body weight of 70 kg and this was confirmed in study PKM6270. Daily doses of 0.1 mg/kg and 0.2 mg/kg were selected for pediatric trials. The maximum doses given to adults in either BID (10 mg) or TID (7.5 mg) regimens were not to be exceeded in pediatric trials.

Children 2-7 years received alfuzosin oral solution TID with a maximum daily dose of 7.5 mg. Adolescents 8-16 years received alfuzosin oral tablet BID with a maximum daily dose of 10 mg. Adolescents who were unable to swallow tablet, preferred solution, or had body weight < 30 kg, had the option of using the oral solution (with maximum daily dose of 7.5 mg).

7 Review of Safety

Safety Summary

The overall safety and tolerability of alfuzosin in children and adolescents with neurogenic bladder is acceptable. The safety profile is consistent with the pharmacology of an alpha-adrenergic antagonist, with the most common adverse events being infection-related. The primary vasodilatory event was dizziness, which occurred infrequently, and most of the cases were mild in intensity. No significant safety findings were noted for QT interval, visual or sleepiness assessments.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The clinical safety review is based on two phase 3 trials (EFC5722, EFC6269) and one phase 1 study (PKM6270). The safety data were not pooled. The safety review focuses on the findings of EFC5722, as this was the only large and controlled study; findings of studies EFC6269 and PKM6270 are discussed only if they provide additional important safety information.

7.1.2 Categorization of Adverse Events

Adverse events were classified into primary system organ classes and preferred terms using the MedDRA (Medical Dictionary for Regulatory Activities) dictionary (version 10.1 or higher). The verbatim AE terms were mapped to the MedDRA terms and were found to be acceptable.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

No pooling of safety data was conducted. The studies differed in design and duration of treatment and the study populations from the two phase 3 trials (EFC5722, EFC6269) were dissimilar. Approximately 75% of the safety database was from study EFC5722.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

This sNDA contains safety data from the 3 studies (EFC5722, EFC6269, and PKM6270) conducted in children ages 2 – 16 years with elevated detrusor LPP of

neuropathic etiology. Studies EFC5722 and EFC6269 had a 40-week, open-label (OL) safety extension, following the initial 12 weeks of double-blind treatment. Overall, a total of 223 patients received at least one dose of alfuzosin; 87 patients were exposed to alfuzosin for 1 year (65 patients from EFC5722; 22 patients from EFC6269). The only placebo-controlled safety data (N = 57) came from study EFC5722 for the initial 12 weeks of double-blind (DB) treatment.

EFC5722: The safety population for the DB period consists of 172 subjects, 163 of whom entered the OL period. Among these 163 patients, 80 (41 in the 0.1 mg group and 39 in the 0.2 mg group) were in the younger age group and 83 were in the older age group (39 in the 0.1 mg group and 44 in the 0.2 mg group). One hundred-fifty three (153) subjects completed the entire study (DB and OL), 73 were in the younger age group and 80 were in the older age group; 75 were from the 0.1 mg dose group and 78 were in the 0.2 mg dose group.

EFC6269: 25 patients were enrolled (20 with bilateral hydronephrosis, 5 with unilateral hydronephrosis) and treated with alfuzosin 0.2 mg/kg/day. Twenty-four (24) patients completed the initial 12-weeks treatment phase. Of the 23 patients who continued into the 40-week open-label safety extension, 22 completed the study. One patient (2-7 year age group) discontinued during the first 12 weeks because of conflict in schedule and another patient, also in the 2-7 year age group), discontinued during the open-label extension because of lack of efficacy.

PKM6270: 29 patients were enrolled and treated (14 received alfuzosin 0.1 mg/kg/day, 15 received alfuzosin 0.2 mg/kg/day). Fifteen patients were in the younger age group and 14 patients in the older age group. Twenty-eight of 29 patients completed the 4 weeks of treatment; one patient in the younger age group discontinued prematurely due to acute bronchitis.

7.2.2 Explorations for Dose Response

Two doses (0.1 mg/kg/day, 0.2 mg/kg/day) were evaluated in the 3 pediatric clinical trials.

7.2.3 Special Animal and/or In Vitro Testing

At the Division's request, the Applicant completed a juvenile rat program evaluating the toxicology of alfuzosin on behavior, reproductive, and endocrine parameters in young male and female animals. The reader is referred to the toxicologist's review for details. No significant preclinical safety signals were observed that warranted additional safety evaluation in the clinical studies.

7.2.4 Routine Clinical Testing

Safety assessments included adverse events (AEs), physical examination, assessments of alertness (Epworth sleepiness scale) and visual changes (Practice E for children test), vital signs, safety electrocardiogram (ECG), laboratory tests (hematology, chemistry, and hormone analysis), urinalysis and documentation of urinary tract infections (UTIs).

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Alfuzosin is an alpha-adrenergic antagonist that has vasodilatory pharmacodynamic effects. Important labeled AEs for alpha-adrenergic antagonists in adults include postural hypotension/syncope and dizziness. Both study EFC5722 and study EFC6269 prospectively defined vasodilatory events (e.g., dizziness, malaise, orthostatic hypotension, syncope) as AEs of special interest. See section 7.3.5 (Submission Specific Primary Safety Concerns) for further discussion.

7.3 Major Safety Results

7.3.1 Deaths

No death occurred in the entire safety database.

7.3.2 Nonfatal Serious Adverse Events

EFC 5722:

- Double-blind period: One placebo patient (weight decreased in a 7 year-old) and 2 alfuzosin patients (both 0.1 mg) (shunt malfunction in a 3 year-old and epilepsy in an 11 year-old) had a serious AE, none of which were considered to be treatment-related. All 3 patients entered the open-label period.
- Open-label study period (includes 1-week follow-up off treatment): 18 patients (10 in 0.1 mg dose group, 8 in 0.2 mg dose group) experienced at least one SAE. Thirteen subjects were in the younger age group and five were in the older age group. The SAEs are listed below (one subject may have more than one SAE)
    - In the **0.1 mg** group:
        - 2 subjects with pneumonia, 1 subject each with malnutrition, acquired hydrocele, cystitis, head contusion, epilepsy, Arnold-Chiari malformation, respiratory failure from severe thoracic malformation, renal impairment, tonsillar hypertrophy, urethral hemorrhage, and tethered cord syndrome.
    - In the **0.2 mg** group:

- 2 subjects with decubitus ulcer, 1 subject each with varicella, viral infection, femur fracture, shunt malformation, pyelonephritis, tethered cord syndrome, and pneumonia

No SAEs during the OL period were considered to be treatment-related and this reviewer concurs.

EFC6269: Four of 25 patients (16%) reported SAEs (2 subjects each in each age group). These SAEs included mild vasovagal syncope in a 2 year-old, multiple SAEs in a 5-year old (femur fracture, urinary calculus, renal impairment, ureteric injury, and pyelonephritis), severe convulsion in an 11 year-old, and multiple UTIs in a 13 year-old. The mild vasovagal syncope occurred on Day 234 and Day 236 in the 2 year-old (patient 616001006) with a history of hydrocephalus with a ventriculo-peritoneal (VP) shunt, meningomyelocele, and spinal cord injury. The patient held her breath (due to emotional reasons) and lost consciousness for a minute prior to recovering spontaneously without any corrective treatment. A severe convulsion occurred on Day 348 in an 11 year-old (patient 616002001) with a history of hydrocephalus with a VP shunt and meningomyelocele. Corrective treatment was administered and the patient recovered the same day. A CT scan showed moderate hydrocephalus. No specific etiology was uncovered during the work up of the convulsion.

No SAEs were considered by the investigator to be treatment-related and this reviewer concurs. No subjects with SAEs discontinued prematurely because of AEs.

Reviewer's comment*: This reviewer does not consider the "vasovagal syncope" that lasted a minute reported for the 2 year-old patient who held her breath to be due to blood pressure changes.*

Reviewer's comment: *Seizures occur frequently in children with shunted hydrocephalus. Although most seizures occur at the time of the diagnosis of hydrocephalus, shunt placement and complications may predispose to epilepsy. In study EFC5722, 1 placebo subject, one subject in 0.1 mg group, and 2 subjects in 0.2 mg reported at least one seizure throughout the study.*

PKM6270: No SAEs occurred during the study.

7.3.3 Dropouts and/or Discontinuations

EFC5722:

- Double-blind period: One placebo patient (dizziness, fall) and 3 alfuzosin patients (pruritic rash in 0.1 mg group, diarrhea x 2 subjects in 0.2 mg group) discontinued due to adverse events.
- Safety extension period: Four subjects prematurely discontinued the safety extension period due to AEs (2 patients in each dose group). In the 0.2 mg group, one subject

each discontinued due to diarrhea, which was considered to be drug-related, and scoliosis. In the 0.1 mg group, one subject discontinued because of irritability (subject 5722-250-001-004) and another (subject 5722-840-002-007) discontinued because of abnormal behavior and urinary incontinence. Subject 5722-250-001-004 was a 5 year-old male patient with a history of spinal cord injury/spinal cord neoplasm who experienced a severe AE of irritability (behavioral problem) on Day 136, which resolved without corrective treatment by Day 139. The investigator assessed the AE to be drug-related. Subject 5722-840-002-007 was a 10 year-old female patient with a history of hydrocephalus and meningomyelocele who experienced a mild AE of abnormal behavior (no other detail was provided) on Day 145, which resolved on an unspecified date. The investigator did not consider the AE to be drug-related.

Reviewer's comment*: A review of the adverse event dataset of EFC5722 did not reveal any trend in behavior changes (e.g., irritability, moodiness, aggression) in patients treated with alfuzosin.*

EFC6269: No patient discontinued because of an AE in the entire study period.

PKM6270: One subject (4 year-old receiving alfuzosin 0.2 mg/kg/day) discontinued due to acute bronchitis. The investigator did not exclude drug-causality.

7.3.4 Significant Adverse Events

7.3.5 Submission Specific Primary Safety Concerns

EFC5722:
Double-blind period: One placebo patient reported moderate dizziness which led to study discontinuation on Day 52. One 13 year-old subject treated with alfuzosin 0.2 mg/kg/day experienced hypotension and moderate dizziness on Day 47, which were considered to be drug-related. The AEs resolved after 3 days without treatment and the patient completed the entire study.

Open-label period: A 12 year-old male patient with a history of hydrocephalus, meningomyelocele, and seizures in the 0.2 mg dose group experienced a moderate AE of dizziness on Day 255. The AE resolved after 2 days without any treatment and the patient completed the study. The investigator did not consider the AE to be drug-related.

Reviewer's comment: *A review of the dataset of adverse events reported during the double-blind period indicated that one patient in the 0.2 mg dose group reported a mild "loss of balance" and 2 placebo subjects experienced accidental falls. No AEs of syncope or orthostatic hypotension were reported.*

EFC6269: One vasovagal syncope from breath-holding occurred in a 2 year-old female patient described in the serious adverse events section. A 16 year-old subject reported a mild episode of dizziness on Day 1 after alfuzosin exposure (0.2 mg/kg/day), which resolved spontaneously after 2 days and which did not lead to drug discontinuation.

PKM6270: One patient in the 8-16 year old age group treated with alfuzosin 0.2 mg/kg/day experienced a mild episode of dizziness, which did not result in drug discontinuation.

Reviewer's comment: *In the 3 pediatric studies with alfuzosin, 4 patients of 223 (1.8%) who received at least one dose of alfuzosin experienced dizziness, all at the higher dose of alfuzosin of 0.2 mg/kg/day (compared to 1 of 57 (1.8%) placebo patients). None of the dizziness episodes that occurred on active drug treatment were serious or led to premature drug discontinuation.*

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

EFC5722
In the entire study (double-blind and open-label), 128 of 172 patients (74%) reported at least one AE. Sixty-seven (67/84, or 80%) of patients in the younger age group had AEs; 61 (61/88 or 69%) of patients in the older age group had AEs.

Double-blind: Overall, 101 of 172 subjects (59%) reported 201 AEs. A slightly higher proportion of younger patients reported AEs compared to the older patients (32% vs. 27%). The incidence of AEs ranged from 51% in the alfuzosin 0.1 mg group to 65% in the placebo group. Most common AEs by Preferred Term were nasopharyngitis, pharyngitis, and cystitis. Pyrexia, respiratory tract infection, diarrhea, headache, and cough were reported at a higher incidence in both alfuzosin groups compared to placebo. Table 13 shows common AEs reported by at least 5 subjects.

Table 13: Common AEs reported by at least 5 subjects by Preferred Term (Safety, EFC5722)

Preferred Term	Placebo N=57 n (%)	0.1 mg N=57 n (%)	0.2 mg N=58 n (%)	Total N=172 n (%)
Any AEs 2-7 y/o 8-16 y/o	37 (65) *18 *19	29 (51) *18 *11	35 (60) *19 *16	101 (59) *55 (32) *46 (27)
Nasopharyngitis	7	2	4	13
Pharyngitis	3	6	2	11
Cystitis	4	1	5	10
Pyrexia*	1	2	5	8
Respiratory tract infection*	2	3	3	8
Upper respiratory tract infection	3	3	2	8
Urinary tract infection	3	3	1	7
Vomiting	3	1	3	7
Diarrhea*	1	3	2	6
Headache*	1	2	3	6
Cough*	1	2	2	5

*Incidence of AE was higher in both drug groups compared to placebo
Source: (b) (4), Module 5.3.5.1.25, adae.xpt, Medical Officer's analysis

Reviewer's comment: *Upper respiratory tract infection, headache, and diarrhea are labeled adverse events in the alfuzosin prescribing information for the BPH indication.*

During the double-blind period, 8 subjects had AEs of severe intensity. These included 4 patients in placebo group (weight decreased, arthritis infective, abdominal pain, pyrexia), 2 patients in the 0.1 mg group (abdominal pain after colonoscopy, epilepsy), and 2 patients in the 0.2 mg group (diarrhea, asymptomatic bacteriuria).

Open-label period: Overall, 98 of 163 patients (60%) reported at least one AE (49 patients in each dose group). Among these 98 patients, 52 were in the younger age group (N=80) and 46 were in the older age group (N=83). In the 0.1 mg group, 20 of 49 subjects who reported AEs were previously randomized to placebo in the DB period. In the 0.2 mg group, 16 of 49 subjects who reported AEs were previously randomized to placebo in the DB period. The most common AEs by Preferred Terms were nasopharyngitis, diarrhea, and urinary tract infection. Table 14 shows common AEs reported by at least 5 patients during the open-label period.

Table 14: Common AEs reported by at least 5 patients by Preferred Term (Safety, EFC5722)

Preferred Term	0.1 mg N=80 n (%)	0.2 mg N=83 n (%)	Total N=163 n (%)
Any AEs	49 (61)	49 (59)	98 (61)
Nasopharyngitis	6	10	16
Diarrhea	6	8	14
Urinary tract infection	8	5	13
Cystitis	5	7	12
Pharyngotonsillitis	6	6	12
Pyrexia	4	7	11
Pharyngitis	4	4	8
Vomiting	4	4	8
Respiratory tract infection	5	2	7
Upper respiratory tract infection	2	5	7
Otitis media	2	3	5
Pyelonephritis	4	1	5

Source: NDA 21-287/S016, Module 5.3.5.1.25.3, adae.xpt, Medical Officer's analysis

During the open-label period, 11 patients (6 in the 0.1 mg dose group and 5 in the 0.2 mg group) had AEs of severe intensity. The severe AEs in the 0.1 group included pneumonia, malnutrition, irritability, respiratory failure due to severe thoracic malformation, renal impairment, and tethered cord syndrome. Severe AEs in the 0.2 mg group included varicella, femur fracture, decubitus ulcer, pyelonephritis, tethered cord syndrome, and pneumonia.

Reviewer's comment: *The profile of common AEs were similar between those observed during the double-blind and open-label periods of the study, except for diarrhea, which was more frequently reported in the open-label period. The majority of common AEs were infectious in nature, although there was no clear dose-response pattern.*

In study EFC6962 and study PKM6270, the common AEs were similar to those observed in EFC5722.

7.4.2 Laboratory Findings

Laboratory findings are discussed for study EFC5722 only.

Laboratory adverse events:
In the double-blind period, one 16 year-old female treated with alfuzosin 0.2 mg/kg/day had an AE of increased serum testosterone level and decreased serum estradiol level. Subsequent hormonal levels were within normal limits. The self-limited hormonal changes in one pubertal female patient are unlikely represent a safety signal.

Laboratory outliers:
- Liver enzymes: a 3 year-old patient (792003002) treated with alfuzosin 0.1 mg had a baseline alkaline phosphatase level 1.7X above upper limit of normal, which persisted during the treatment period but did not increase further.
- Serum sodium level: 2 subjects with normal serum sodium levels at baseline had serum sodium levels of 150 mmol/L and 154 mmol/L at Week 12, which returned to normal at subsequent visits.

Measurement of central tendency:
Median and mean changes from baseline in drug groups compared to placebo did not indicate a clear trend of laboratory changes in hematology, chemistry, or hormone levels.

7.4.3 Vital Signs

EFC5722:
Table 15 shows changes in heart rate in patients with normal baseline heart rate and changes from baseline systolic or diastolic blood pressure and blood pressure exceeding pre-specified thresholds. Slightly more subjects in the alfuzosin 0.2 mg group than placebo or 0.1 mg dose group experienced decreases from supine systolic BP or diastolic BP exceeding pre-specified threshold. As mentioned previously, one placebo subject and 2 subjects in the 0.2 mg alfuzosin group reported dizziness. No blood-pressure change-related syncope occurred in any subject.

Table 15: Vital sign changes during the double-blind period (Safety, EFC5722)

Vital Sign Parameters	Placebo	0.1 mg	0.2 mg
Heart Rate			
*Low	*0/55	*1/51	*1/52
*High	*4/55	*4/51	6/52
Supine SBP			
*Decrease from baseline ≥ 20 mmHg	*6/57	*3/57	*10/58
*Increase from baseline ≥ 20 mmHg	*3/57	*3/57	*4/58
Supine DBP			
*Decrease from baseline ≥ 10 mmHg	*15/57	*15/57	*19/58
*Increase from baseline ≥ 10 mmHg	*15/57	*13/57	*8/58

Source: NDA 21-287/S016, Module 5.3.5.1, Study report, p. 87, Table 31

No subject had a clinically significant measurement of vital sign reported as an AE.

EFC6269: Ten subjects had a heart increase ≥ 15 bpm on orthostatic measurement (range 16-40 bpm). Two subjects had orthostatic SBP decrease from baseline of ≥ 20 mmHg. Eight subjects had orthostatic DBP decrease from baseline ≥ 10 mmHg (range: -11 to -32 mmHg). All of these subjects were asymptomatic.

7.4.4 Electrocardiograms (ECGs)

EFC5722:
Overall, no significant differences were observed among the 3 treatment groups in changes in ECG parameters over time, including QTc.

One patient in the 0.2 mg dose group had QTc prolongation ≥ 500 msec and 1 patient in the 0.1 mg dose group had QTc Bazett increase > 60 msec from baseline:

- QTc Bazett increase > 60 msec from baseline: subject 005722-356-105-015 was a 4 year-old female patient treated with alfuzosin 0.1 mg with an increase in QTc Bazett from 378 ms at baseline to 448 ms (and an increase in QTc Fridericia frm 343 ms at baseline to 382 ms) at Day 7. Subsequent QTc were within normal range at subsequent visits.
- QTc Bazett ≥ 500 msec: subject 005722-891-103-003 was a 12 year-old male patient with a baseline QTc Bazett of 437 msec who had a QTc Bazett of 500 msec at an scheduled visit on Day 88. The QTc Bazett values were less than 500 msec on subsequent visits.

Table 16 shows QTc changes exceeding pre-defined thresholds of increases from baseline of 30-60 msec, >60 msec, and ≥ 500 msec among subjects with normal QTc interval at baseline.

Table 16: QTc changes from baseline exceeding thresholds in patients with normal QTc at baseline (Safety, EFC5722)

	Placebo	Alfuzosin 0.1 mg	Alfuzosin 0.2 mg
QTc Bazett (msec)			
*Increase from baseline 30-60	*9/34 (27%)	*9/37 (24%)	*7/43 (16%)
*Increase from baseline > 60	*0/34	*1/37 (3%)	*0/43
*≥ 500	*0/34	*0/37	*0/43
QTc Fridericia (msec)			
*Increase from baseline 30-60	*6/54 (11%)	*10/56 (18%)	*5/57 (9%)
*Increase from baseline > 60	*0/54	*0/56	*0/57
*≥ 500	*0.54	*0/56	*0/57

Source: NDA 21-287/S016, Module 5.3.5.1, Study report, p. 89, Table 32

EFC6269:
No subjects had prolonged QTc ≥ 500 ms or increase from baseline QTc > 60 ms. Two of 25 subjects had QTc Fridericia increase from baseline 30-60 ms; 5/15 subjects had QTc Bazett increase from baseline 30-60 ms.

EFC6270:
One patient (4 year-old male, 0.1 mg/kg/day) with a baseline QTcF of 343 msec had an increase in QTcF interval between 30-60 msec at Visit 3 (395 msec) and >60 msec at Visit 4 (406 msec). His end of study visit value was normal (371 msec). A pediatric cardiologist considered the findings to not be clinically meaningful.

Reviewer's comment: *A thorough QT study in the healthy adults treated with alfuzosin did not demonstrate a clear safety signal for QT prolongation. During the double-blind, controlled period of study EFC5722, the findings of QTc prolongation were similar between placebo and alfuzosin groups. The clinical significance of several subjects on alfuzosin with QTc prolongation exceeding pre-defined threshold detected on safety ECGs is unknown.*

7.4.5 Special Safety Studies/Clinical Trials

In study EFC5722, no significant changes from baseline were observed for any of the 3 treatment groups in the alertness assessment using the modified Epworth sleepiness scale or the visual assessment using the practice E test.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

In study EFC5722, the AEs of dizziness and diarrhea occurred more frequently in the alfuzosin 0.2 mg dose group compared to the 0.1 mg dose group.

7.6 Additional Safety Evaluations

7.6.2 Human Reproduction and Pregnancy Data

No pregnancy occurred during the pediatric program of alfuzosin. Alfuzosin is a pregnancy category B based on preclinical studies indicating no evidence of fetal toxicity or teratogenicity at doses that provide systemic exposure 3 to 12,000 times higher than clinical dose.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Alfuzosin does not have any known drug abuse/withdrawal/rebound potential. No cases of overdose in the pediatric population have been reported.

8 Postmarket Experience

Alfuzosin is not approved for use in the pediatric population in any country. Post-marketing information of alfuzosin use in the pediatric population was not submitted in this submission.

9 Appendices

9.2 Labeling Recommendations

The Applicant did not seek a new indication for the pediatric population. The Applicant proposed to update the pediatric sections of the Uroxatral prescribing information (PI) to include the clinical safety and efficacy data obtained from the pediatric trials submitted in this supplement. This reviewer recommends that only pediatric data from the adequately controlled study (EFC5722), be presented in the PI. Study 6269 was an exploratory, open-label study in a limited number of subjects and provided minimal informative data for labeling purposes.

The Division consulted SEALD and OSE to evaluate the prescribing information and patient labeling, respectively, for redundancy in information and outdated presentation of information. The pharmacology/toxicology and clinical pharmacology teams also provided input to their respective sections of the label. In all, the labeling changes did not provide for major substantive changes in labeling content.

The clinical team recommended a new Warnings and Precautions (W & P) of priapism to the PI of Uroxatral. Although the verbiage of the priapism W & P is “class labeled” for alpha-adrenergic antagonists, this reviewer noted that this W & P only appeared in the PI of products that had postmarketing cases of priapism (tamsulosin, doxazosin IR, terazosin) and not the PI of products with no postmarketing cases reported (silodosin, doxazosin XR). Uroxatral currently does not have a W & P of priapism; however, postmarketing cases of priapism have been reported and labeled in the postmarketing section of the PI of Uroxatral. Therefore, this reviewer believes a W & P of priapism is warranted in the PI of Uroxatral.

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

/s/

CHRISTINE P NGUYEN
12/13/2010

SURESH KAUL
12/13/2010