CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
21287s016

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA:021287/S-016 (document number 167)	Submission Date: 6/16/2010, 7/9/2010, 8/6/2010, 8/10/2010
Brand Name	Uroxatral®
Generic Name	Alfuzosin HCl
Reviewer	LaiMing Lee, Ph.D.
Team Leader	Myong-Jin Kim, Pharm.D.
Pharmacometrics Reviewer	Jiang Liu, Ph.D.
Pharmacometrics Team Leader	Pravin Jadhav, Ph.D.
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Reproductive and Urologic Products
Sponsor	sanofi-aventis
Submission Type	Pediatric Efficacy Supplement (SES)
Formulation; Strengths; Regimen	Oral solution, 0.2 mg/mL (7.5 mg) given three times a day and extended release tablet, 1.5 mg (9 mg) given twice daily
Evaluated Indication	Treatment of children age 2-16 years with elevated detrusor leak point pressure with or without hydronephrosis of neuropathic etiology

An Optional Inter-Division Level OCP Briefing was held on November 20, 2010 and was attended by Sayed Al Habet, Hyunjin Kim, Myong-Jin Kim, Pravin Jadhav, Ruby Leong, Jiang Liu, Christine Nguyen, Kellie Reynolds, Xinning Yang and Lin Zhou.

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1. Executive Summary

Sanofi aventis received approval of alfuzosin hydrochloride (HCl) on June 12, 2003 under NDA 021278 under the trade name Uroxatral®. Alfuzosin is an alpha1-adrenergic receptor antagonist and is indicated for the treatment of signs and symptoms of benign prostatic hyperplasia (BPH) in adults. Uroxatral® is not indicated for the treatment of hypertension. The approved dosing instruction states that alfuzosin 10 mg extended-release (ER) tablets are to be taken once daily immediately after the same meal each day. Tablets should not be chewed or crushed. There are no specific instructions for dose adjustments in specific populations. Alfuzosin is contraindicated in patients with moderate or severe hepatic impairment, in patients taking a potent CYP3A4 inhibitor, and in patients with hypersensitivity to alfuzosin or any of the ingredients.

The sponsor submitted a Pediatric Efficacy Supplement on June 16, 2010 in response to a formal pediatric Written Request (WR) issued by the Agency on February 21, 2006. The supplement contains 4 clinical studies (1 pharmacokinetic (PK), 1 bioavailability, 1 pivotal efficacy and safety, and 1 supportive exploratory efficacy and safety). The sponsor also submitted a population PK analysis report based on the two efficacy and safety studies and one PK study. In addition, it contains draft labeling with additions to the HIGHLIGHTS-USE IN SPECIFIC POPULATIONS, FULL PRESCRIBING INFORMATION-USE IN SPECIFIC POPULATIONS-PEDIATRIC USE, and CLINICAL PHARMACOLOGY-PEDIATRIC USE sections. The sponsor does not seek a new indication for Uroxatral due to an inability to demonstrate clinical efficacy in pediatrics; however, they are proposing to update their label with the pediatric data obtained from the studies. Pediatric exclusivity was granted to the sponsor in September 2010 after it was determined that all WR requirements were met. This review details the findings from the PK and bioavailability studies, and findings from the Pharmacometric review of the population PK report. Details from the pivotal and exploratory safety and efficacy studies can be found in the Clinical review by Dr. Christine Nguyen.

Background:

The Agency issued a formal Pediatric WR on February 21, 2006 requesting the sponsor to conduct and submit the following studies:

Study 1 (PKM6270): A 4-week, open-label, randomized, multiple dose, parallel dose group pharmacokinetics and safety study in pediatric patients, age 2-16 years, with elevated detrusor leak point pressure (LPP) ($\geq$40 cm H_2O) of neurologic origin. Pharmacodynamic measurement (LPP) should be performed in all patients at baseline and in those patients who complete the 4-week study.

Study 2 (EFC5722): A 12-week, double blind, randomized, placebo-controlled, parallel dose, efficacy, pharmacodynamic and safety study comparing two doses of alfuzosin followed by a 40-week (10 month) open-label extension phase in pediatric patients, age 2-16 years, with elevated detrusor LPP ($\geq$40 cm H_2O) of neurologic origin. Population pharmacokinetics will be investigated at 12 weeks.

Study 3 (EFC6269): A 12-week, open-label, non-comparative pharmacodynamic and safety study in pediatric patients, age 2-16 years, with grade 1 or 2 hydronephrosis associated with elevated detrusor LPP ($\geq$40 cm H_2O) of neurologic origin followed by a

40-week (10-month) extension phase. Population pharmacokinetics should be investigated at 12 weeks.

The Agency also encouraged the sponsor to develop a commercially-marketable formulation for use in children. It was stated in the WR that bioavailability of any formulation used in the studies be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults. Therefore, the sponsor conducted a bioavailability study (Study BDR10380) to compare the adult ER tablets against the pediatric solution and oral tablet in a single center, open-label, randomized, repeated dose (3 days), three-period, crossover study in 15 healthy adult males.

The sponsor submitted two amendments to the WR on May 16, 2006 and June 6, 2008: (1) to modify the due date the final study report submission to June 16, 2010 and (2) to allow for the inclusion of pediatric patients with Grade 3 hydronephrosis.

On June 16, 2010, the sponsor submitted the Pediatric Efficacy Supplement (S-016) to NDA 021287.

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 has reviewed the NDA 021287 Supplement 16 (Pediatric Efficacy Supplement) and finds it acceptable from a Clinical Pharmacology perspective, provided the labeling comments are adequately addressed.

1.2 Phase IV Commitments

None

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Alfuzosin was adminstered with food in the PK study to maximize absorption.

Single dose PK: Following a single dose of alfuzosin solution on Day 1 at 0.1 mg/kg/day, mean (SD) AUC_{0-4} was 13.9 (5.93) ng.hr/mL and mean (SD) Cmax was 6.41 (3.99) ng/mL. Following a single dose of alfuzosin solution on Day 1 at 0.2 mg/kg/day, mean (SD) AUC_{0-4} was 42.9 (22.1) ng.hr/mL and mean (SD) Cmax was 17.1 (10.1) ng/mL. After a single dose of alfuzosin, AUC_{0-4} was 3.1 times higher when the dose was doubled from 0.1 to 0.2 mg/kg/day.

Following a single dose of alfuzosin tablet on Day 1 at 0.1 mg/kg/day, mean (SD) AUC_{0-12} was 24.2 (9.92) ng.hr/mL and mean (SD) Cmax was 3.41 (2.20) ng/mL. Following a single dose of alfuzosin tablet on Day 1 at 0.2 mg/kg/day, mean (SD) AUC_{0-12} was 50.0 (15.4) ng.hr/mL and mean (SD) Cmax was 7.26 (1.76) ng/mL. After a single dose of alfuzosin tablet, AUC_{0-12} was 2.1 times higher when the dose was doubled from 0.1 to 0.2 mg/kg/day.

Multiple dose PK: Following multiple doses of alfuzosin solution on Day 7 at 0.1 mg/kg/day, mean (SD) AUC_{0-4} was 16.9 (6.7) ng.hr/mL and mean (SD) Cmax was 6.89 (3.40) ng/mL. Following multiple doses of alfuzosin solution on Day 7 at 0.2 mg/kg/day,

mean (SD) AUC_{0-4} was 55.9 (33.9) ng.hr/mL and mean (SD) Cmax was 22.3 (13.8) ng/mL. After multiple doses of alfuzosin solution, AUC_{0-4} was 3.3 times higher when the dose was doubled from 0.1 to 0.2 mg/kg/day. The accumulation ratio at 0.1 mg/kg/day dose (AUC_{0-4} Day 7/ AUC_{0-4} Day 1) was 1.22. The accumulation ratio at 0.2 mg/kg/day dose (AUC_{0-4} Day 7/ AUC_{0-4} Day 1) was 1.30.

Following multiple doses of alfuzosin tablet on Day 7 at 0.1 mg/kg/day, mean (SD) AUC_{0-12} was 56.5 (11.4) ng.hr/mL and mean (SD) Cmax was 5.85 (2.91) ng/mL. Following multiple doses of alfuzosin tablet on Day 7 at 0.2 mg/kg/day, mean (SD) AUC_{0-12} was 82.5 (19.9) ng.hr/mL and mean (SD) Cmax was 12.4 (2.9) ng/mL. After multiple doses of alfuzosin, AUC_{0-12} was 1.5 times higher when the dose was doubled from 0.1 to 0.2 mg/kg/day. The accumulation ratio at 0.1 mg/kg/day dose (AUC_{0-12} Day 7/ AUC_{0-12} Day 1) was 2.33. The accumulation ratio at 0.2 mg/kg/day dose (AUC_{0-12} Day 7/ AUC_{0-12} Day 1) was 1.65.

Formulations: The sponsor developed two pediatric formulations – oral solution and oral extended release tablets. In an open-label, randomized, repeated dose (3 days), three-way crossover study, the relative bioavailability of the two pediatric formulations and adult oral ER tablets were evaluated in 15 healthy adult male subjects following a high fat breakfast.

The pediatric formulations and adult tablets demonstrated similar oral bioavailability. The mean (SD) AUC_{0-24} was 181 $\pm$ 52.9 ng.hr/mL for the pediatric solution. The mean (SD) AUC_{0-24} was 196 $\pm$ 66.9 ng.hr/mL for the pediatric tablet. The mean (SD) AUC_{0-24} was 180 $\pm$ 85.9 ng.hr/mL for the adult tablet. The mean (SD) Cmax was 13.9 $\pm$ 4.01, 13.5 $\pm$ 4.22, 14.5 $\pm$ 6.82 for the pediatric solution, pediatric tablet, and adult tablet, respectively.

Pharmacodynamics: For the pivotal pharmacodynamic study EFC5722, the primary endpoint was the proportion of patients with detrusor LPP < 40 cm H_2O at the end of the double-blind treatment period (Week 12). The secondary endpoints were the absolute and relative change in detrusor LPP from baseline. At the end of the 12-week double-blind study phase, a comparable proportion of patients in both alfuzosin treatment groups and the placebo group reported LPP <40 cmH_2O (placebo: 23/57 patients; alfuzosin 0.1 mg/kg/day: 23/57 patients; alfuzosin 0.2 mg/kg/day: 28/58 patients).

For secondary endpoints (the absolute and relative change in detrusor LPP from baseline), there was slightly better lowering of LPP with the higher (0.2 mg/kg/day) alfuzosin group, compared with the lower dose alfuzosin group and the placebo group. However, the difference was not statistically significant. The mean (SD) absolute change from baseline was -5.4 (2.79), -11.7 (2.80), and -12.5 (2.78) cm H_2O for placebo, 0.1 mg/kg/day, and 0.2 mg/kg/day group, respectively. The mean (SD) relative change from baseline was –9.2% (5.53), -20.6% (5.56), and -23.5% (5.51) for placebo, 0.1 mg/kg/day, and 0.2 mg/kg/day groups, respectively.

Subgroup analyses found there was no difference between the alfuzosin dose groups and the placebo group for the LPP responder rate in the subgroups defined by age, gender, race, and dose.

Population PK analysis detected a significant positive relationship between alfuzosin clearance and the patient's body weight. With weight-adjusted dosing, the systemic

exposure (based on $AUC_{0\text{-}24,ss}$) in heavier (~70 kg) pediatric patients is approximately 2-fold higher compared to that of exposure in lighter (~10 kg) patients.

Overall, the sponsor was unable to demonstrate clinical efficacy in pediatrics and does not seek a new indication for Uroxatral. They are, however, proposing to update their label with the pediatric data obtained from the studies.

2 Question-Based Review

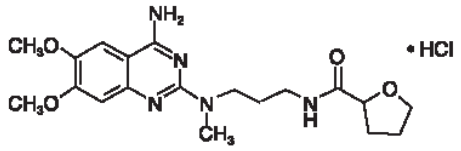
2.1 General Attributes of the drug

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

Uroxatral is approved for the treatment of BPH. The ER tablet 10 mg was approved in the U.S. under NDA 21287 on June 12, 2003. Three formulations/doses/dosing regimen of alfuzosin HCl approved in the European Union between 1987 and 1999 consists of immediate-release (IR) tablet 2.5 mg three times a day (TID), ER tablet 5 mg twice a day (BID), and ER tablet 10 mg once a day (QD) under the trade name Xatral®.

What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Alfuzosin HCl is a white to off-white crystalline powder that melts at approximately 240°C. It is freely soluble in water, sparingly soluble in alcohol, and practically insoluble in dichloromethane. The chemical name is (R,S)-N-[3-(4-amino-6,7-dimethyoxy-2-quinazolinyl) methylamino] propyl] tetrahydro-2-furancarboxamide hydrochloride. The empirical formula of alfuzosin HCl is $C_{19}H_{27}N_5O_4.HCl$. The molecular weight is 425.9. The structural formula is:



Alfuzosin was originally approved as an ER tablet for use in adults. The sponsor developed and evaluated two formulations – an oral solution and an oral ER tablet – for use in children age 2 to 16 years. For younger children 2 to 7 years who are unable to swallow tablets, an oral solution 0.2 mg/mL was developed. For older children and adolescents 8 to 16 years, an oral ER tablet 1.5 mg was developed.

2.1.3 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Alfuzosin is an alpha1-adrenoceptor antagonist that exhibits preferential alpha1-adrenoceptor antagonist properties at the level of the lower urinary tract. It is currently approved for the treatment of BPH in adult males. The sponsor sought to treat pediatric patients (age 2 to 16 years) with elevated detrusor LPP with or without hydronephrosis of neurological etiology. As an alpha1-adrenergic receptor antagonist with muscle relaxing properties, alfuzosin can potentially relax the bladder muscle and urethral resistance and thereby reduce the detrusor LPP. However, the sponsor was unable to demonstrate efficacy in reducing detrusor LPP in pediatric patients with either alfuzosin dose groups, compared to placebo.

2.2 General Clinical Pharmacology

2.2.1 What is the drug development approach for supporting drug approval and labeling in pediatrics?

The sponsor is not seeking a new indication or dosing claim for alfuzosin due to an inability to demonstrate clinical efficacy in pediatrics; however, they are proposing to update their label with the pediatric data obtained from the studies. In order to evaluate alfuzosin in the pediatric population, the sponsor developed two formulations - an oral solution 0.2 mg/mL and an oral ER tablet 1.5 mg - appropriate for use in children age 2 to 16 years. For the younger children 2 to 7 years, the oral solution was given TID with a dosing interval of about 4 hours, at breakfast, lunch, and dinner. For the older children and adolescents, the ER tablets were given BID with a dosing interval of about 12 hours, at breakfast and dinner. Children in both groups received alfuzosin at either 0.1 or 0.2 mg/kg/day, while the approved adult dose is 10 mg once daily. The sponsor selected the pediatric doses 0.1 and 0.2 mg/kg/day to cover alfuzosin exposure from 10 mg QD ER dose in adults.

2.2.2 What are the proposed age ranges and distribution of patients in the pediatric studies? Does the age range in the studies reflect the distribution of the disease being studied?

The sponsor evaluated alfuzosin in children age 2 to 16 years. This age range adequately covers children with elevated detrusor LPP associated with a known neurological disorder.

2.2.3 What are the primary endpoints measured in clinical pharmacology and clinical studies? Are they appropriate endpoints for pediatric studies?

For PK study PKM6270, the pharmacodynamic criteria were change in detrusor LPP at baseline and Week 4 (end of study) in urodynamic laboratories utilizing an artificial bladder filling method. For the pivotal pharmacodynamic study EFC5722, the primary endpoint was the proportion of patients with detrusor LPP < 40 cm H_2O at the end of the double-blind treatment period (Week 12). The secondary endpoints were the absolute and relative change in detrusor LPP from baseline. Study EFC6269 was an efficacy 12-week and 40-week safety extension, open-label, exploratory, non-comparative study evaluating the efficacy of alfuzosin 0.2 mg/kg/day in children and adolescents age 2 to 16 years with newly diagnosed or progressive hydronephrosis due to neuropathic bladder dysfunction. There were no pharmacodynamic measurements in bioavailability study BDR10380.

2.2.4 Are the active moieties in the plasma appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes, the sponsor reports plasma concentrations of alfuzosin in the PK and BA studies. According to the approved product label, alfuzosin undergoes extensive hepatic metabolism with 11% of the administered dose excreted unchanged in the urine. Alfuzosin is metabolized by three metabolic pathways: oxidation, O-demethylation, and N-dealkylation. The metabolites are not pharmacologically active. CYP3A4 is the principal hepatic enzyme isoform involved in its metabolism.

2.2.5 Exposure-Response Evaluation

2.2.5.1 What are the characteristics of the exposure (dose)-response relationships for efficacy?

The exposure-response relationship from the pivotal pharmacodynamic study EFC5722 to support the indication in pediatrics was evaluated by Pharmacometrics Reviewer Jiang Liu. An exposure-response relationship for primary and secondary endpoints has not been established.

At the end of the 12-week double-blind study phase, a comparable proportion of patients in both alfuzosin treatment groups and the placebo group reported LPP <40 cmH_2O (placebo: 23/57 patients; alfuzosin 0.1 mg/kg/day: 23/57 patients; alfuzosin 0.2 mg/kg/day: 28/58 patients).

Detrusor Leak Point Pressure (cmH_2O): proportion of patients with LPP < 40 cm H_2O at Week 12

		Alfuzosin (mg/kg/day)	
	Placebo (N=57)	0.1 mg/kg/day (N=57)	0.2 mg/kg/day (N=58)
LPP			
< 40 cm H_2O	23 (40.4%)	23 (40.4%)	28 (48.3%)
≥ 40 cm H_2O or missing	34 (59.6%)	34 (59.6%)	30 (51.7%)
Difference in response vs placebo		0%	7.9%
95% CI diff vs placebo		0.0 (-17.5; 17.5)	7.9 (-10.0; 25.1)
p-values vs placebo		1.000	0.909

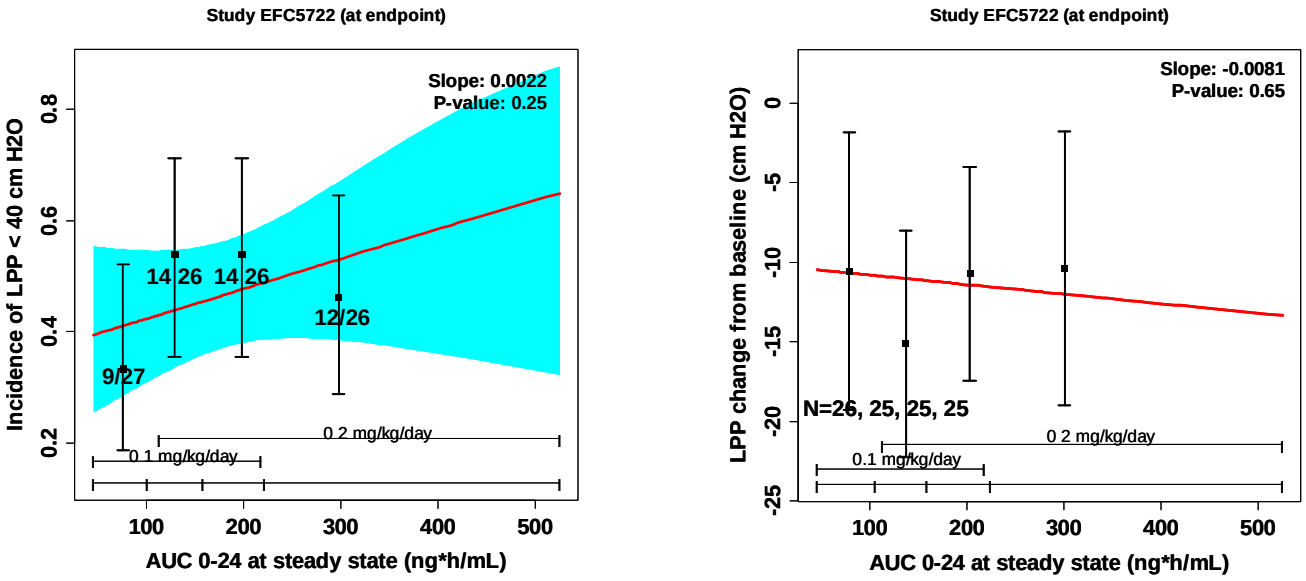
For secondary endpoints (the absolute and relative change in detrusor LPP from baseline), there was slightly better lowering of LPP with the higher (0.2 mg/kg/day) alfuzosin group, compared with the lower dose alfuzosin group and the placebo group. However, the difference was not statistically significant. The mean (SD) absolute change from baseline was -5.4 (2.79), -11.7 (2.80), and -12.5 (2.78) cm H_2O for placebo, 0.1 mg/kg/day, and 0.2 mg/kg/day group, respectively. The mean (SD) relative change from baseline was –9.2% (5.53), -20.6% (5.56), and -23.5% (5.51) for placebo, 0.1 mg/kg/day, and 0.2 mg/kg/day groups, respectively.

Detrusor Leak Point Pressure (cmH_2O): mean change in LPP and relative change of LPP from baseline

		Alfuzosin (mg/kg/day)	
	Placebo (N=57)	0.1 mg/kg/day (N=57)	0.2 mg/kg/day (N=58)
Baseline LPP – mean (SD)	54.2 (12.6)	53.3 (13.4)	50.9 (10.0
Endpoint LPP – mean (SD)	48.2 (23.4)	41.6 (18.2)	39.4 (19.5)
Absolute change from baseline (cmH_2O)			
LSMean (SE)	-5.4 (2.79)	-11.7 (2.80)	-12.5 (2.78)
LSMean difference (SE) vs. placebo		-6.2 (3.80)	-7.1 (3.77)
p-values vs. placebo		0.104	0.063
Relative change from baseline (%)			
LSMean (SE)	-9.2 (5.53)	-20.6 (5.56)	-23.5 (5.51)
LSMean difference (SE) vs. placebo		-11.4 (7.54)	-14.3 (7.48)
p-values vs. placebo		0.133	0.058

The exposure-response relationships for primary and secondary efficacy endpoints based on the sponsor's model derived $AUC_{0\text{-}24,ss}$ or $C_{max,ss}$ that were shallow and not statistically significant.

The following figure is the exposure-response relationships for primary (left) and secondary (right) efficacy endpoints.



The review of available data does not support clinical efficacy of alfuzosin HCl for reduction in detrusor LPP in pediatric patients age 2 to 16 years with known neurological deficit. The exposure-response analyses for efficacy did not provide evidence of effectiveness in this application.

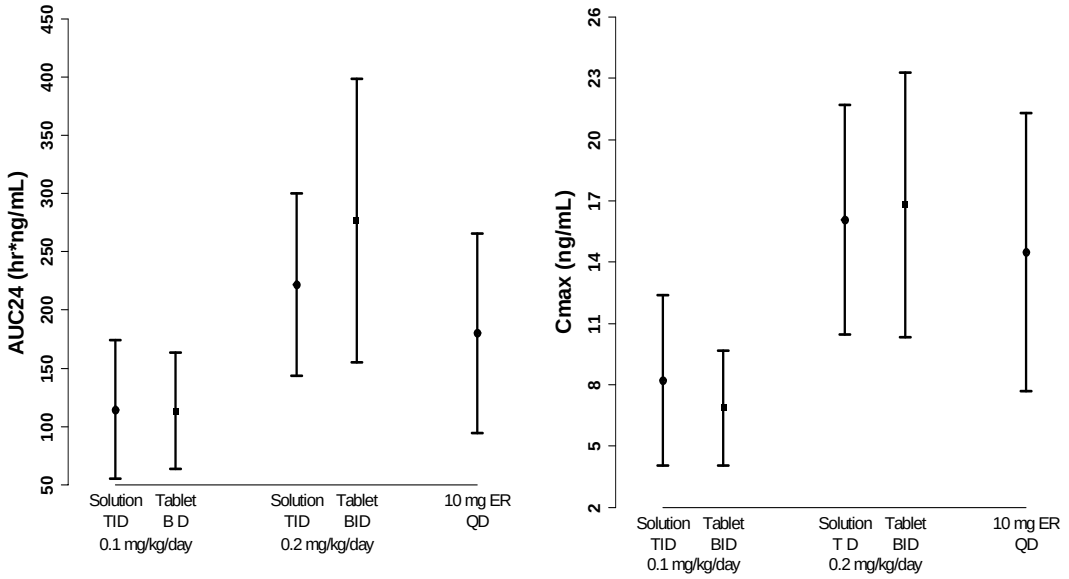
2.2.5.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

The most common adverse events reported in the clinical studies (incidences > 2%) for the approval of Uroxatral in adult males were dizziness, upper respiratory infection, headache, and fatigue. Alpha blockers such as alfuzosin may result in postural hypotension resulting from dizziness, syncope, and fatigue. In the pivotal study EFC5722, dizziness was reported infrequently and almost equally in all three treatment groups (placebo: 1/57 patients; 0.1 mg/kg/day alfuzosin: 0/57 patients; 0.2 mg/kg/day: 1/58 patients). Upper respiratory infection occurred to a similar degree in all three groups (placebo: 3/57 patients; 0.1 mg/kg/day alfuzosin: 3/57 patients; 0.2 mg/kg/day: 2/58 patients).

Headache was slightly higher with dose (placebo: 1/57 patients; 0.1 mg/kg/day alfuzosin: 2/57 patients; 0.2 mg/kg/day: 3/58 patients). Lethargy/fatigue was slightly higher in the placebo (placebo: 1/57 patients; 0.1 mg/kg/day alfuzosin: 0/57 patients; 0.2 mg/kg/day: 0/58 patients). Overall, the incidences of adverse events (AEs) in both alfuzosin groups were similar to placebo group and no exposure response can be established for safety.

2.2.5.3 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response?

The approved adult dose is 10 mg alfuzosin once daily. Adjusting for adult male body weight of 70 kg, the weight based dose for adults is 0.14 mg/kg/day. The pediatric doses selected for the PK, BA, and pivotal safety and pharmacodynamic studies submitted in this pediatric supplement were 0.1 and 0.2 mg/kg/day, which fall within the lower and higher end of the approved adult dose. Based on PK analysis, the 0.1 mg/kg/day dose in pediatrics provided exposure (AUC_{0-24} and Cmax) slightly lower and the 0.2 mg/kg/day dose in pediatrics provided exposure slightly higher than that of the 10 mg QD dose in adults (see Pharmacometrics review).



The extent of absorption is 50% lower under fasting conditions; therefore alfuzosin should be taken immediately following a meal, according to the approved label for Uroxatral adult ER tablets. It is likely that the sponsor conducted the clinical studies with food in order to maximize alfuzosin bioavailability, though not specifically stated by the sponsor in the reports. This is acceptable.

2.2.6 Pharmacokinetic Characteristics

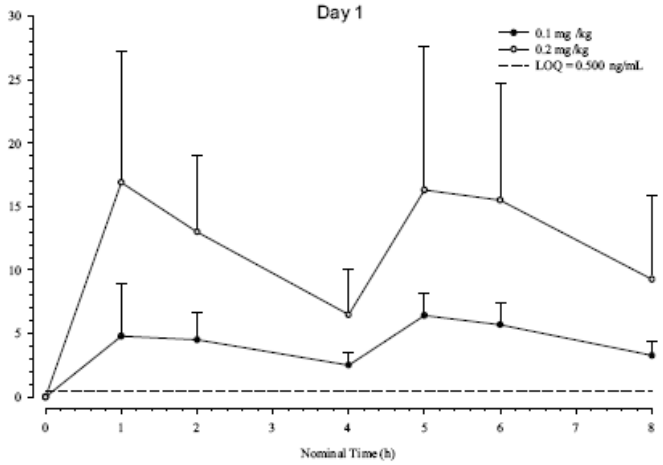
2.2.6.1 What is the single dose PK of alfuzosin?

Alfuzosin is extensively metabolized in the liver by three metabolic pathways: oxidation, O-demethylation, and N-dealkylation. The metabolites are not pharmacologically active. In PK study PKM6270, children were given alfuzosin solution (TID) or tablets (BID) for 7 days at doses of 0.1 or 0.2 mg/kg/day. For the oral solution containing 0.2 mg/mL alfuzosin, the dose regimen for children 2 to 7 years was (1) 0.1 mg/kg/day divided into 3 doses given at breakfast, lunch, and dinner (0.033 mg/kg TID) (N=7) or (2) 0.2 mg/kg/day divided into 3 doses given at breakfast, lunch, and dinner (0.066 mg/kg TID) (N=8). For the oral tablet containing 1.5 mg alfuzosin, the dose regimen for children 8 to 16 years was (1) 0.1 mg/kg/day divided into 2 doses given at breakfast and dinner (0.05

mg/kg BID) (N=7) or (2) 0.2 mg/kg/day divided into 2 doses given at breakfast and dinner, administered 12 hours apart (0.1 mg/kg BID) (N=8).

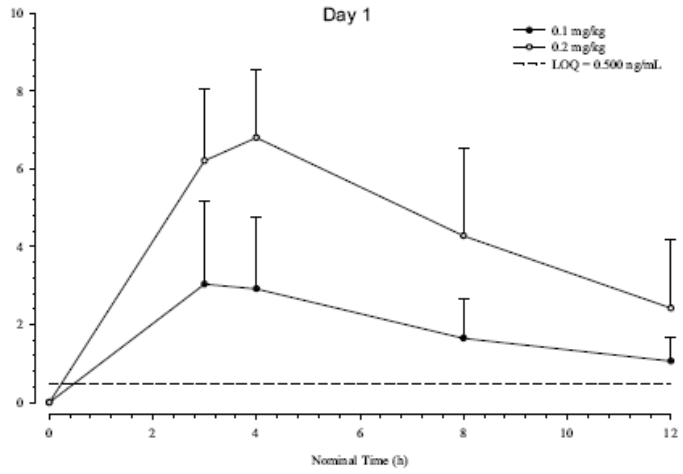
Following a single dose of alfuzosin solution on Day 1 at 0.1 mg/kg/day, mean (SD) AUC_{0-4} and mean (SD) Cmax was 13.9 (5.93) ng.hr/mL and 6.41 (3.99) ng/mL, respectively. Following a single dose of alfuzosin solution on Day 1 at 0.2 mg/kg/day, mean (SD) AUC_{0-4} and mean (SD) Cmax was 42.9 (22.1) ng.hr/mL and 17.1 (10.1) ng/mL, respectively. After a single dose of alfuzosin solution, AUC_{0-4} was 3.1 times higher when the dose was doubled from 0.1 to 0.2 mg/kg/day.

The following figure is the plasma concentration-time profile for **alfuzosin solution** given as 0.1 and 0.2 mg/kg/day in children age 2 to 7 years on **Day 1**.



Following a single dose of alfuzosin tablet on Day 1 at 0.1 mg/kg/day, mean (SD) AUC_{0-12} and mean (SD) Cmax was 24.2 (9.92) ng.hr/mL and 3.41 (2.20) ng/mL, respectively. Following a single dose of alfuzosin tablet on Day 1 at 0.2 mg/kg/day, mean (SD) AUC_{0-12} and mean (SD) Cmax was 50.0 (15.4) ng.hr/mL and 7.26 (1.76) ng/mL, respectively. After a single dose of alfuzosin tablet, AUC_{0-12} was 2.1 times higher when the dose was doubled from 0.1 to 0.2 mg/kg/day.

The following figure is the plasma concentration-time profile for **alfuzosin tablets** given as 0.1 and 0.2 mg/kg/day in children and adolescents age 8 to 16 years on **Day 1.**

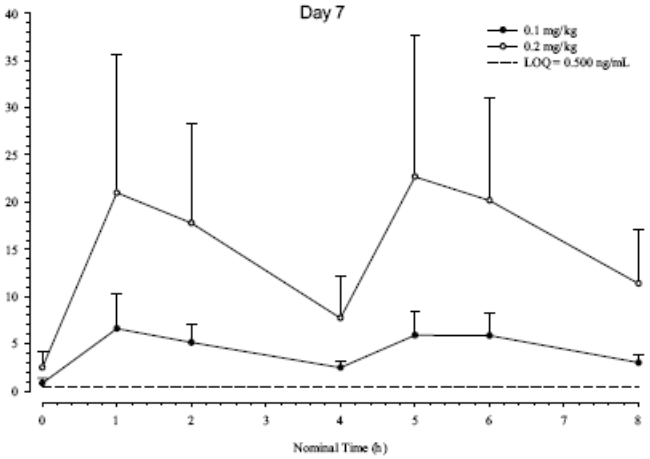


2.2.5.3. What is the multiple dose PK of alfuzosin?

Following multiple doses of alfuzosin solution on Day 7 at 0.1 mg/kg/day, mean (SD) AUC_{0-4} and mean (SD) Cmax was 16.9 (6.7) ng.hr/mL and 6.89 (3.40) ng/mL, respectively. Following multiple doses of alfuzosin solution on Day 7 at 0.2 mg/kg/day, mean (SD) AUC_{0-4} and mean (SD) Cmax was 55.9 (33.9) ng.hr/mL and 22.3 (13.8) ng/mL, respectively. After multiple doses of alfuzosin solution, AUC_{0-4} was 3.3 times higher when the dose was doubled from 0.1 to 0.2 mg/kg/day.

The accumulation ratio at 0.1 mg/kg/day dose (AUC_{0-4} Day 7/ AUC_{0-4} Day 1) was 1.22. The accumulation ratio at 0.2 mg/kg/day dose (AUC_{0-4} Day 7/AUC_{0-4} Day 1) was 1.30.

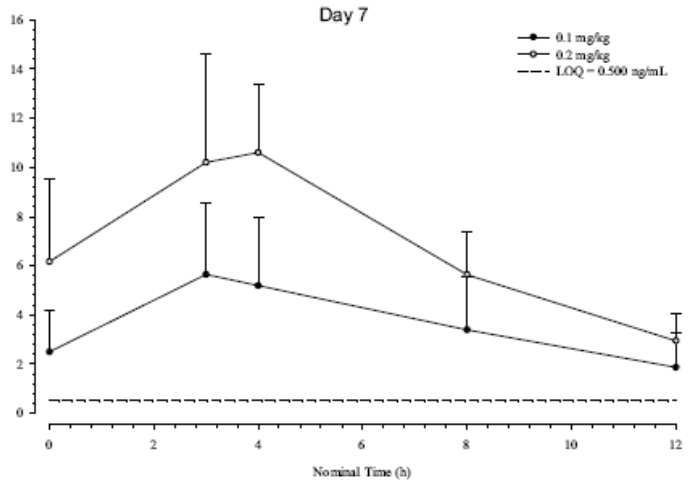
The following figure is the plasma concentration-time profile for **alfuzosin solution** given as 0.1 and 0.2 mg/kg/day in children age 2 to 7 years on **Day 7**.



Following multiple doses of alfuzosin tablets on Day 7 at 0.1 mg/kg/day, mean (SD) AUC_{0-12} and mean (SD) Cmax was 56.5 (11.4) ng.hr/mL and 5.85 (2.91) ng/mL, respectively. Following multiple doses of alfuzosin tablets on Day 7 at 0.2 mg/kg/day, mean (SD) AUC_{0-12} and mean (SD) Cmax was 82.5 (19.9) ng.hr/mL and 12.4 (2.9) ng/mL, respectively. After multiple doses of alfuzosin tablets, AUC_{0-12} was 1.5 times higher when the dose was doubled from 0.1 to 0.2 mg/kg/day.

The accumulation ratio at 0.1 mg/kg/day dose (AUC_{0-12} Day 7/ AUC_{0-12} Day 1) was 2.33. The accumulation ratio at 0.2 mg/kg/day dose (AUC_{0-12} Day 7/ AUC_{0-12} Day 1) was 1.65.

The following figure is the plasma concentration-time profile for **alfuzosin tablet** given as 0.1 and 0.2 mg/kg/day in children and adolescents age 8 to 16 years on **Day 7.**



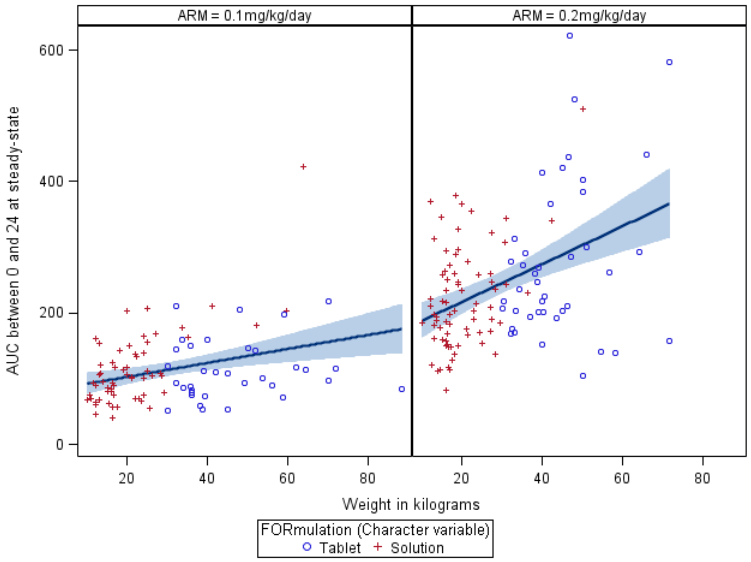
2.3 Intrinsic Factors

2.3.1 What intrinsic factors (gender, body weight, race, and age) influence exposure (PK usually) and/or response and what is the impact of any differences in exposure on efficacy or safety responses? (see Pharmacometrics review)

Subgroup analyses found there was no difference between the alfuzosin dose groups and the placebo group for the LPP responder rate in the subgroups defined by age, gender, race, and dose.

Population PK analysis detected a significant positive relationship between alfuzosin clearance and the patient's body weight. With weight-adjusted dosing, the systemic exposure (based on $AUC_{0-24,ss}$) in heavier (~70 kg) pediatric patients is approximately 2-fold higher compared to that of exposure in lighter (~10 kg) patients.

The following figure is derived alfuzosin exposure versus body weight:



In patients 2 to 7 years of age, a slightly higher proportion of patients in both alfuzosin treatment groups reported LPP <40 cmH_2O at the end of the 12-week double-blind study phase (placebo: 9/28 patients; alfuzosin 0.1 mg/kg/day: 15/28 patients; alfuzosin 0.2 mg/kg/day: 13/28 patients). However, all 95% CIs for the respective odd ratios included 1 indicating no statistically significant difference between the alfuzosin dose groups and placebo. In patients 8 to 16 years of age, a slightly higher proportion of patients in the placebo group and in the alfuzosin 0.2 mg/kg/day group reported LPP <40 cmH_2O (placebo: 14/29 patients; alfuzosin 0.1 mg/kg/day: 8/29 patients; alfuzosin 0.2 mg/kg/day: 15/30 patients). An additional analysis was carried out to evaluate the LPP response for the subgroup of patients with a baseline LPP range 41-45 cm H_2O. The results are consistent with the results of the primary analysis. The difference in response versus placebo was -10.5% [95% CI -41.1; 23.3] for the alfuzosin 0.1 mg/kg/day group and +17.3% [95% CI –15.0; 45.5] for the alfuzosin 0.2 mg/kg/day group.

Though not an intrinsic factor, a subgroup analysis by the Pharmacometric reviewer found no difference between the alfuzosin dose groups and the placebo group for the LPP responder rate in the subgroups defined by formulation, anticholinergic drug use or geographic area. The absorption rate of alfuzosin was higher in the solution compared to the ER tablet.

The Pharmacometrics reviewer exposure-response analysis also found no significant correlation between change from baseline in diastolic blood pressure, systolic blood pressure, and heart rate and alfuzosin exposure.

2.3 Extrinsic Factors

2.3.1 What extrinsic factors (renal) influence exposure (PK usually) and/or response and what is the impact of any differences in exposure on efficacy or safety responses?

No formal studies were conducted in the pediatric population given alfuzosin to evaluate the affect of extrinsic factors on the PK, efficacy, or safety responses.

Subgroup analyses found there was no difference between the alfuzosin dose groups and the placebo group for the LPP responder rate in the subgroup defined by renal function (creatinine clearance).

2.5 General Biopharmaceutics

2.5.2 Is the formulation appropriate for each age group? What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

The sponsor developed and evaluated two formulations – an oral solution and an oral ER tablet – for use in children age 2 to 16 years. For younger children 2 to 7 years who are unable to swallow tablets, an oral solution 0.2 mg/mL was developed. For older children and adolescents 8 to 16 years, an oral ER tablet 1.5 mg was developed. The two formulations are appropriate for each age group.

The sponsor evaluated the relative bioavailability of the pediatric formulations (oral solution and oral ER tablet) to the adult oral ER tablets in 15 healthy adult male subjects following a high fat breakfast in an open-label, randomized, repeated dose (3 days), three-way crossover study (Study BDR10380).

It should be noted that a direct comparison between the adult formulation and two pediatric formulations is challenging given the different dosing regimens – once daily for the adult ER tablet, twice daily for the pediatric ER tablet, and three times daily for the pediatric solution. The relative bioavailability of alfuzosin from the three formulations was compared using the PK parameter AUC_{0-24}.

The following table summarizes PK parameters observed over 24 hours on Day 3 with the two pediatric formulations and the adult formulation:

	Formulation Dose; Dosing Regimen		
PK Parameter Mean $\pm$ SD	Pediatric Solution 7.5 mg; 12.5 mL, TID	Pediatric ER Tablet 9 mg; 3 x 1.5 mg, BID	Adult ER Tablet 10 mg; 1 x 10 mg, QD
AUC_{0-24} (ng.hr/mL)	181 $\pm$ 52.9	196 $\pm$ 66.9	180 $\pm$ 85.9
AUC_{0-24} normalized to 10 mg (ng hr/mL)	242 $\pm$ 70.6	217 $\pm$ 74.3	180 $\pm$ 85.9
Cmax (ng/mL)	13.9 $\pm$ 4.01	13.5 $\pm$ 4.22	14.5 $\pm$ 6.82

When compared to the adult tablet 10 mg dose, the bioavailability of the pediatric solution and pediatric ER tablet were 34% and 21% higher, respectively. Not normalized to the adult dose, the mean Cmax values at steady-state for all three formulations were similar at 14 ng/mL.

The sponsor states that when the pediatric formulations at the dose administered during the study were compared to the adult tablet, the pediatric solution 7.5 mg was bioequivalent to the adult tablet 10 mg with respect to AUC_{0-24} (point estimate (90% CI): 1.06 (0.96 to 1.17)) and Cmax (point estimate (90% CI): 1.00 (0.88 to 1.15)). When the pediatric tablet was compared to the adult tablet, the pediatric tablet 9 mg did not meet the bioequivalence criteria and is therefore NOT bioequivalent to the adult tablet 10 mg

with respect to AUC_{0-24} (point estimate (90% CI): 1.14 (1.03 to 1.26)). Determination of bioequivalence based on AUC_{0-24} is not accurate in this case considering the different dosing regimens from the three formulations; however, it does provide a relative comparison of bioavailability.

2.5.3 What is the effect of food on the BA of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

The effect of food on the bioavailability of alfuzosin was evaluated in the original NDA. It was shown that extent of absorption is 50% lower under fasting conditions. Therefore, patients are instructed to take alfuzosin immediately after the same meal each day. In this pediatric supplement, children were given alfuzosin after a meal in PK study PKM6270 and pivotal efficacy study EFC5722.

2.6 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Alfuzosin plasma concentrations were assayed using liquid chromatography/mass spectroscopy method.

2.6.3 What is the range of the standard curve? What are the lower and upper limits of quantification (LLOQ/ULOQ)? What are the accuracy, precision and selectivity at these limits?

Calibration standards were prepared by spiking human plasma with aliquots of stock solutions to
give alfuzosin concentrations at 0.500, 1.00, 2.00, 5.00, 10.0, 20.0 and 50.0 ng/mL. Triplicate samples were run at the upper limits (50.0 ng/mL) and the lower limits (0.500 ng/mL) ends of the calibration curve with single samples in between. The analytical run included two plasma blanks with internal standard. All calibration standard samples, including those at LLOQ and ULOQ, fell within $\pm$ 15.0%.

Quality control (QC) samples were prepared in pools by spiking human plasma with an aliquot of
stock solutions to give alfuzosin concentrations at 1.00, 20.0 and 50.0 ng/mL. The QC samples were aliquoted and stored frozen at -20 ± 5°C until the day they were used. QC samples were stored no longer than 31 months before used. All QC samples fell within $\pm$ 15.0%.

3 Detailed Labeling Recommendations

The sponsor is not seeking a new indication for alfuzosin in the pediatric population; therefore, pharmacokinetic data and relative bioavailability data comparing the pediatric formulations to the adult formulation is not relevant in this scenario. The proposed labeling updates from the sponsor under HIGHLIGHTS and Pharmacokinetics are acceptable from a Clinical Pharmacology perspective. This reviewer recommended additional labeling changes under DOSAGE AND ADMINISTRATION in the HIGHLIGHTS and FULL PRESCRIBING INFORMATION to clarify the timing of alfuzosin administration with food.

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4.2 Individual Study Reviews

Study PKM6270

Title: Four-week, open-label, multicenter, randomized, parallel-group study to investigate the pharmacokinetics, safety, tolerability and the effects on leak point pressure of 2 oral doses of alfuzosin (0.1 mg/kg/day; 0.2 mg/kg/day) in children and adolescents 2 to 16 years-of-age with elevated detrusor leak point pressure (LPP) of neuropathic etiology.

Objective: The primary objective was to investigate the pharmacokinetics of two doses of alfuzosin (0.1 and 0.2 mg/kg/day) given as a solution containing 0.2 mg/mL alfuzosin or as extended release tablets containing 1.5 mg alfuzosin in children and adolescents 2 to 16 years of age with elevated detrusor LPP (>40 cm H_2O) of neuropathic etiology stratified into 2 age groups (2 to 7 years and 8 to 16 years). The secondary objectives were to investigate the safety and tolerability of the 2 dose regimens and to determine the effect of the 2 dose regimens on detrusor LPP.

Methods: This was a multicenter, multinational (3 in Serbia and 2 in the United States), 4 week, open-label, randomized, parallel group, pharmacokinetic study of 2 oral doses of alfuzosin (0.1 and 0.2 mg/kg/day) in children and adolescents. The daily dose was adjusted by body weight. For the oral solution containing 0.2 mg/mL alfuzosin, the dose regimen for children 2 to 7 years was (1) 0.1 mg/kg/day divided into 3 doses given at breakfast, lunch, and dinner (0.033 mg/kg three times daily (TID)) (N=7) or (2) 0.2 mg/kg/day divided into 3 doses given at breakfast, lunch, and dinner (0.066 mg/kg TID) (N=8). For the oral tablets containing 1.5 mg alfuzosin, the dose regimen for children 8 to 16 years was (1) 0.1 mg/kg/day divided into 2 doses given at breakfast and dinner (0.05 mg/kg twice daily (BID)) (N=7) or (2) 0.2 mg/kg/day divided into 2 doses given at breakfast and dinner, administered 12 hours apart (0.1 mg/kg BID) (N=8).

Pharmacokinetic Sampling: Blood samples (1 mL) were taken on Day 1 and Day 7 $\pm$ 2 days. For the oral solution (TID dosing), blood samples were collected before the morning dose (t=0), then at 1, 2, 4 (before the noon dose), 5, 6, and 8 hours after dosing. For the oral tablet (BID dosing), blood samples were collected before the morning dose (t=0), then at 3, 4, 8 and 12 hours after dosing. The sponsor assessed the following PK parameters: Ctrough, Cmax, AUC_{0-4}, AUC_{4-8}, and AUC_{0-8} for the oral solution given TID, and AUC_{0-12} for the oral tablet given BID. Accumulation ratio (Rac) was also calculated.

Pharmacodynamics Assessment: Detrusor LPP was evaluated for pharmacodynamic efficacy of alfuzosin and was defined as the lowest detrusor pressure at which urine leakage occurred in the absence of either a detrusor contraction or increased abdominal pressure (expressed in cm H_2O). The relative change in detrusor LPP at endpoint (Day 28 $\pm$ 7 days) compared to baseline was calculated as follows:

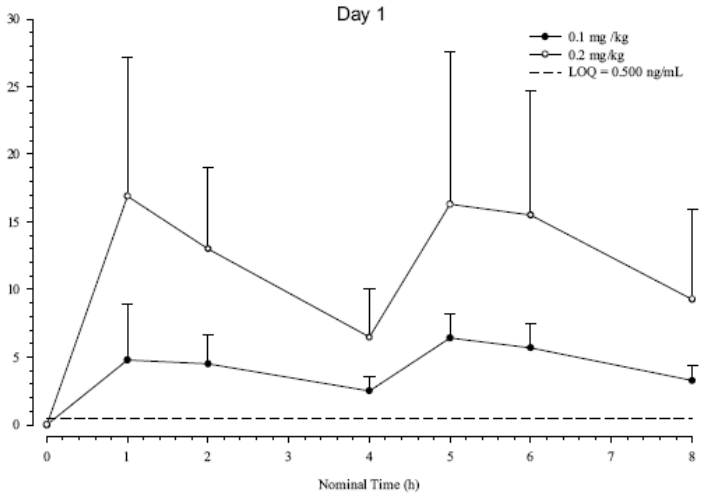
$$\frac{100 \times (\text{LPP at endpoint [cm } H_2O] - \text{LPP at baseline [cm } H_2O])}{\text{Baseline LPP [cm } H_2O]}$$

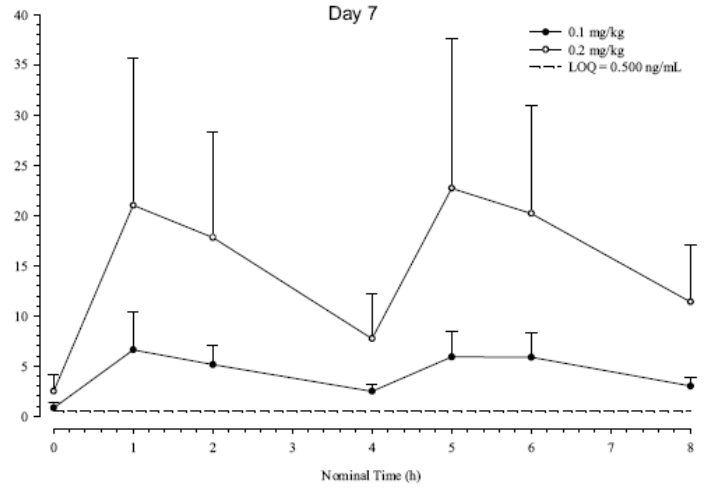
Pharmacokinetics Results: When alfuzosin was given as a solution in a TID regimen at 0.1 mg/kg/day to children 2 to 7 years, mean (SD) AUC_{0-8} on Day 7 and Day 1 were 35.2 (13.1) and 33.0 (6.55) ng.hr/mL, respectively. The accumulation ratio (AUC_{0-8} Day 7/AUC_{0-8} Day 1) was 1.06. At 0.2 mg/kg/day, mean (SD) AUC_{0-8} on Day 7 and Day 1 were 123 (69.3) and 93.7 (49.3) ng.hr/mL, respectively. The accumulation ratio (AUC_{0-8} Day 7/AUC_{0-8} Day 1) was 1.31.

When alfuzosin was given as an oral tablet in a BID regimen at 0.1 mg/kg/day to children and adolescents 8 to 16 years, mean (SD) AUC_{0-12} on Day 7 and Day 1 were 56.5 (11.4) and 24.2 (9.92) ng.hr/mL, respectively. The accumulation ratio (AUC_{0-12} Day 7/AUC_{0-12} Day 1) was 2.33. At 0.2 mg/kg/day, mean (SD) AUC_{0-12} on Day 7 and Day 1 were 82.5 (19.9) and 50.0 (15.4) ng.hr/mL, respectively. The accumulation ratio (AUC_{0-12} Day 7/AUC_{0-12} Day 1) was 1.65.

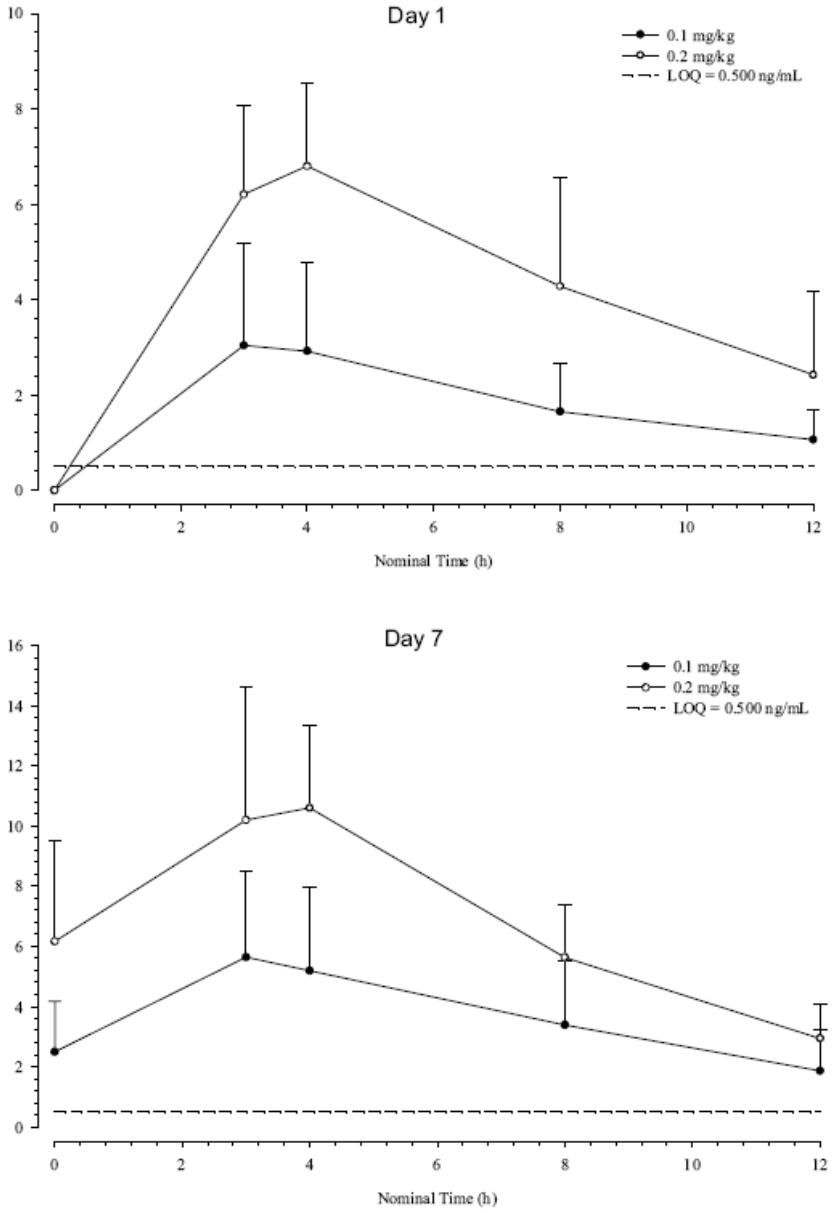
The mean AUC_{0-8} on Day 7 in children 2 to 7 years who received alfuzosin solution at 0.2 mg/kg/day was 3.5-fold higher (123 vs. 35.2 ng.hr/mL), compared to the 0.1 mg/kg/day dose. The mean AUC_{0-12} on Day 7 in children and adolescents 8 to 16 years who received alfuzosin tablets at 0.2 mg/kg/day was 1.5-fold higher (82.5 vs. 56.6 ng.hr/mL), compared to the 0.1 mg/kg/day dose. The 2-fold increase in dose lead to a 3.5-fold increase in AUC_{0-8} in younger children receiving alfuzosin solution and a 1.5-fold increase in AUC_{0-12} in older children who received alfuzosin tablets. Dose proportionality was not established with either formulations; however, the number of subjects enrolled in the study was low.

The following figure is the mean (SD) alfuzosin plasma concentration versus time profiles for the solution given as 0.1 and 0.2 mg/kg/day (TID regimen) in children 2-7 years; morning and noon doses on Day 1 and Day 7:





The following figure is the mean (SD) alfuzosin plasma concentration versus time profiles for the tablets given as 0.1 and 0.2 mg/kg/day (BID regimen) in children 8-12 years; morning doses on Day 1 and Day 7:



The following table summarizes the PK parameters observed in children (2-7 years) with alfuzosin given as a solution (TID solution):

	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	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]	18.4±6.58 (36) [17.4]	35.2±13.1 (37) [33.3]
Rac					[1.22]	[0.94]	[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	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]	67.0±35.7 (53) [57.1]	123±69.3 (56) [104]
Rac					[1.22]	[1.33]	[1.25]

Tabulated values are Mean ± SD (CV%) [Geometric Mean] except for tmax 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

The following table summarizes the PK parameters observed in children (8-16 years) with alfuzosin given as a tablet (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	5.85±2.91 (50) [4.91]	3.00 (0.00-7.88)	56.5±11.4 (20) [55.5] N=5
Rac			[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	12.4±2.85 (23) [12.1]	3.17 (2.98-4.02)	82.5±19.9 (24) [80.1]
Rac			[1.67]

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

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Individual PK profiles for alfuzosin tablet on Day 7 (sponsor's figure 14.2.5.2.4.4)

Pharmacodynamic Results: After 28 days of treatment with alfuzosin, the pharmacodynamic results show a mean (SD) decrease in detrusor LPP of 10.3 (25.7) cm H_2O from 69.5 to 59.3 cm H_2O in the 0.2 mg/kg/day group. The mean (SD) decrease in detrusor LPP was 3.3 (26.2) cm

H_2O from 68.4 to 65.1 cm H_2O in the 0.1 mg/kg/day group. The median changes from baseline in LPP were -6.5 and -16.0 cm H_2O in the 0.1 and 0.2 mg/kg/day group, respectively.

It appears as though alfuzosin may have benefitted some limited number of patients. Five of 14 patients (35.7%) in the 0.1 mg/kg/day group and 3 of 15 patients in the 0.2 mg/kg/day group had LPP < 40 cm H_2O at endpoint. In the 0.1 mg/kg/day group, the baseline LPP values were 42, 42, 42, 49, and 67 cm H_2O, and endpoint values at 31, 36, 36, 24, and 35 cm H_2O. In the 0.2 mg/kg/day group, the baseline values were 41, 41, and 80 cm H_2O, and endpoints values at 9, 25, and 37 cm H_2O. It is not possible to conclude that alfuzosin was effective based on these limited pharmacodynamic findings, and given the level of variability in the data and low number of subjects in each treatment group.

The following table is the descriptive statistics by dose for detrusor leak point pressure (sponsor's table 17):

	Alfuzosin	
Detrusor LPP (cmH_2O)	0.1 mg/kg/day (N=14)	0.2 mg/kg/day (N=15)
Baseline		
Mean (SD)	68.4 (29.4)	69.5 (26.4)
Median	59.0	60.0
Q1 ; Q3	49.0; 80.0	55.0; 80.0
Min : Max	42 : 132	41 : 133
Endpoint		
Mean (SD)	65.1 (48.6)	59.3 (38.6)
Median	43.5	50.0
Q1 ; Q3	36.0; 74.0	40.0; 57.0
Min : Max	24 : 198	9 : 167
<40 cmH_2O	5 (35.7%)	3 (20.0%)
≥40 cmH_2O	9 (64.3%)	12 (80.0%)
Endpoint change from baseline		
Mean (SD)	-3.3 (26.2)	-10.3 (25.7)
Median	-6.5	-16.0
Q1 ; Q3	-21.0 ; 5.0	-30.0 ; -2.0
Min : Max	-32 : 78	-43 : 47
Endpoint percent change from baseline		
Mean (SD)	-11.0 (29.6)	-17.6 (37.0)
Median	-14.1	-26.3
Q1 ; Q3	-32.3 ; 3.8	-37.5 ; -3.6
Min : Max	-51 : 65	-78 : 78

Adverse Events: There was a higher frequency of treatment-emergent adverse events (TEAE) reported by children in the 2 to 7 years group. In the 0.1 mg/kg/day dose group, there were 4 TEAE in younger children, compared to 1 TEAE with older children. In the 0.2 mg/kg/day dose group, there were 5 TEAE in younger children, compared to 1 with older children. The TEAEs were infectious disorders and included pharyngotonsillitis, E. coli urinary tract infection, acute bronchitis, gastroenteritis and respiratory tract infection). One 4-year-old patient on the 0.2 mg/kg/day discontinued from the study due acute bronchitis.

The following table is the safety profile by dose and formulation (sponsor's table 19):

	Alfuzosin			
	0.1 mg/kg/day		0.2 mg/kg/day	
	Solution (2-7 years) (N=7)	Tablets (8-16 years) (N=7)	Solution (2-7 years) (N=8)	Tablets (8-16 years) (N=7)
Patients with any TEAE	4 (57.1%)	1(14.3%)	5 (62.5%)	1 (14.3%)
Patients with any serious TEAE	0	0	0	0
Patients with any TEAE leading to death	0	0	0	0
Patients with any TEAE leading to permanent study drug discontinuation	0	0	1 (12.5%)	0

MedDRA Version 9.1

Conclusions:
When alfuzosin was given as a solution (TID) to children ages 2 to 7 years, the accumulation ratios (AUC_{0-8} Day 7/AUC_{0-8} Day 1) were 1.06 and 1.31 at doses 0.1 and 0.2 mg/kg/day, respectively. When alfuzosin was given as a tablet (BID) to children and adolescents ages 8-16 years, the accumulation ratios (AUC_{0-12} Day 7/AUC_{0-12} Day 1) were 2.33 and 1.65 at doses 0.1 and 0.2 mg/kg/day, respectively.

Children ages 2 to 7 years who received alfuzosin solution at 0.2 mg/kg/day had a 3.5-fold higher AUC_{0-8}, compared to the lower 0.1 mg/kg/day dose.

Children and adolescents ages 8 to 16 years who received alfuzosin solution at 0.2 mg/kg/day had a 1.5-fold higher AUC_{0-12}, compared to the lower 0.1 mg/kg/day dose.

There were too few subjects in the study to establish dose proportionality for both formulations.

It appears as though alfuzosin may have benefitted some limited number of patients. Five of 14 patients (35.7%) in the 0.1 mg/kg/day group and 3 of 15 patients in the 0.2 mg/kg/day group had LPP < 40 cm H_2O at endpoint. However, it is not possible to conclude that alfuzosin was effective based on the limited pharmacodynamic findings, and given the level of variability in the data and low number of subjects in each treatment group.

Study BDR10380

Title: Relative bioavailability study comparing two pediatric formulations of alfuzosin (0.2 mg/mL TID solution and 1.5 mg BID extended release tablet) to the 10 mg adult OD tablet in healthy adult male subjects.

Objective: The primary objective of the study was to determine the relative bioavailability of each of the two pediatric formulations of alfuzosin (0.2 mg/mL solution and 1.5 mg tablets) versus the reference 10 mg once daily adult extended release tablet formulation. The secondary objective was to assess the clinical and laboratory safety of the two pediatric and one adult formulations in healthy adult subjects.

Methods: This was a single center, open-label, randomized, repeated dose (3 days), 3-period with 3-sequence crossover study. Each treatment period was separated by a 4 ($\pm$1)-day washout period. Subjects were institutionalized from Day -1 to Day 4 of each period. Subjects in Treatment A received a total daily dose of 7.5 mg given as 12.5 mL (2.5 mg) TID pediatric solution. Subjects in Treatment B received a total daily dose of 9 mg given as 3 x 1.5 mg BID pediatric tablet. Subjects in Treatment C received a total daily dose of 10 mg given as 1 x 10 mg adult tablet. Each treatment was administered for 3 full days according to the dosing intervals with 240 mL of noncarbonated water. Morning doses were administered after a high fat breakfast. Fifteen healthy adult male subjects with a mean (SD) age of 26.6 (7.4) years and ranged from 19 and 44 years were enrolled and completed the study. The mean (SD) weight was 77.46 (9.35) and ranged from 65.0 and 94.5 kg). There were 9 Caucasian, 3 Blacks, 1 Asian, and 2 Others in the group.

Pharmacokinetic Sampling: The sponsor assessed the following pharmacokinetic parameters on Day 3: AUC_{0-24} normalized to 10 mg, AUC_{0-24}, and Cmax. Ctrough, Cmax, and tmax were obtained directly from experimental observations. Blood samples were collected on Day 3 at the following times:
For the pediatric oral solution: predose, 1, 2, 3, 4, 5, 6, and 8 hours after the first dosing (predose of the second dose), and 1, 2, 3, 4, 5, 6, and 8 hours after the second dosing (predose of the third dose), and 1, 2, 3, 4, 5, 6, and 8 hours after the third dosing.
For the pediatric oral tablet: predose, 1, 2, 3, 4, 5, 6, 8 and 12 hours after the first dosing (predose of the second dose), and 1, 2, 3, 4, 5, 6, 8, and 12 hours after the second dosing.
For the adult oral tablet: predose, 1, 2, 3, 4, 5, 6, 8, 12, 16, and 24 hours post dose.

Results: The mean (SD) AUC_{0-24} was 181 (52.9), 196 (66.9), and 180 (85.9) ng.hr/mL following administration with the pediatric solution 7.5 mg dose, pediatric tablet 9 mg, and adult tablet 10 mg, respectively. Compared to the adult tablet, the exposure was similar with the pediatric solution, but was slightly higher with the pediatric tablet. The mean (SD) Cmax values were similar across the three formulations compared and were 13.9 (4.01), 13.5 (4.22), and 14.5 (6.82) ng/mL following administration with the pediatric solution 7.5 mg dose, pediatric tablet 9 mg, and adult tablet 10 mg, respectively.

When the exposure from the pediatric formulations were normalized to the 10 mg adult dose, the mean (SD) AUC_{0-24} was 242 (70.6) and 217 (74.3) ng.hr/mL for the pediatric solution and tablet, respectively. Compared to the adult tablet with a mean (SD) AUC_{0-24} of 180 (85.9) ng.hr/mL, the exposure from the pediatric solution and pediatric tablet were 34% and 21% higher, respectively.

The following table is a summary of PK parameters observed over 24 hours on Day 3 with the two pediatric formulations and the adult formulation (sponsor's table 13):

Treatment	Treatment A	Treatment B	Treatment C
Alfuzosin Formulation	Pediatric Solution	Pediatric ER tablet	Adult ER tablet
Daily dose	7.5 mg	9 mg	10 mg
Dose regimen	12.5 mL, TID	3x1.5 mg, BID	1x10 mg, OD
N	15	15	15
C_{max}	13.9 ± 4.01	13.5 ± 4.22	14.5 ± 6.82
(ng/mL)	(29) [13.4]	(31) [13.0]	(47) [13.3]
AUC_{0-24} norm. to 10 mg	242 ± 70.6	217 ± 74.3	180 ± 85.9
(h.ng/mL)	(29) [232]	(34) [208]	(48) [164]
AUC_{0-24}	181 ± 52.9	196 ± 66.9	180 ± 85.9
(h.ng/mL)	(29) [174]	(34) [187]	(48) [164]

Tabulated values are Mean ± SD (CV%) [Geometric Mean]

The geometric mean AUC ratio (90% CI) for the pediatric solution (AUC_{0-24} pediatric solution/AUC_{0-24} adult tablet) and pediatric tablet (AUC_{0-24} pediatric tablet/AUC_{0-24} adult tablet) were 1.06 (0.96 to 1.17) and 1.14 (1.03 to 1.26), respectively. When the exposure was normalized to the 10 mg adult dose, the geometric mean AUC ratio (90% CI) for the pediatric solution (AUC_{0-24} pediatric solution/AUC_{0-24} adult tablet) and pediatric tablet (AUC_{0-24} pediatric tablet/AUC_{0-24} adult tablet) were 1.42 (1.28 to 1.57) and 1.27 (1.15 to 1.40), respectively.

Comparing the two pediatric formulations, the geometric mean AUC_{0-24} ratio (90% CI) for the pediatric solution versus the pediatric tablet was 0.93 (0.86 to 1.01). The geometric mean Cmax ratio (90% CI) for the pediatric solution versus the pediatric tablet was 1.03 (0.94 to 1.13).

As mentioned above, the mean Cmax for all three formulations were all similar at approximately 14 ng/mL; therefore all geometric mean ratios for Cmax were approximately 1.

The following tables summarize the formulation effect on the geometric mean ratio estimates of Treatment A and B versus Treatment C, and Treatment A versus Treatment B with 90% CIs (sponsor's table 15 & 16):

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)

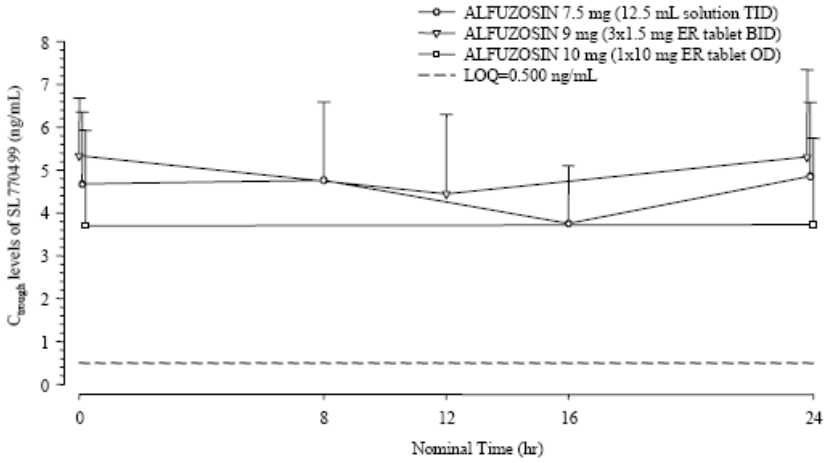
Treatment A = alfuzosin 7.5 mg (12.5 mL pediatric solution TID)
Treatment B = alfuzosin 9 mg (3 x 1.5 mg pediatric ER tablets BID)
Treatment C = alfuzosin 10 mg (1 x 10 mg adult ER tablet OD)

Parameter	Comparison	Estimate	90% CI
AUC_{0-24} (ng.h/mL)	A vs. B	0.93	(0.86 to 1.01)
C_{max} (ng/mL)	A vs. B	1.03	(0.94 to 1.13)

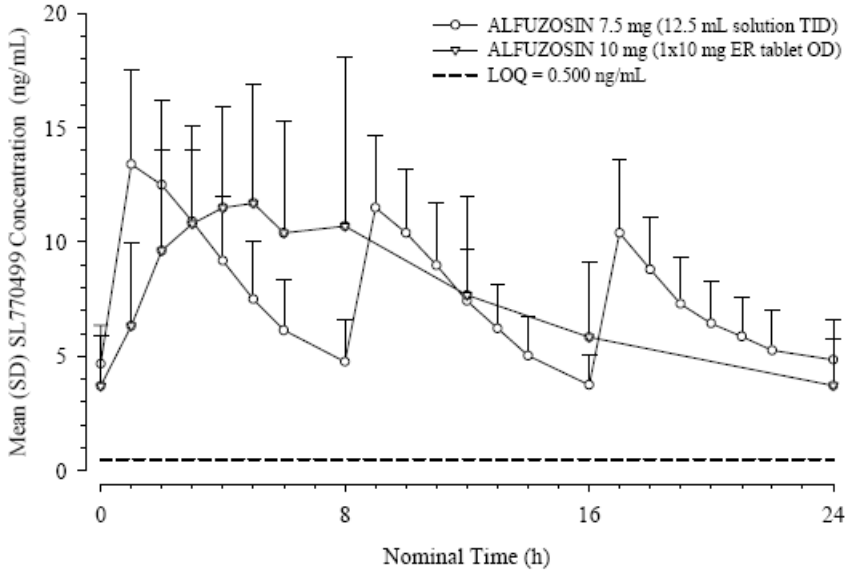
Treatment A = alfuzosin 7.5 mg (12.5 mL pediatric solution TID)
Treatment B = alfuzosin 9 mg (3 x 1.5-mg pediatric ER tablets BID)

It appears that steady state was achieved on Day 3 for all three formulations. Trough concentrations for pediatric solution, pediatric tablet, and adult tablet were 4.6, 5.5, and 3.7 ng/mL on Day 3, respectively.

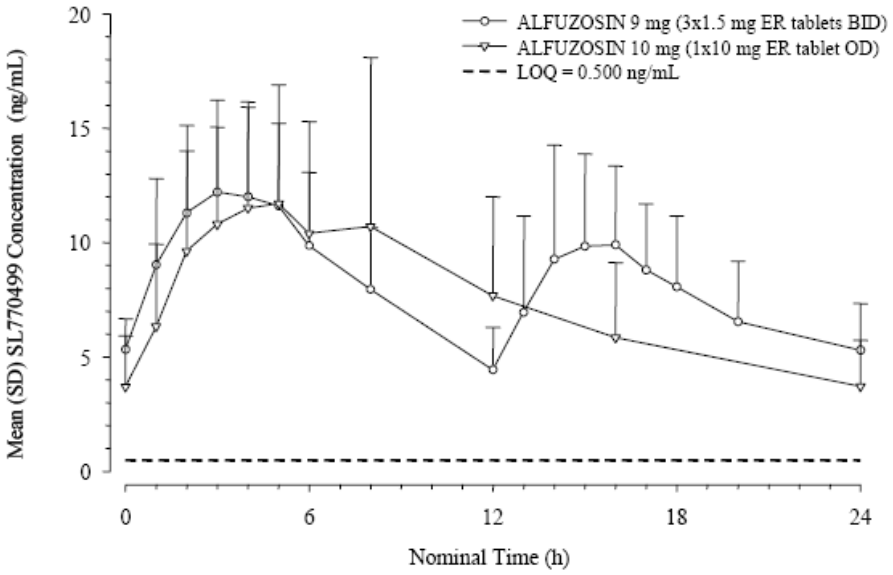
The following figure is the mean (SD) alfuzosin trough concentrations observed on Day 3 for all formulations (sponsor's figure 2):



The following figure is the mean (SD) plasma alfuzosin concentration versus time profiles with the pediatric solution and adult ER tablet on Day 3 (sponsor's figure 3):



The following figure is the mean (SD) plasma alfuzosin concentration versus time profiles with the pediatric ER tablet and adult ER tablet on Day 3 (sponsor's figure 4):



Adverse Events: There were nearly equal numbers of treatment-emergent adverse events (TEAE) in all three treatment groups – 5 in the pediatric solution, 5 in the pediatric tablet, and 6 in the adult tablet. The TEAE ranged from infections, headache, dizziness, respiratory, dry skin, asthenia, and procedural dizziness. All were mild or moderate in severity and no significant differences in TEAE between the groups were observed.

The following table is a summary of TEAEs (sponsor's table 11):

Primary System Organ Class Preferred term	Treatment A (N=15) n (%)	Treatment B (N=15) n (%)	Treatment C (N=15) n (%)
Any class	5 (33.3)	5 (33.3)	6 (40.0)
Infections and infestations	3 (20.0)	4 (26.7)	0 (0)
Gastroenteritis	0 (0)	2 (13.3)	0 (0)
Influenza	1 (6.7)	0 (0)	0 (0)
Nasopharyngitis	1 (6.7)	2 (13.3)	0 (0)
Pharyngitis	1 (6.7)	0 (0)	0 (0)
Nervous system disorders	1 (6.7)	1 (6.7)	3 (20.0)
Headache	1 (6.7)	1 (6.7)	3 (20.0)
Dizziness postural	0 (0)	0 (0)	1 (6.7)
Respiratory, thoracic and mediastinal disorders	0 (0)	0 (0)	2 (13.3)
Epistaxis	0 (0)	0 (0)	2 (13.3)
Gastrointestinal disorders	1 (6.7)	0 (0)	0 (0)
Dry mouth	1 (6.7)	0 (0)	0 (0)
Skin and subcutaneous tissue disorders	0 (0)	0 (0)	1 (6.7)
Dry skin	0 (0)	0 (0)	1 (6.7)
Pruritus	0 (0)	0 (0)	1 (6.7)
General disorders and administration site conditions	0 (0)	1 (6.7)	1 (6.7)
Asthenia	0 (0)	1 (6.7)	1 (6.7)
Injury, poisoning and procedural complications	0 (0)	0 (0)	1 (6.7)
Procedural dizziness	0 (0)	0 (0)	1 (6.7)

Treatment A: alfuzosin 7.5 mg (12.5 mL solution TID); Treatment B: alfuzosin 9 mg (3 x 1.5-mg ER tablets BID)
Treatment C: alfuzosin 10 mg (1 x 10-mg tablet OD)
TEAE = Treatment Emergent Adverse Event
N = number of subjects exposed, n (%) = number and % of subjects with at least one TEAE in each category.
An adverse event is considered as treatment emergent if it occurred from the time of first investigational product administration up to 24h after the timepoint (included) corresponding to the last drug intake in the TID treatment group - ie, Day 4 24:00 time (clock), for each period.
PGM = Table (9.2.2)1.sas out= Table (9.2.2)1.lst (26AUG2008 - 10:07)

Conclusions:
When compared to the adult tablet 10 mg dose, the bioavailability of the pediatric solution and pediatric extended release tablet were 34% and 21% higher, respectively. The mean Cmax values at steady state for all three formulations were similar at 14 ng/mL.

When the pediatric formulations at the dose administered during the study were compared to the adult tablet, the pediatric solution 7.5 mg was bioequivalent to the adult tablet 10 mg with respect to AUC_{0-24} (point estimate (90% CI): 1.06 (0.96 to 1.17)) and Cmax (point estimate (90% CI): 1.00 (0.88 to 1.15)). When the pediatric tablet was compared to the adult tablet, the pediatric tablet 9 mg did not meet the bioequivalence criteria and is therefore NOT bioequivalent to the adult tablet 10 mg with respect to AUC_{0-24} (point estimate (90% CI): 1.14 (1.03 to 1.26)).

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 021287 **Applicant: Sanofi-Aventis** **Stamp Date: June 16, 2010**

Drug Name: Alfuzosin HCl **NDA Type: Pediatric Supplement**

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
Criteria for Refusal to File (RTF)				
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X		The sponsor conducted relative bioavailability study between pediatric oral solution & extended releases tablet and adult extended release tablet
2	Has the applicant provided metabolism and drug-drug interaction information?		X	The sponsor is relying on the information from the original NDA
Criteria for Assessing Quality of an NDA				
	Data			
3	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X		
4	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			n/a
	Studies and Analyses			
5	Has the applicant made an appropriate attempt to determine the reasonable dose individualization strategy for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X		
6	Did the applicant follow the scientific advice provided regarding matters related to dose selection?	X		
7	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted in a format as described in the Exposure-Response guidance?	X		
8	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X		
9	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	X		
10	Did the applicant submit all the pediatric exclusivity data, as described in the WR?	X		
11	Is the appropriate pharmacokinetic information submitted?	X		
12	Is there adequate information on the pharmacokinetics	X		

	and exposure-response in the clinical pharmacology section of the label?			
	General			
13	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA organized in a manner to allow substantive review to begin?	X		
14	Is the clinical pharmacology and biopharmaceutical section of the NDA indexed and paginated in a manner to allow substantive review to begin?	X		
15	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA legible so that a substantive review can begin?	X		
16	Are the clinical pharmacology and biopharmaceutical studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X		
17	Was the translation from another language important or needed for publication?			n/a

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? ___YES_____

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

There were no review issues to be conveyed to the sponsor.

LaiMing Lee

Reviewing Clinical Pharmacologist Date

Myong-Jin Kim

Team Leader/Supervisor Date

Filing Memo

Clinical Pharmacology Review

NDA: 21-287
Compound: Alfuzosin HCl
Sponsor: Sanofi-aventis

Date: July 9, 2010
Reviewer: LaiMing Lee, Ph.D.

Background: Alfuzosin hydrochloride (Uroxatral®) is an alpha$_1$-adrenoreceptor antagonist indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia in adult males. It was approved for marketing in the U.S. on June 12, 2003 under NDA 21-287. Alfuzosin is an extended-release oral tablet (10 mg). The Division of Reproductive and Urologic Products (DRUP) issued a Pediatric Written Request to Sanofi-aventis on February 21, 2006 for three studies: one pharmacokinetic (PK) study with exploratory pharmacodynamics (PD) (Study 1), one pivotal pharmacodynamic study (Study 2), and one supportive efficacy and safety study in pediatric patients with known neurological conditions, hydronephrosis, and neurogenic bladder (Study 3). (b) (4) The sponsor developed two pediatric dosage forms: oral solution (0.2 mg/mL) given three times daily (TID) and a prolonged-release tablet (1.5 mg) given twice daily (BID). The approved product for adults is available as an extended-release tablet, 10 mg.

Studies requested by DRUP:
Study 1 is a 4-week, open-label, randomized, multiple dose, parallel dose group PK and safety study in pediatric patients, age 2-16 years, with elevated detrusor leak point pressure (LPP) ($\geq$40 cm H_2O) of neurologic origin. Pharmacodynamic measurement (LPP) should be performed in all patients at baseline and in those patients who complete the 4-week study. The objectives of the study are: (1) to characterize the PK of two doses of alfuzosin (0.1 mg/kg/day and 0.2 mg/kg/day) given as a solution containing 0.2 mg/mL of alfuzosin or tablets containing alfuzosin 1.5 mg in children and adolescents 2-16 years of age with elevated detrusor LPP of neurologic etiology stratified into two age groups (2-7 years and 8-16 years); (2) to investigate the safety and tolerability of the two doses of alfuzosin in children and adolescents; and (3) to evaluate the effect of two doses of alfuzosin on detrusor LPP in children and adolescents.

Study 2 is a 12-week, double-blind, randomized, placebo-controlled, parallel dose, efficacy, PD and safety study comparing two doses of alfuzosin followed by a 40-week (10 month) open-label extension phase in pediatric patients, age 2-16 years, with elevated detrusor LPP ($\geq$40 cm H_2O) of neurologic origin. Populations PK will be investigated at 12 weeks. The objectives of the study are (1) to evaluate the efficacy of alfuzosin in comparison to placebo on the detrusor LPP in children and adolescents 2-16 years of age with elevated detrusor LPP ($\geq$40 cm H_2O) of neurologic etiology; (2) to investigate the safety and tolerability of two doses of alfuzosin in comparison to placebo in children and adolescents; (3) to evaluate the effects of two doses of alfuzosin in comparison to placebo on detrusor compliance and urinary tract infection; (4) to investigate the population PK of alfuzosin; and (5) to evaluate the 12-month long-term safety of alfuzosin 0.1 mg/kg/day and 0.2 mg/kg/day.

Study 3 is a 12-week, open-label, non-comparative PD and safety study in pediatric patients, age 2-16 years, with grade 1, 2, or 3 hydronephrosis associated with elevated detrusor LPP ($\geq$40 cm H_2O) of neurologic origin followed by a 40-week (10 month) extension phase. Population PK will be evaluated. The objectives of the study are (1) to determine the efficacy of alfuzosin in the treatment of children and

adolescents 2-16 years with newly diagnosed or progressive hydronephrosis due to neuropathic bladder dysfunction; (2) to investigate the safety and tolerability of alfuzosin 0.2 mg/kg/day in children and adolescents; (3) to investigate the number of UTI episodes; and (4) to investigate the population PK of alfuzosin.

Additional information requested:
- Development of a commercially marketable & age-appropriate dosage formulation
- Relative bioavailability study in adults of any age appropriate formulation used in the studies compared to the approved drug

Studies submitted by the Sponsor:
PK 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. 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 evaluate the PK of two doses of alfuzosin (0.1 or 0.2 mg/kg/day) given as a solution (alfuzosin 0.2 mg/mL) TID in children (2 to 7 years) and given as tablets (alfuzosin 1.5 mg per tablet) BID regimen in children or adolescents (8-16 years).

Table 3 - Descriptive statistics on alfuzosin plasma pharmacokinetic parameters observed in children (2-7 years) with alfuzosin given as solution (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]	1.50 (1.00-2.02)	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]
	N=6	N=6					
Day 7 N=7	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]	18.4±6.58 (36) [17.4]	35.2±13.1 (37) [33.3]
Rac					[1.22]	[0.94]	[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	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]	67.0±35.7 (53) [57.1]	123±69.3 (56) [104]
Rac					[1.22]	[1.33]	[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

Table 4 - Descriptive statistics on alfuzosin plasma pharmacokinetic parameters observed in children and adolescents (8-16 yrs) with alfuzosin given as tablets (BID regimen)

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

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

The sponsor states that AUC0-8 on Day 7 with the solution of alfuzosin at 0.2 mg/kg/day was 3.1-fold higher than that observed with 0.1 mg/kg/day. AUC0-12 on Day 7 in children or adolescent with alfuzosin 0.2 mg/kg/day administered as tablets was 1.4-fold higher than that observed with 0.1 mg/kg/day.

PK study POH0209: The objective this study was to develop and qualify a population PK model for alfuzosin based on PK data obtained in patients from the PK study and two clinical efficacy & safety studies (Studies PKM6270, EFC5722 and EFC6269, respectively) in order to provide an assessment of the alfuzosin PK variability and to assess the influence of key demographic parameters (e.g. body weight, age, sex, and race), renal function and formulation (solution and tablet) on the PK of alfuzosin. The secondary objective was to use the final model to provide individual estimates of alfuzosin exposure (AUC0-24, Cmax, and minimum concentration (Ctrough) at steady state) in patients. The sponsor states that sex, age, race, CLCr and dose had no significant effect on the variability of the PK of alfuzosin. The significant covariates explaining alfuzosin PK variability in patients were formulation and body weight.

Bioavailability study BDR 10380: Study BDR10380 was a Phase 1, single center, open-label, randomized, repeat-dose (3 days), 3-period with 3-sequence crossover study. Each treatment period was separated by a 4 ± 1-day washout period. Healthy adult male subjects age 19-44 years with a mean weight of 77 kg were institutionalized from Day -1 to Day 4 of each 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 TID solution and 1.5 mg BID extended-release tablet) versus the adult extended-release 10 mg OD tablet reference formulation.

The following table is a summary of PK parameters observed over 24 hours on Day 3 with the 2 pediatric formulations (TID solution (Treatment A) and BID tablet (Treatment B)) and the adult formulation (ER tablet (Treatment C))

Treatment	Treatment A	Treatment B	Treatment C
Alfuzosin Formulation	Pediatric Solution	Pediatric ER tablet	Adult ER tablet
Daily dose	7.5 mg	9 mg	10 mg
Dose regimen	12.5 mL, TID	3x1.5 mg, BID	1x10 mg, OD
N	15	15	15
C_{max} (ng/mL)	13.9 ± 4.01 (29) [13.4]	13.5 ± 4.22 (31) [13.0]	14.5 ± 6.82 (47) [13.3]
AUC_{0-24} norm. to 10 mg (h.ng/mL)	242 ± 70.6 (29) [232]	217 ± 74.3 (34) [208]	180 ± 85.9 (48) [164]
AUC_{0-24} (h.ng/mL)	181 ± 52.9 (29) [174]	196 ± 66.9 (34) [187]	180 ± 85.9 (48) [164]

Tabulated values are Mean ± SD (CV%) [Geometric Mean]

The following table is the geometric mean ratio estimates of the three different formulations. Treatments A and B versus the reference (Treatment C), and Treatment A versus Treatment B with 90% CIs

Table 1 - 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)

Table 2 - Formulation effect – comparison of pediatric formulations (90% CIs): Treatment A versus Treatment B

Parameter	Comparison	Estimate	90% CI
AUC_{0-24} (ng.h/mL)	A vs. B	0.93	(0.86 to 1.01)
C_{max} (ng/mL)	A vs. B	1.03	(0.94 to 1.13)

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)

The sponsor states that at the same dose level of 10 mg (based on AUC0-24 normalized to 10 mg), the bioavailability of the pediatric solution and the pediatric ER tablet were 42% and 27% higher, respectively, than the bioavailability of the approved adult ER tablet. The sponsor also states that at the doses administered during the study, 7.5 mg for the pediatric solution and 9 mg for the pediatric ER tablet (based on AUC0-24), similar exposure to the adult 10-mg ER tablet was observed for the pediatric solution since the 90% CIs were fully contained in the (0.8, 1.25) bioequivalence interval, while the pediatric ER tablet exposure remained slightly higher by 14% (90% CI upper limit slightly outside of the bioequivalence interval; 90% CIs).

Efficacy study EFC5722: This was a pivotal, randomized, double-blind, placebo-controlled, parallel-group, multicenter, multinational study comparing the efficacy of 2 doses of alfuzosin to placebo in children and adolescents 2-16 years of age with elevated detrusor LPP ≥40 cm H2O of neuropathic etiology. The study consisted of a 12-week double-blind phase to evaluate the efficacy and safety and a 40-week open-label safety extension phase. Of the 172 patients were enrolled into the study, 57 patients were randomized to placebo, 57 to alfuzosin 0.1 mg/kg/day and 58 to alfuzosin 0.2 mg/kg/day. All 172 randomized patients were treated with study medication, 167 of which completed the initial 12-week double-blind study phase. The sponsor states that at the end of the 12-week study treatment, a comparable proportion of patients in both alfuzosin dose groups and the placebo group were responders with LPP <40 cm H_2O (difference in response versus placebo, alfuzosin 0.1 mg/kg/day adjusted p=1.0; alfuzosin 0.2 mg/kg/day adjusted p=0.9090. There was no superiority of either of the alfuzosin dose groups over placebo treatment.

Efficacy study EFC6269: This was a open-label, exploratory, non-comparative study to evaluate the efficacy of alfuzosin 0.2 mg/kg/day in children and adolescents of both genders 2-16 years of age with newly diagnosed or progressive hydronephrosis due to neuropathic bladder dysfunction. The study consisted of 2 phases, the 12-week efficacy phase and the 40-week extension study phase. Patients who had completed the 12-week open-label efficacy study phase were offered to continue in the 40-week open-label safety extension study. Patients then continued with their treatment regimen. Two study periods were considered to assess the efficacy and to obtain a complete 1-year safety profile: the 12-week study period and the whole study period. The primary objective of this study was to determine efficacy of alfuzosin in the treatment of children and adolescents 2-16 years of age presenting with a detrusor LPP of 40 cm H_2O or greater and with newly diagnosed or progressive hydronephrosis associated with elevated detrusor LPP of neuropathic etiology. The sponsor states that no efficacy of alfuzosin could be demonstrated as only 10/25 (40.0%) patients reported complete response (defined as an improvement of hydronephrosis grading ≥1 in both kidneys), while 60% of the patients experienced partial response, no change or worsening in grade of hydronephrosis.

Formulation: Adult Alfuzosin is currently available as an extended-release tablet 10 mg. The pediatric formulations evaluated in the clinical studies are an extended-release tablet and oral solution.

Adult extended-release tablet 10 mg	(b) (4)
Alfuzosin HCl 10 mg	
colloidal silicon dioxide	
ethylcellulose	
hydrogenated castor oil	
hydroxypropyl methylcellulose	
magnesium stearate	
mannitol	
microcrystalline cellulose	
povidone	
yellow ferric oxide	

	(b) (4)	

Recommendation:

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds that the Human Pharmacokinetics and Bioavailability section for NDA 21-287 Supplement-16 (pediatric supplement, document 167) is fileable.

_____ _____
LaiMing Lee, Ph.D. Reviewer Date

_____ _____
Myong-Jin Kim, Pharm.D., Team Leader Date

OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

Application Number	NDA 21-287 S16
Submission Date	16 June 2010
Drug Name	Alfuzosin HCl
Proposed Indication	Treatment of pediatric patients, age 2 to 16 years, with elevated detrusor leak point pressure associated with a known neurological disorder
Clinical Division	Division of Reproductive and Urology Products
Primary CP Reviewer	LaiMing Lee, PhD
Primary PM Reviewer	Jiang Liu, Ph.D.
Secondary CP Reviewer	Myong-Jin Kim, Ph.D.
Secondary PM Reviewer	Pravin Jadhav, Ph.D.
Sponsor	Sanofi aventis

Summary of Findings

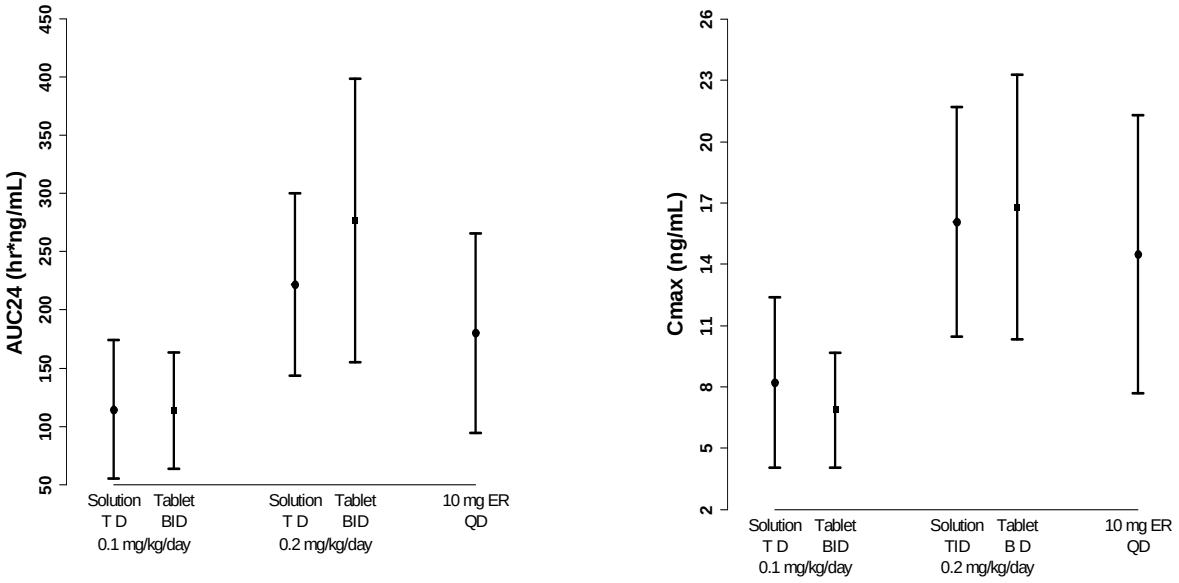
Key Review Questions

The purpose of this review is to address the following key questions.

Are alfuzosin exposures in pediatrics after 0.1 and 0.2 mg/kg/day doses reasonably similar to exposures after 10 mg QD ER dose in adults?

Yes. Based on PK analysis, these two doses in pediatrics reasonably covered the exposures achieved after 10 mg QD ER dose in adults (Figure 1). From population PK estimation, the 0.1 mg/kg/day dose in pediatrics provided exposure (C_{max_ss}: 7.73 ± 3.78 ng/mL and $AUC_{0\text{-}24\_ss}$: 114 ± 54.7 h*ng/mL) slightly lower and the 0.2 mg/kg/day dose in pediatrics provided exposure (C_{max_ss}: 16.3 ± 5.92 ng/mL and $AUC_{0\text{-}24\_ss}$: 242 ± 99.4 h*ng/mL) slightly higher than that of the 10 mg QD dose in adults (C_{max_ss}: 14.5 ± 6.82 ng/mL and $AUC_{0\text{-}24\_ss}$: 180 ± 85.9 h*ng/mL from bioavailability study BDR10380).

Figure 1. The 0.1 mg/kg/day dose provided exposure slightly lower and the 0.2 mg/kg/day dose in pediatrics provided exposure slightly higher than that of the 10 mg QD dose in adults: $AUC_{0\text{-}24}$ (left) and C_{max} (right)

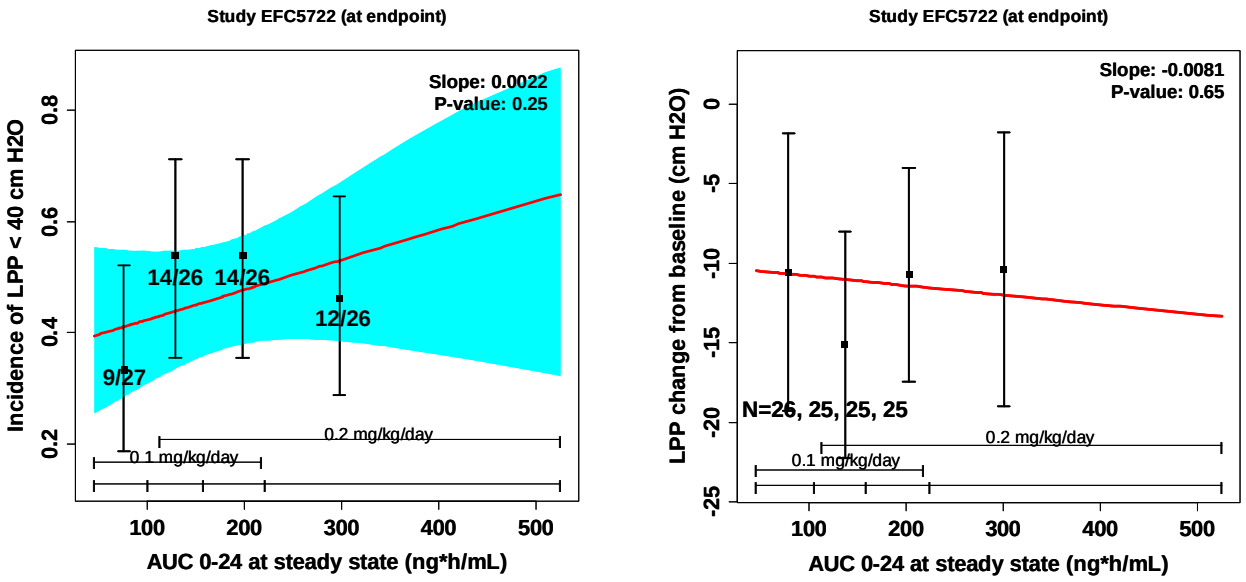


Note: the pediatric exposure data are from population PK estimation; the adult data are from bioavailability study BDR10380.

Does the exposure-response relationship for efficacy support the indication in pediatrics?

No. There was little or no difference among alfuzosin treatment groups and placebo for the primary efficacy endpoint, the proportion of patients with detrusor leak point pressure (LPP) <40 cmH2O at Week 12. As shown in Table 3, at the end of the 12-week double-blind study phase, a comparable proportion of patients in both alfuzosin treatment groups (0.1 mg/kg/day: 23/57 patients; 0.2 mg/kg/day: 28/58 patients) and the placebo (placebo: 23/57 patients) group reported LPP <40 cmH2O. For secondary efficacy endpoints (the absolute and relative change in detrusor LPP from baseline), the 0.2 mg/kg alfuzosin treatment group was numerically better than the 0.1 mg/kg and placebo groups. However, the difference was not statistically significant (Table 4). The exposure-response relationships for primary and secondary efficacy endpoints based on model derived $AUC_{0\text{-}24\_ss}$ or C_{max_ss} were shallow and not statistically significant (Figure 2).

Figure 2. The exposure-response relationships for primary (left) and secondary (right) efficacy endpoints



Recommendations

The review of available data does not support clinical efficacy of alfuzosin HCl for reduction in detrusor leak point pressure (LPP) in pediatric patients age 2 – 16 years with known neurological deficit. The exposure-response analyses for efficacy did not provide evidence of effectiveness in this application.

Label Statements

NA.

Pertinent regulatory background

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

In response to the FDA's pediatric Written Request (WR), the sponsor submited 3 pediatric studies in pediatric patients ages 2 – 16 years with elevated detrusor leak point pressure (LPP) of neurologic etiology (1 pharmacokinetic study [PKM6270], 1 pivotal efficacy study [EFC5722], and 1 supportive exploratory efficacy and safety study in children with hydronephrosis [EFC6269]) and a relative bioavailability study (BDR10380) in healthy adults comparing the approved alfuzosin product in adults (10 mg OD tablet) to the 2 pediatric formulations (0.2

mg/mL solution and 1.5 mg tablet). The Applicant does not seek a new indication for alfuzosin in pediatric patients, but proposes to update the product label to include the pediatric data obtained from the studies conducted under the Written Request.

Results of Analysis

Dose selection of alfuzosin in pediatric population

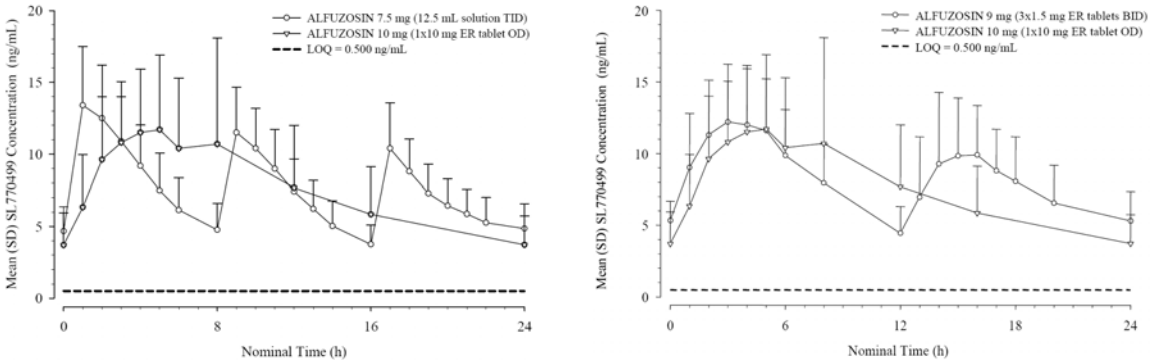
The sponsor developed two age-appropriate formulations for this pediatric program. The alfuzosin solution (0.2 mg/mL) was to be administered three times daily (TID) with a dosing interval of at least 4 hours. The proposed alfuzosin 1.5 mg tablet was to be administered twice daily (BID) with a dosing interval of approximately 12 hours. The pharmacokinetics (PK) of the solution is comparable to the immediate-release tablets marketed in Europe for adults. The tablets used in older children have a formulation, manufacturing process, and release characteristics (dissolution data) similar to the 5 mg twice daily (BID) prolonged release tablet marketed in Europe.

In the bioavailability study (BDR10380), the steady state exposures observed after solution (given at the 7.5 mg daily TID dose with C_{max_ss} (mean ± SD): 13.9 ± 4.01 ng/mL and $AUC_{0\text{-}24\_ss}$: 181 ± 52.9 h*ng/mL) and tablet (given at 9 mg daily BID dose with C_{max_ss}: 13.5 ± 4.22 ng/mL and $AUC_{0\text{-}24\_ss}$: 196 ± 66.9 h*ng/mL) were similar to exposures after the extended-release tablet (given as 10 mg QD with C_{max_ss}: 14.5 ± 6.82 ng/mL and $AUC_{0\text{-}24\_ss}$: 180 ± 85.9 h*ng/mL) (Figure 3 and Table 1). The selected 0.1 and 0.2 mg/kg/day dose range with a dose ceiling (10 mg daily for BID or 7.5 mg daily for TID respectively) covered the adult weight-adjusted doses. Population PK analysis confirmed the 0.1 mg/kg/day dose in pediatrics provided exposure (with C_{max_ss}: 7.73 ± 3.78 ng/mL and $AUC_{0\text{-}24\_ss}$: 114 ± 54.7 h*ng/mL) slightly lower and the 0.2 mg/kg/day dose in pediatrics provided exposure (with C_{max_ss}: 16.3 ± 5.92 ng/mL and $AUC_{0\text{-}24\_ss}$: 242 ± 99.4 h*ng/mL) slightly higher than that of the 10 mg QD dose in adults from study BDR10380.

Population PK analysis detected a significant positive relationship between alfuzosin clearance and the patient's body weight. With weight-adjusted dosing, the systemic exposure (based on $AUC_{0\text{-}24\_ss}$) in heavier (~70 kg) pediatric patients is approximately double compared to that of exposures in lighter (~10 kg) patients (The following **figure**).

Reviewer's comments:
The studied 0.1 mg/kg/day and 0.2 mg/kg/day doses in pediatric pivotal trial are reasonable.

Figure 3. Mean (SD) plasma alfuzosin concentration-time profiles observed with the pediatric solution, tablet and the adult ER tablet on Day 3



Source: Sponsor's Study Report of BDR10380: Figure 3 & 4, page 43

Table 1. Descriptive statistics of plasma alfuzosin parameters observed over 24 hours for each formulation on Day 3

Treatment	Treatment A	Treatment B	Treatment C
Alfuzosin formulation	Pediatric Solution	Pediatric ER tablet	Adult ER tablet
Daily dose	7.5 mg	9 mg	10 mg
Dose regimen	12.5 mL, TID	3x1.5 mg, BID	1x10 mg, OD
N	15	15	15
C_{max} (ng/mL)	13.9 ± 4.01 (29) [13.4]	13.5 ± 4.22 (31) [13.0]	14.5 ± 6.82 (47) [13.3]
AUC_{0-24} norm. to 10 mg (h.ng/mL)	242 ± 70.6 (29) [232]	217 ± 74.3 (34) [208]	180 ± 85.9 (48) [164]
AUC_{0-24} (h.ng/mL)	181 ± 52.9 (29) [174]	196 ± 66.9 (34) [187]	180 ± 85.9 (48) [164]

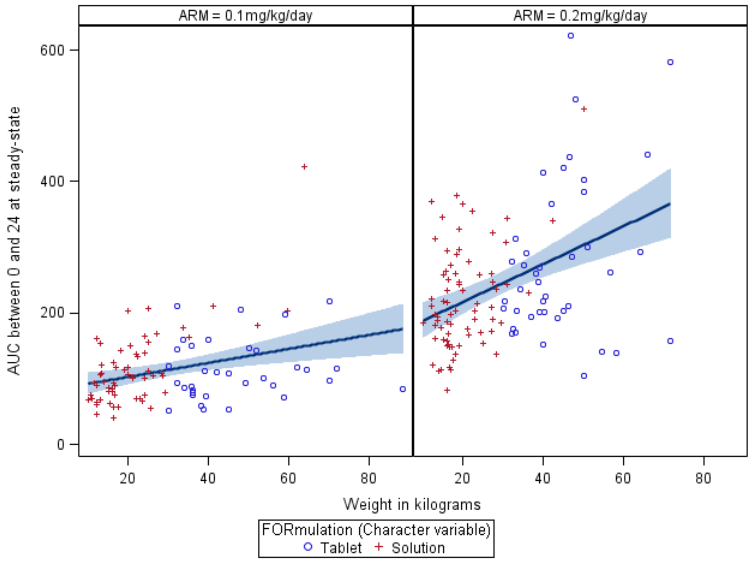
Tabulated values are Mean ± SD (CV%) [Geometric Mean]

Source: Sponsor's study report of bdr10380: Table 13, page 44

Table 2. Mean (SD) alfuzosin exposure at steady state derived from population PK analysis

Formulation	ARM						ARM					
	0.1mg/kg/day			0.2mg/kg/day			0.1mg/kg/day			0.2mg/kg/day		
	AUC0_24ss (h*ng/mL)			AUC0_24ss (h*ng/mL)			Cmax_ss (ng/mL)			Cmax_ss (ng/mL)		
	N	Mean	Std	N	Mean	Std	N	Mean	Std	N	Mean	Std
Solution	60	114.55	59.50	74	222.00	78.61	60	8.21	4.18	74	16.10	5.62
Tablet	34	113.35	45.94	41	277.64	121.84	34	6.87	2.80	41	16.79	6.48
All	94	114.11	54.73	115	241.83	99.41	94	7.73	3.78	115	16.34	5.92

Figure 4. Derived alfuzosin exposure versus body weight



Assessment of exposure-response for efficacy/safety

Efficacy

A total of 172 pediatric patients with elevated LPP ≥ 40 cm H2O associated with a neurologic condition were enrolled in the pivotal efficacy study EFC5722. The patients were stratified by age groups (2-7 and 8-16 years of age), alfuzosin dose groups (0.1 mg/kg/day and 0.2 mg/kg/day), and by current use of anticholinergic/antimuscarinic medication. The primary efficacy endpoint was the proportion of patients with detrusor LPP <40 cmH2O at Week 12. As shown in Table 3, at the end of the 12-week double-blind study phase, a comparable proportion of patients in both alfuzosin treatment groups and the placebo group reported LPP <40 cmH2O (placebo: 23/57 patients; alfuzosin 0.1 mg/kg/day: 23/57 patients; alfuzosin 0.2 mg/kg/day: 28/58 patients). Subgroup analyses found there was no difference between the alfuzosin dose

groups and the placebo group for the LPP responder rate in the subgroups defined by formulation, anticholinergic drug use, gender or geographic area. In patients 2–7 years of age, a slightly higher proportion of patients in both alfuzosin treatment groups reported LPP <40 cmH2O at the end of the 12-week double-blind study phase (placebo: 9/28 patients; alfuzosin 0.1 mg/kg/day: 15/28 patients; alfuzosin 0.2 mg/kg/day: 13/28 patients). However, all 95% CIs for the respective odd ratios included 1 indicating no statistically significant difference between the alfuzosin dose groups and placebo. In patients 8–16 years of age, a slightly higher proportion of patients in the placebo group and in the alfuzosin 0.2 mg/kg/day group reported LPP <40 cmH2O (placebo: 14/29 patients; alfuzosin 0.1 mg/kg/day: 8/29 patients; alfuzosin 0.2 mg/kg/day: 15/30 patients). An additional analysis was carried out to evaluate the LPP response for the subgroup of patients with a baseline LPP range 41-45 cm H2O. The results are consistent with the results of the primary analysis. The difference in response versus placebo was -10.5% [95% CI -41.1; 23.3] for the alfuzosin 0.1 mg/kg/day group and +17.3% [95% CI –15.0; 45.5] for the alfuzosin 0.2 mg/kg/day group.

Table 3. Detrusor leak point pressure (LPP; cmH2O): Number (%) of patients with LPP <40 cmH2O at endpoint (Double-blind phase; ITT population)

		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 are 2-sided and built based on Wilson's score method without continuity correction
Note : [b] p-values come from Fisher's exact test
Note : [c] p-values are adjusted for multiplicity by Hochberg procedure
PGM=SL77049910/EFC5722/CSR/BS/PGM_RPT/EFF_LPP_pop_I_T.sas OUT=OUTPUT/EFF_LPP_pop_I_T_j.rtf (04DEC2009 - 16:55)

Source: Sponsor's Study Report of EFC5722: Table 16, page 61

The secondary endpoints, absolute and relative change in detrusor LPP from baseline, were numerically larger in both alfuzosin groups compared to the placebo group. However, the difference was not statistically significant (Table 4). The cumulative distributions of the LPP change from baseline for the 3 treatment groups were also comparable, but slightly favored the alfuzosin treatments (Figure 5).

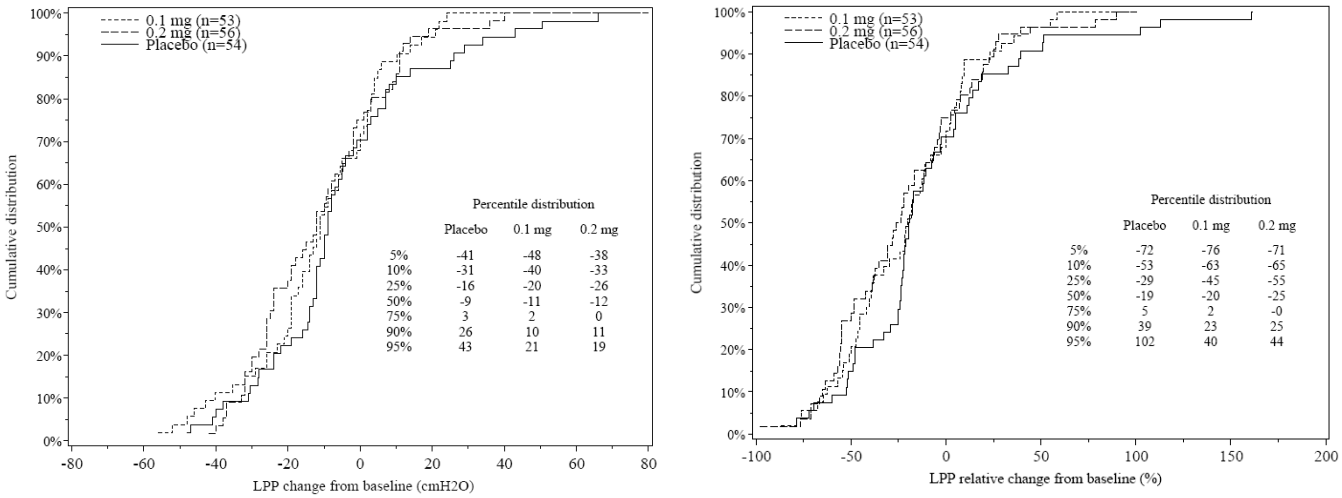
Table 4. Detrusor leak point pressure (cmH2O): Mean change of LPP and relative change of LPP from baseline; descriptive statistics (Double-blind phase; ITT population)

		Alfuzosin (mg/kg/day)	
	Placebo (N=57)	0.1 (N=57)	0.2 (N=58)
Baseline			
Number	54	53	56
Mean (SD)	54.2 (12.6)	53.3 (13.4)	50.9 (10.0)
Median	51.5	48.0	48.0
Q1 : Q3	43.0 : 63.0	43.0 : 59.0	43.0 : 56.5
Min : Max	40 : 85	40 : 93	40 : 89
Endpoint			
Number	54	53	56
Mean (SD)	48.2 (23.4)	41.6 (18.2)	39.4 (19.5)
Median	42.0	41.0	39.5
Q1 : Q3	32.0 : 57.0	27.0 : 56.0	26.0 : 49.0
Min : Max	11 : 107	7 : 88	1 : 100
Change from baseline at endpoint (cmH_2O)			
Number	54	53	56
LSMean (SE)	-5.4 (2.79)	-11.7 (2.80)	-12.5 (2.78)
LSMean difference (SE) vs Placebo	-	-6.2 (3.80)	-7.1 (3.77)
95% CI vs Placebo	-	(-13.72 to 1.29)	(-14.51 to 0.39)
p-values vs Placebo [a]	-	0.1040	0.0630
Adjusted p-values vs Placebo [b]	-	0.1040	0.1040
Relative change from baseline at endpoint (%)			
Number	54	53	56
LSMean (SE)	-9.2 (5.53)	-20.6 (5.56)	-23.5 (5.51)
LSMean difference (SE) vs Placebo	-	-11.4 (7.54)	-14.3 (7.48)
95% CI vs Placebo	-	(-26.27 to 3.53)	(-29.10 to 0.47)
p-values vs Placebo [a]	-	0.1338	0.0576
Adjusted p-values vs Placebo [b]	-	0.1338	0.1152

Note : [a] p-values come from covariance analysis using centered baseline value as covariate
Note : [b] p-values are adjusted for multiplicity by Hochberg procedure

Source: Sponsor's Study Report of EFC5722: Table 17, page 66

Figure 5. Cumulative distributions of absolute change (left) and relative (%) change (right) in detrusor LPP from baseline (cm H2O) (ITT population)



Source: Sponsor's Study Report of EFC5722: Figure 7 & 8, page 132 & 133

Reviewer's comments:
The dose-response analyses for primary and secondary efficacy endpoints in the pivotal study EFC5277 did not detect significant relationship to support effectiveness. Assuming the observed effect size is true (48% in the 0.2 mg/kg/day vs. 40% in placebo), the sample size for the pivotal trial need increase to ~1200 patients to observe a significant result with 80% of power. However, for all efficacy endpoints the high dose alfuzosin treatment was numerically better than the low dose alfuzosin group and the placebo group. This observation is also consistent in the 4-week PK, safety and efficacy study PKM6270. To investigate whether the exposure-response for efficacy (b) (4) *fulfill the Written Request, the exposure-response analysis for efficacy was further explored. As shown in Figure 2, the exposure-response relationships for primary and secondary efficacy endpoints were shallow and not statistically significant. Further, similar results were also consistently observed previously for the same class of drug, flomax, which did not support the same proposed indication in pediatrics (the response rates of achieving LPP<40 cm H_2O for the placebo, low, medium, and high dose groups were 35.3%, 45.7%, 27.3%, and 42.4% respectively. There was no statistically significant difference between flomax treatment groups and placebo and there was no evidence of exposure-response relationship: see Dr. Chong M. Kim's review and the flomax label for details.)*

Safety

Compared to that in adult BPH patients, no significant new safety signals were identified in pediatric patients, age 2 to 16 years, with elevated detrusor leak point pressure associated with a known neurological disorder. The blood pressure changes are in special interest according to the pharmacological property of alfuzosin. However, exposure-response analyses did not detected any significant correlation between change from baseline in diastolic blood pressure, systolic blood pressure, and heart rate and alfuzosin exposure.

Previous thorough QT studies in the healthy adults treated with single high dose (alfuzosin 40 mg of adult extended-release tablet) or combining 10 mg alfuzosin with 100 mg sildenafil (at steady-state) did not demonstrate a clear safety signal for QT prolongation. Although, a significant exposure-response in the change from baseline in QTcF at the visits Week 13/14 was detected, the clinical significance of this observation is un-interpretable.

Listing of Analyses Data sets, Codes and Output Files

File Name	Description	Location in \\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\
adpkpd.sas	Exposure analysis	Alfuzosin_NDA21287_JL\ER Analyses
LPPBLCH_AUC.r	ER plot for LPP change from baseline	Alfuzosin_NDA21287_JL\ER Analyses
LPP40_AUC.r	ER plot for the incidence of LPP < 40 cm H_2O	Alfuzosin_NDA21287_JL\ER Analyses

Appendix

Population Pharmacokinetic Analysis

Population PK model was developed in children and adolescents included in three clinical trials (PKM6270, EFC5722 and EFC6269). The total data set was composed of 209 patients (841 concentration-time points), 134 were administered the solution formulation (572 samples) and 75 were administered the tablet (269 samples). The structural PK model was a two-compartment model with a formulation-dependent absorption constant.

The formulation was included as a straightaway covariate on Ka:

$$Ka\ (1/h) = TVKA + \theta(6) \bullet (1 - FORN)\ .$$

The CL/F was related to body weight according to:

$$CL/F\ (L/h) = 7.88 + 0.535 \bullet WT.$$

Final population pharmacokinetic parameters obtained on the Total Data Set are presented in Table 5. In this dataset, Sex, Age, Race, CLCR and Dose (coded as binary covariate: 0.1 mg/kg/day or 0.2 mg/kg/day) were not found to have any statistically significant influence on the PK of alfuzosin. The model qualification based on individual plots of rich data showed a good agreement between predicted and observed plasma concentrations of alfuzosin for both formulations (solution and tablet). Model qualification based on bootstrap and visual predictive check (VPC) suggests the final model is robust and performing well.

Table 5. Population pharmacokinetic parameter estimates for alfuzosin (the final model)

Parameter	Estimate	% RSE	[95%CI] – (Shrinkage %)
$\theta_{(1)}$ (CL/F , L/h)	7.88	22.2 %	[4.37 ; 11.4] – (NA)
$\theta_{(2)}$ (V2/F, L)	12.9	21.8 %	[7.31 ; 18.6] – (NA)
$\theta_{(3)}$ (Q/F, L/h)	Fixed to 5.7	NA	[NA ; NA] – (NA)
$\theta_{(4)}$ (V3/F, L)	185	15.7 %	[127 ; 243] – (NA)
$\theta_{(5)}$ (Ka, h^{-1}) 'Ka for tablet = $\theta_{(5)}$'	0.0990	11.5 %	[0.0761 ; 0.122] – (NA)
$\theta_{(6)}$ (formulation effect on Ka) [a] 'Ka for solution = $\theta_{(5)} + \theta_{(6)}$'	0.194	11.9 %	[0.147 ; 0.240] – (NA)
$\theta_{(7)}$ (body weight effect on CL/F)	0.535	14.1 %	[0.383; 0.686] – (NA)
	Interindividual variability (CV%)		
CL/F	42.2 %	12.4 %	[36.6 ; 47.1] – (11.2 %)
V2/F	57.5 %	46.9 %	[14.4 ; 80.1] – (72.4 %)
V3/F	159 %	20.8 %	[121 ; 189] – (74.1 %)
Ka	39.0 %	23.0 %	[28.7 ; 47.1] – (42.3 %)
	Residual variability		
σ (%)	36.5 %	7.84 %	[33.5 ; 39.3] – (68.4 %)

F: bioavailability. %RSE: Percentage of Relative Standard Error (100% * SE / Estimate). 95%CI: 95% confidence interval.
θ and ω are the PopPK parameters (θ) and the variance of their associated interindividual variability (ω).
σ is the associated variance of the residual (intraindividual) error variable (ε).
[a] : Ka = $\theta_{(5)}$ if tablet and Ka = $\theta_{(5)} + \theta_{(6)}$ if solution
NA: not applicable.

Source: Sponsor's Population PK Analysis Report: Table III, page 5

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/s/

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12/10/2010

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