

**Public Assessment Report  
for paediatric studies submitted in accordance  
with Article 46 of Regulation (EC) No1901/2006, as  
amended**

**Xatral  
(alfuzosin)**

**SE/W/012/pdWS/001**

**Marketing Authorisation Holder: sanofi-aventis**

<b>Rapporteur:</b>	SE
<b>Finalisation procedure (day 120):</b>	2011-04-15
<b>Date of Public PdAR</b>	2011-06-16

## ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Xatral, Xatral OD
INN (or common name) of the active substance(s):	alfuzosin
MAH:	sanofi-aventis
Currently approved Indication(s)	Treatment of moderate to severe symptoms of benign prostatic hyperplasia. (Xatral 2.5 and 5 mg)  Treatment of moderate to severe symptoms of benign prostatic hyperplasia (BPH) including adjunctive therapy with urethral catheterization for acute urinary retention (AUR) related to BPH and management following catheter removal (Xatral OD 10 mg)
Pharmaco-therapeutic group (ATC Code):	G04C A01
Pharmaceutical form(s) and strength(s):	Film-coated tablet 2.5 mg Prolonged-release tablet 5 mg Prolonged-release tablet 10 mg

## I. EXECUTIVE SUMMARY

SmPC changes are proposed in sections 4.2 and 5.1, with corresponding changes in the PL.

## II. RECOMMENDATION

The MAH should no later than 15 May 2011 submit a type IB variation to implement the SPC amendments agreed in this procedure:

### Section 4.2

#### *Paediatric population:*

Efficacy of alfuzosin has not been demonstrated in children aged 2 to 16 years (see section 5.1). Therefore, alfuzosin is not indicated for use in paediatric population.

### Section 5.1

#### *Paediatric population*

Alfuzosin is not indicated for use in the paediatric population (see section 4.2).

Efficacy of alfuzosin hydrochloride was not demonstrated in the two studies conducted in 197 patients 2 to 16 years of age with elevated detrusor leak point pressure (LPP $\geq$ 40 cm H<sub>2</sub>O) of neurologic origin. Patients were treated with alfuzosin hydrochloride 0.1 mg/kg/day or 0.2 mg/kg/day using adapted paediatric formulations.

The MAH should also implement corresponding text in the PL.

## III. INTRODUCTION

On the 27 August 2010 the MAH submitted 3 completed paediatric studies for alfuzosin (Xatral), in accordance with Articles 45 and 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use. Two preclinical toxicity studies in juvenile rats were also submitted.

A short critical expert overview has also been provided by the MAH, together with literature references.

The MAH proposed the following regulatory action:

- Amendment of section 4.2 of the SPC, declaring that efficacy of the product has not been demonstrated in children aged 2 to 16 years
- Amendment of section 5.1 with information on paediatric studies performed with the product.

## IV. SCIENTIFIC DISCUSSION

### IV.1 Information on the pharmaceutical formulation used in the studies

Two oral formulations (extended-release tablets and immediate-release oral solution) were used in the three paediatric clinical studies depending on the age of the patient. No change in the composition or manufacturing process occurred during the course of the three clinical studies.

Tablets were supplied for oral administration as film-coated extended-release tablets containing 1.5 mg of alfuzosin hydrochloride.

Solution was supplied for oral administration as a 0.2 mg/mL solution, packaged in 150 mL glass bottles.

None of the formulations used in the paediatric clinical studies are currently marketed.

### IV.2 Preclinical aspects

#### 1. Introduction

In the pre-clinical juvenile toxicity program for alfuzosin a 2-week dose-range finding study (Study No. 27526) and a main study (Study No. 27779) were performed, together with some complementary studies for microscopic evaluation and target organ identification (JUV0022) and for toxicokinetic evaluation (DIV1311).

#### 2. Preclinical studies

##### IV.2.1 2-Week toxicity study by oral route (gavage) in juvenile rats

###### Study No. 27526 TSR/DIV0909

The objective of this preliminary study was to evaluate the potential toxicity of the test item, Alfuzosin, following daily administration by the oral route (gavage) to juvenile rats for 2 weeks from post-natal day 10 (PND 10) to post-natal day 23 (PND 23) inclusive.

A total of 200 juvenile Sprague Dawley (100 male and 100 female) rats were allocated to four groups and received the test item, Alfuzosin, at doses of 10, 50 or 250 mg/kg/day or the vehicle. Each group was composed of ten males and ten females. Satellite sub-groups consisting of (20 males and 20 females per dose-level) except for control were included for the determination of plasma levels of the test item on days 1 and 14 at designated time-points: 0.5, 2, 4, 8 and 24 hours after administration.

No death occurred during the study. No clinical signs were noted during the study. No marked effects on body weights were observed. At 250 mg/kg/day body weight gain was significantly reduced during the first week of treatment. Regarding hematology and blood biochemistry, mean number of white blood cells, lymphocytes and albumin concentrations were significantly lower in both sexes at 250 mg/kg/day. No macroscopic treatment related observation was noted.

In conclusion, the no adverse effect level (NOAEL) after Alfuzosin treatment under the study conditions was 50 mg/kg/day, based on body weight gain reduction during the first week of treatment in both sexes together with reduced albumin concentrations and reduction of mean number of white blood cells and lymphocytes.

## IV.2.2 Oral toxicity study in juvenile rats

### Study No. 27779RSR/DIV0910 (and complementary study JUV0022)

In the main study, Sprague Dawley rats were treated from Day 10 postnatal until Day 0 of gestation for the females, and, for the males, throughout mating and until Day 15 of gestation for the corresponding female. The duration of treatment (at least 10 weeks for females and 12 weeks for males) was intended to cover the period of development corresponding to infancy, childhood, and adolescence.

#### Study information:

<i>Species/strain</i>	Sprague-Dawley rat
<i>Number of animals/</i>	Set 1: 18 satellite animals
<i>Group/sex</i>	Set 2: 20 satellite animals
	Principal animals:24
<i>Route of</i>	Oral (gavage)
<i>administration</i>	
<i>Dosage (mg/kg/day)</i>	0, 10, 50, 250

The study 27779RSR/DIV0910 focused on the parameters that had been identified as possible targets after treatment in juvenile animals and the complementary study JUV0022 focused on microscopic examination as all possible parameters could not be determined within a single study.

#### Parameter studied:

- Adult behaviour
- Serum hormone concentrations (TSH, T3, T4, estradiol, testosterone)
- Reproduction and embryonic development
- Auditory startle reflex
- Water T-maze test
- Motor activity (automated infra-red sensor equipment)
- The age of appearance of sexual maturity (balanopreputial separation or vaginal perforation)
- Microscopic examination
- Organ toxicity

Mortality was seen at the high dose of 250 mg/kg/day in seven animals from the principal group and 11 from satellite group. The dose 250 mg/kg/day exceeded the maximum tolerated dose (MTD) based on the high mortality rate whereas 50 and 10 mg/kg/day were well tolerated.

The high dose of 250 mg/kg/day induced a marked toxicity characterized by effects on clinical condition (mortality, clinical signs, reduction in body weight gain followed in females only by a slight increase) and on developmental landmarks (in males: delay in balanopreputial cleavage and minor changes in seminal vesicle weights; in females: slight decrease in motor activity and increase in the first learning phase of T-maze, lengthening in estrous cycles and decrease in fertility and minor changes in adrenals weights; in both sexes: minor changes in hormonal status).

Alfuzosin-related organ weight changes consisted of increased liver weights (with no microscopic correlate) and increased spleen weights in females at 50 mg/kg/day and both sexes at 250 mg/kg/day, reversible, except for the liver weight increase in males that was partially reversible. All of the alfuzosin-related clinical and anatomic pathology findings were partially or fully reversible by the end of the 4-week recovery period.

## Clinical signs

### Clinical signs

- During pre-mating period:

Clinical Observations	M	F	M	F	M	F	M	F
Dose: mg/kg/day		0		10		50		250
- Eyes half-closed	0	0	20	19	24	24	24	23
- Ptyalism	0	0	0	0	3	0	19	8

- During pregnancy period:

Clinical Observations	F	F	F	F
Dose: mg/kg/day	0	10	50	250
- Eyes half-closed	0	6	17	16
- Ptyalism	0	0	0	5

The intermediate dose of 50 mg/kg/day induced slight effects on clinical condition characterized by clinical signs (mainly eyes partially closed) during several weeks and a transient reduction in body weight gain limited to the first week of treatment. Furthermore, the low dose of 10 mg/kg/day induced only clinical signs (eye partially closed) just at the end of the dosing period.

The toxicokinetic data showed a dose dependent increase in plasma levels, and animals at all doses were exposed to the compound. The levels seen were comparable to those observed in adult animals, and as for the adults, levels of alfuzosin were higher in female compared to male animals and there was some evidence of accumulation over time.

**Text table 1 - Summary of mean SL77.0499  $C_{max}$  and AUC<sub>0-24</sub> after repeated administrations of SL77.0499-10**

Sex	Dose (mg/kg)	$C_{max}$ (ng/mL)		AUC <sub>0-24</sub> (ng.h/mL)	
		Day 30	Day 60	Day 30	Day 60
Male	10	138	289	499	742
	50	1730	3420	7170	11900
	250	11400	13300	120000	163000
Female	10	261	563	911	1570
	50	2600	3950	10100	16300
	250	13900	21600	147000	182000

$C_{max}$ : maximum observed concentration; AUC<sub>0-24</sub>: area under the plasma concentration time curve from time 0 to 24h post-dose; Values are rounded to 3 significant figures

At 10 mg/kg/day, the corresponding maximum concentration ( $C_{max}$ ) and area under the plasma concentration versus time curve (AUC) values were 138/289 or 261/563 ng/mL and 499/742 or 911/1570 ng.h/mL on Days 30/60 in males or females, respectively (Study JUV0022). This dose is 50 times the highest dose (0.2 mg/kg/day)

tested in children and adolescents. The exposure in terms of  $C_{max}$  is at least 7.5-fold higher in animals compared to children (based on the highest  $C_{max}$  = 18.5 ng/mL, observed in children). The exposure in terms of AUC is at least 1.8-fold higher in animals compared to children (based on the highest AUC<sub>0-24h</sub> = 278 ng.h/mL, observed in children).

The dose of 10 mg/kg/day was considered to be a no observed adverse effect level (NOAEL) based upon clinical signs (closed eyelids) observed at this dose and based upon disturbance of the estrus cycle from 50 mg/kg/day upwards. Furthermore, the study in juvenile animals has shown results similar to those in adults animals with regard to systemic toxicity.

Assessor's comment: Two non-clinical juvenile studies were presented. One dose-range finding studies (2-week gavage administration) and one main study). The aim of these studies was to study the parameters that had been identified as possible targets after treatment in juvenile animals.

The administered doses Alfuzosin were 10, 50 and 250 mg/kg/day. Marked toxicity (mortality, clinical signs, reduction of body weight gain, developmental landmarks) was observed at the highest dose. The 250 mg/kg/day dose level is considered to be above the maximum tolerated dose (MTD). At the intermediate and lowest dose, 50 and 10 mg/kg/day, Alfuzosin induced slight effects on clinical conditions (mainly eyes partially closed; in both doses). The assessor agrees that the NOAEL for Alfuzosin under the present study conditions should be set at 10 mg/kg/day based on clinical signs (closed eyelids) observed from 50 mg/kg/day upwards. The clinical signs (closed eyelids) at 10 mg/kg/day appeared at the end of the study with low frequency and should not be considered as adverse.

The model used to study juvenile endpoints of Alfuzosin is considered as adequate. Furthermore, the margin of exposure was calculated and compared to the highest exposure detected in children. At 10 mg/kg/day, the exposure in terms of C<sub>max</sub> was at least 5-fold higher in animals compared to children. The AUC in animals was comparable to children.

### IV.3 Clinical aspects

#### 1. Introduction

The MAH submitted final reports for the following studies:

- Study **EFC5722 (ALFACHIN)**: A 12-week, multicenter, double-blind, randomized, placebo-controlled, parallel-group study to investigate the efficacy, pharmacodynamic and safety of two doses of alfuzosin (0.1 mg/kg/day; 0.2 mg/kg/day) in the treatment of children and adolescents 2-16 years of age with elevated detrusor leak point pressure of neuropathic etiology followed by a 40-week open-label extension
- Study **EFC6269 (ALFAHYDRO)**: A 12-week, multicenter, open-label, non-comparative study to investigate pharmacodynamic and safety of alfuzosin 0.2 mg/kg/day in the treatment of children and adolescents 2 - 16 years of age with hydronephrosis associated with elevated detrusor leak point pressure of neuropathic etiology followed by a 40-week open-label extension
- Study **PKM6270 (ALFACHIP)**: A 4-week, open-label, multicenter, randomised, 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 of neuropathic etiology

The MAH also provided literature references on the use of alfa-receptor blockers in the paediatric population:

1. Schulte-Baukloh et al: Alfuzosin in the treatment of high leak-point pressure in children with neurogenic bladder (BJU International, 2002:90, 716-20). The authors found alfuzosin to decrease detrusor leak point pressure in 17 children with neurogenic bladder in this open uncontrolled study.
2. Austin et al: Alfa-adrenergic blockade in children with neuropathic and nonneuropathic voiding dysfunction (J Urol, Vol 162, 1064 -67, 1999). Seventeen children with different etiology to voiding dysfunction were treated with doxazosin in this uncontrolled study; 14 of these patient improved.

- Cain et al: Alpha blocker therapy for children with dysfunctional voiding and urinary retention (J Urol Vol 170, 1514-17, 2003). Fifty –five patients with a mean age of 8 years with symptoms of urinary incontinence, urgency and urinary tract infection were treated with doxazocin. Post-void residual decreased after treatment.

None of these studies was placebo-controlled and randomised and only one of the studies used alfuzosin as alfa-receptor blocker.

## 2. Clinical studies

### ➤ Pharmacokinetics

Pharmacokinetics and safety of the two paediatric formulations were first evaluated in Study ALFACHIP. In addition, a population pharmacokinetics (PopPK) analysis was conducted using pooled PK data from three clinical studies (Studies ALFACHIP, ALFACHIN and ALFAHYDRO).

#### **Study ALFACHIP (PKM6270)**

This study was an international, multicenter, randomized, open-label, parallel-group, PK study of 2 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  $\geq 40$  cm H<sub>2</sub>O. After a screening period of up to 4 weeks, patients were randomized and received study treatment for 4 weeks. The treatment period was followed by a 1-week follow up period.

The primary objective of this study was to investigate the PK of two doses of alfuzosin (0.1 or 0.2 mg/kg/day) given as a solution (alfuzosin 0.2 mg/mL) 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). Blood samples for the determination of alfuzosin plasma concentrations (T0 [before the morning dose], T1, T2, T4 [before the noon dose], T5, T6, T8 post dosing with solution and T0 [before the morning dose], T4, T6, T8 and T12 post dosing with tablet) were drawn on Day 1 and on Day 7. Alfuzosin plasma concentrations were assayed using a validated electrospray liquid chromatography tandem mass spectrometry (LC-MS/MS) method with limit of quantification of 0.5 ng/mL.

Overall, 29 patients were enrolled into the study: 14 patients were randomized to alfuzosin 0.1 mg/kg/day and 15 to alfuzosin 0.2 mg/kg/day and 28 patients completed study treatment. One patient in the 0.2 mg/day dose group (2 to 7 years age group) discontinued the study prematurely due to a treatment-emergent adverse event (TEAE).

Descriptive statistics on alfuzosin plasma PK parameters are summarized by age group in Table 2 and in Table 3.

Regarding baseline characteristics, 15 patients were included in the 2-7 year age group and 14 patients in the 8-16 year age group. Overall, 18/29 (62.1%) patients were female and 26/29 were Caucasians. According to the Tanner puberty score, 11/18 of the female patients and 8/11 of the male patients were pre-adolescent. The mean age of the patients was 7.6 years (range: 3 to 16 years) and the mean weight was 29.8 kg (range: 12.0 to 62.0 kg).

**Table 2. 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]
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)

<sup>1</sup> PK parameters after the first drug intake of the day

<sup>2</sup> PK parameters after the second drug intake of the day

**Table 3. 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 N=7	3.41±2.20 (65) [2.86]	3.43 (2.95-8.00)	24.2±9.92 (41) [22.3]
Day 7 N=7	5.85±2.91 (50) [4.91]	3.00 (0.00-7.88)	56.5±11.4 (20) [55.5]
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  $t_{max}$  where values are Median (Min, Max)

With alfuzosin given as a solution to children, the accumulation ratios ( $AUC_{0-8}$  Day 7/ $AUC_{0-8}$  Day 1) were 1.02 at 0.1 mg/kg/day and 1.25 at 0.2 mg/kg/day (Table 2). With tablets administered to children or adolescent, the accumulation ratio ( $AUC_{0-12}$  Day 7/  $AUC_{0-12}$  Day 1) was 2.49 at 0.1 mg/kg/day and 1.67 at 0.2 mg/kg/day (Table 3).

$AUC_{0-8}$  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. A high total variability was observed for both doses (56 % at 0.2 mg/kg on Day 7 versus 37 % at 0.1 mg/kg on Day 7).

$AUC_{0-12}$  on Day 7 in children or adolescent with alfuzosin 0.2 mg/kg/day as tablets was 1.4-fold higher than that observed with 0.1 mg/kg/day. A moderate total variability was observed for both doses (24% at 0.2 mg/kg on Day 7 versus 20% at 0.1 mg/kg on Day 7).

Assessors comment: The doses administered in this study correspond reasonably with the most common adult dose of 10 mg/day (5 mg BID for the 5 mg prolonged-release tablet or 10 mg QD for the 10 mg prolonged-release tablet), which would translate into a dose of 0.2 mg/kg/day in an adult patient weighing 50 kg and 0.14 mg/kg/day in a patient weighing 70 kg. There was no adult group included for comparison in this study and no comparison with adult historical PK data was made.

The data indicate a deviation from dose proportionality, especially in the younger age group, with C<sub>max</sub> and AUC being 3-4-fold higher at 0.2 mg/kg/day compared with 0.1 mg/kg/day. The sponsor refers to the relative low number of subjects by dose and the variability in PK parameters as a possible explanation. This was a parallel group study and this may also affect the results. Individual demographic data could not be found in the study report to assess e.g. age & weight distribution in the different groups. However, the mean or median age or weight did not differ substantially between the dose groups.

No indications of a time dependency in the pharmacokinetics were observed after 7 days dosing. There appeared to be no major gender effect in either age group, however, the numbers in each group were small.

The variability was relatively high and a high variability in the pharmacokinetics of alfuzosin has been observed also in adults.

### **Study POH0209**

The objective of Study POH0209 was to develop and qualify a PopPK model for alfuzosin based on PK data obtained in patients from three clinical efficacy/safety studies (Studies ALFACHIP, ALFACHIN and ALFAHYDRO) in order to provide an assessment of the alfuzosin PK variability and to assess the influence of key demographic parameters (i.e. 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 (AUC<sub>0-24</sub>, C<sub>max</sub>, and minimum concentration [C<sub>trough</sub>] at steady state) in patients.

In Study EFC5722 (ALFACHIN) one blood sample was collected at any time after dosing on Week 12 and 52 and, 1 to 2 hours after dosing with solution or 2 to 4 hours after dosing with tablet on Week 26. Three samples were collected on Week 13, before dosing then 1 and 2 hours after dosing in children 8 to 16 years of age receiving alfuzosin solution.

In Study EFC6269 (ALFAHYDRO), one blood sample was collected 1 or 2 hours after solution intake, 2 to 4 hours after tablet administration on Week 12. One sample was collected for both formulations at any time after dosing on Week 26 and Week 52. In children 8 to 16 years of age receiving alfuzosin solution, three samples were collected on Week 17, before dosing, then 1 and 2 hours after dosing. Alfuzosin plasma concentrations were assayed using a validated electrospray LC-MS/MS method with limit of quantification of 0.5 ng/mL.

Overall, 209 patients treated with alfuzosin (841 concentrations), 134 administered with solution (572 samples), 75 administered with the tablet (269 samples) were included in this analysis, which was performed using the NonMEM software. A 2-compartmental PopPK model, with first-order formulation-dependent absorption process, was used for both formulations (solution and tablet).

Interpatient variability in the apparent clearance of alfuzosin, central and peripheral volumes of distribution and absorption rate constant in patients were about 42%, 57.5%, 159% and 39%, respectively. The inter-compartmental clearance being fixed to 5.7 L/h, no inter-patient variability was estimated for this parameter. The residual (intra-individual) variability was about 36.5%.

Sex, age, race, creatinine clearance (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 significant covariates explaining alfuzosin pharmacokinetic variability in patients were formulation and body weight. The absorption rate constant of alfuzosin was 3-fold higher for the solution compared to the extended-release tablet. The apparent clearance of alfuzosin was 1.7-fold higher for a 45 kg child compared to a 20.7 kg child, 45.0 and 20.7 kg being the mean body weight for tablet and solution formulations, respectively.

A summary of the derived exposure variables per arm (0.1 mg/kg/day and 0.2 mg/kg/day), for solution and tablet is presented in Table 4 and Table 5, respectively.

**Table 4. Mean (SD) alfuzosin derived exposure variable in children (2-7 years) with alfuzosin given as solution (TID regimen)**

		0.1 mg/kg/day (n=60)	0.2 mg/kg/day (n=74)
AUC <sub>0-24</sub> at Day 1 (ng.h.mL <sup>-1</sup> )		79.8 (40.8)	156 (50.2)
AUC <sub>0-24</sub> at steady-state (ng.h.mL <sup>-1</sup> )		115 (59.5)	222 (78.6)
Rac_AUC <sub>0-24</sub>		1.43 (0.113)	1.41 (0.125)
0-8h	Day 1	C <sub>max</sub> (ng/mL)	5.92 (3.07)
		C <sub>trough</sub> (ng/mL)	1.14 (0.658)
		AUC <sub>i</sub> (ng.h.mL <sup>-1</sup> )	25.8 (13.2)
	steady-state	C <sub>max</sub> (ng/mL)	9.38 (4.78)
		C <sub>trough</sub> (ng/mL)	2.55 (1.44)
		AUC <sub>i</sub> (ng.h.mL <sup>-1</sup> )	44.9 (23.3)
8-20h	Day 1	C <sub>max</sub> (ng/mL)	6.70 (3.43)
		C <sub>trough</sub> (ng/mL)	0.703 (0.433)
		AUC <sub>i</sub> (ng.h.mL <sup>-1</sup> )	34.0 (17.6)
	steady-state	C <sub>max</sub> (ng/mL)	7.97 (4.07)
		C <sub>trough</sub> (ng/mL)	1.53 (0.906)
		AUC <sub>i</sub> (ng.h.mL <sup>-1</sup> )	46.5 (24.5)
20-24h	Day 1	C <sub>max</sub> (ng/mL)	6.47 (3.29)
		C <sub>trough</sub> (ng/mL)	3.61 (1.90)
		AUC <sub>i</sub> (ng.h.mL <sup>-1</sup> )	20.0 (10.2)
	steady-state	C <sub>max</sub> (ng/mL)	7.27 (3.70)
		C <sub>trough</sub> (ng/mL)	4.37 (2.32)
		AUC <sub>i</sub> (ng.h.mL <sup>-1</sup> )	23.2 (11.9)

i interval intake (0-8h, 8-20h and 20-24h)

**Table 5. Mean (SD) alfuzosin derived exposure variable in children and adolescents (8-16 years) with alfuzosin given as tablets (BID regimen)**

		0.1 mg/kg/day (n=34)	0.2 mg/kg/day (n=41)
AUC <sub>0-24</sub> at Day 1 (ng.h.mL <sup>-1</sup> )		78.6 (32.3)	192 (72.8)
AUC <sub>0-24</sub> at steady-state (ng.h.mL <sup>-1</sup> )		113 (45.9)	278 (122)
Rac_AUC <sub>0-24</sub>		1.45 (0.180)	1.42 (0.127)
0-12h	Day 1	C <sub>max</sub> (ng/mL)	4.38 (2.40)
		C <sub>trough</sub> (ng/mL)	1.63 (0.719)
		AUC <sub>i</sub> (ng.h.mL <sup>-1</sup> )	34.3 (17.3)
	steady-state	C <sub>max</sub> (ng/mL)	6.99 (3.07)
		C <sub>trough</sub> (ng/mL)	2.93 (1.26)
		AUC <sub>i</sub> (ng.h.mL <sup>-1</sup> )	57.6 (24.7)
12-24h	Day 1	C <sub>max</sub> (ng/mL)	5.55 (2.33)
		C <sub>trough</sub> (ng/mL)	2.15 (0.801)
		AUC <sub>i</sub> (ng.h.mL <sup>-1</sup> )	44.3 (17.3)
	steady-state	C <sub>max</sub> (ng/mL)	6.75 (2.73)
		C <sub>trough</sub> (ng/mL)	2.86 (1.21)
		AUC <sub>i</sub> (ng.h.mL <sup>-1</sup> )	55.8 (22.5)

i interval intake (0-12h, 12-24h)

Regarding the derived exposure variables, comparable values were observed when comparing the mean AUC<sub>0-24</sub> of the two formulations: on Day 1, 78.6 and 79.8 ng.h/mL for tablet and solution with 0.1 mg/kg/day, 192 and 156 ng.h/mL for tablet and solution with the 0.2 mg/kg/day (Table 4, Table 5). At steady-state, mean AUC<sub>0-24</sub> were 113 and 115 ng.h/mL for tablet and solution with the 0.1mg/kg/day, 278 and 222 ng.h/mL for tablet and solution with 0.2 mg/kg/day.

The mean AUC<sub>0-24</sub> accumulation ratio (Rac) was also similar in the two formulations whatever the arm (between 1.41 and 1.45). Since the daily dose of the solution was fractioned by 3 (TID) and that of the tablet by 2 (BID), the C<sub>max</sub> values of the 2 formulation were not comparable. However, the C<sub>max</sub> had similar values within the same arm (eg, for 0.1 mg/kg/day, C<sub>max</sub> values ranged between 4.38 and 6.70 ng/mL at Day 1 and between 6.99 and 9.38 ng/mL at steady-state) (Table 4, Table 5).

**Assessors comment:** A detailed assessment of the population PK analysis has not been made in this assessment report, since the overall clinical results are not considered supportive of a paediatric indication by the sponsor. Thus, data relating to for instance co-variate effects will not be used to support a posology in paediatric patients.

The estimated exposure data were roughly comparable to those obtained in study ALFACHIP (and those data are also part of this dataset). Approximately similar exposure (AUC<sub>0-24</sub>) was observed for the solution and tablet groups, respectively, both on day 1 and at steady state. Formulation and body weight were identified as significant covariates. The solution had a higher absorption rate constant compared with the tablet, which is expected. The apparent CL of alfuzosin was higher in children of higher weight.

### ➤ **Clinical studies on efficacy and safety**

**Study PKM6270 (ALFACHIP)** was a 4-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 of neuropathic etiology.

#### Methods

*Objectives:* The *primary objective* was to investigate the pharmacokinetics (PK) of 2 doses of alfuzosin (0.1 and 0.2 mg/kg/day) given as a solution containing 0.2 mg/mL alfuzosin or as tablets containing 1.5 mg alfuzosin in children and adolescents 2 to 16 years-of-age with elevated detrusor LPP ( $\geq 40$  cm H<sub>2</sub>O) 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 leak point pressure (LPP).

*Study design:* This was a multicenter, multinational, 4-week, open-label, randomized, parallel group, pharmacokinetic study.

*Study population/sample size:* Twenty-four patients were planned to be included, 29 were randomized and 29 were treated. All treated patients had a pharmacokinetic evaluation and a safety evaluation, 28 had a pharmacodynamic evaluation.

*Treatments and pharmacokinetic results:* See pharmacokinetic section above.

*Pharmacodynamics:* Change in detrusor LPP was evaluated at baseline and Week 4 (end of study) in urodynamic laboratories utilizing an artificial bladder filling method.

*Statistical methods:* This study was exploratory in nature, investigating the pharmacokinetics, safety and tolerability, and the pharmacodynamics (effect on detrusor LPP) of oral doses of alfuzosin in children before larger patient populations are exposed. Therefore, no formal sample size calculation was performed and all statistical analyses were descriptive. Six patients per dose and age group for each formulation were considered sufficient for the planned assessments.

#### Results

*Baseline data:* Eighteen (62.1%) of the 29 patients were female, 26 of 29 were Caucasian, 3 patients were black, and 2 patients had Hispanic ethnicity. Nineteen patients were pre-adolescent. All patients were aged 3 – 16 years and weighed between 12 and 62 kg, with even distribution of age and weight between dose groups. Mean age in the low dose group was 8.2 years, 7.6 years in the high dose group. The most common disorders underlying the neuropathic bladder disorder were spina bifida, in 19/29 patients, 9 patients had a neural tube defect and 7 patients had a hydrocephalus. The diagnosis of functional bladder outlet obstruction of neuropathic etiology had been known for a median of 3.6 years in the 0.1 mg/kg/day dose group and 2.6 years in the 0.2 mg/kg/day dose group. The most common symptoms reported (in more than 50% of the patients) were in decreasing frequency wetting during the day (25/29 patients) and at night (24/29 patients), frequency and urgency, dribbling or poor stream, and recurrent urinary tract infections. Fourteen of 29 patients had received previous treatments of the neuropathic bladder dysfunction, 6 patients in the 0.1 mg/kg/day dose group and 8 in the 0.2 mg/kg/day dose group. Anticholinergic/ antimuscarinic drugs were the most commonly used drug treatment (N=11 patients). Intermittent clean catheterization was applied in 8 patients. Only one patient in the 0.2 mg/kg/day dose group discontinued study treatment due to a TEAE on Day 22.

**Pharmacodynamics:** At baseline, the median LPP was comparable between the 2 dose groups of alfuzosin 0.1 and 0.2 mg/kg/day. The lower quartile equaled 49 cm H<sub>2</sub>O in the 0.1 mg/kg/day versus 55 cm H<sub>2</sub>O in the 0.2 mg/kg/day group, meaning there were slightly more patients with low baseline LPP in the 0.1 mg/kg/day group than in the 0.2 mg/kg/day group. Median change from baseline in LPP was greater in the 0.2 mg/kg/day dose group (-16.0 cm H<sub>2</sub>O) than in the 0.1 mg/kg/day dose group (-6.5 cm H<sub>2</sub>O). The median % change from baseline was larger in the 0.2 mg/kg/day dose group (-26.3%) as compared with the 0.1 mg/kg/day group (-14.1%). Five of 14 patients (35.7%) in the 0.1 mg/kg/day dose group and 3/15 patients (20.0%) in the 0.2 mg/kg/day dose group had LPP <40 cm H<sub>2</sub>O at endpoint. In the 0.1 mg/kg/day group, the baseline values of these patients were: 42 cm H<sub>2</sub>O for 3 of them, and 49 and 67 cm H<sub>2</sub>O for the 2 others. Their endpoints values were respectively: 31, 36, 36, 24, and 35 cm H<sub>2</sub>O. In the 0.2 mg/kg/day group, the baseline values of these patients were: 41 cm H<sub>2</sub>O for 2 of patients and 80 cm H<sub>2</sub>O for the other one. Their endpoints values were respectively: 9, 25, and 37 cm H<sub>2</sub>O. Wetting during the day improved in more than 50% of the patients in both groups (8/14 patients in the 0.1 mg/kg/day dose group and 9/14 patients in the 0.2 mg/kg/day dose group). Urgency improved in 8/14 patients in the 0.1 mg/kg/day dose group. Two patients in the 0.1 mg/kg/day dose group had aggravation of UTI; in the 0.2 mg/kg/day dose group 2 patients reported aggravation of the wetting during the day and one patient aggravating burn during urination.

**Safety:** Treatment-emergent AEs (TEAEs) were reported with a higher frequency by the children in the 2 - 7 years-of-age groups. The most frequently reported TEAEs were infectious disorders, which were reported mostly in the children 2 to 7 years-of-age. Only 1 patient prematurely discontinued treatment with alfuzosin due to a TEAE (acute bronchitis; 0.2 mg/kg/day dose group as solution). No orthostatic hypotension was found in either dose group. There were no deaths or serious AEs and only 1 withdrawal due to an AE (acute bronchitis) during the study.

**Assessors comment:** Alfuzosin treatment, 0.1 and 0.2 mg/kg/day, was well tolerated in this exploratory study in a paediatric population.

**Study EFC6269 (ALFAHYDRO)** was a 12-week, multicenter, open-label, non-comparative study to investigate pharmacodynamics and safety of alfuzosin 0.2 mg/kg/day in the treatment of children and adolescents 2 - 16 years of age with hydronephrosis associated with elevated detrusor leak point pressure of neuropathic etiology followed by a 40-week open-label extension.

### Methods

**Objectives:** The *primary objective* of the study was to determine efficacy of alfuzosin in the treatment of children and adolescents 2-16 years of age presenting with a detrusor leak point pressure (LPP) of 40 cm H<sub>2</sub>O or greater and with newly diagnosed or progressive hydronephrosis associated with elevated detrusor LPP of neuropathic etiology. *Secondary objectives* were: a) To determine the safety and tolerability of alfuzosin 0.2 mg/kg/day in children and adolescents 2-16 years of age; b) To investigate the number of urinary tract infection (UTI) episodes during the treatment period (symptomatic and documented by urine culture); and c) To assess the pharmacokinetics (population pharmacokinetics).

### *Study design*

**Study population/sample size:** Twenty patients were planned to be enrolled, 25 (12 aged 2 -7 years, 13 aged 8 – 16 years) were enrolled. Patients meeting the following criteria were to be considered for study enrollment: Children and adolescents of either gender 2-16 years of age presenting with newly diagnosed or progressive hydronephrosis (either Grade 1, Grade 2 or Grade 3a; SFU classification) associated with elevated LPP (LPP ≥40 cm) of neuropathic etiology. The change in the grade of hydronephrosis was investigated by ultrasound assessments.

The *Intent-to-treat (ITT) population*), consisted of all included patients who received at least 1 dose of study drug, had at least 1 post-baseline value and, whenever appropriate, a baseline value. Patients without post-baseline grade of hydronephrosis assessment performed before Week 12 were included in the ITT population as non-responders for the primary endpoint. The per-protocol (PP) population included ITT patients with no major efficacy-related protocol deviations. Analysis of the PP population was planned only if the percentage of patients excluded compared to the ITT population was  $\geq 5\%$ .

The *Safety population* consisted of all included patients.

*Recruitment/ Numbers analysed:* Three sites in India, 2 in Poland, 2 in Russia, 2 in Russia, 2 in Taiwan and 1 site each in Slovakia, Turkey and Malaysia recruited 1 – 6 patients each. Twenty-three (92.0%) patients continued into the 40-week safety extension phase and 22 (88.0%) patients completed the whole study period. In the 2 to 7 years age group, 1 (4.0%) patient discontinued the study prematurely during the 12-week efficacy period (subject's decision: study visits did not comply with parent's schedule) and 1 (4.0%) patient discontinued the study prematurely during 40-week safety extension phase (lack of efficacy).

Efficacy was evaluated in the ITT population (25 patients); the PP population was 24 patients.

*Treatments:* Alfuzosin was provided as solution, 0.2 mg/mL, and as tablet, 1.5 mg, for oral administration. The daily dose of the study drug was adjusted to body weight. The solution was administered to children 2-7 years of age, children and adolescents 8-16 years of age if they were unable to swallow tablets or they preferred to take the solution or if they had a body weight  $< 30\text{kg}$ . The total daily dose was divided into 3 doses and administered as a TID regimen (0.2 mg/kg/day = 0.066 mg/kg TID). The maximum daily dose of 7.5 mg alfuzosin corresponded to the maximum TID dose of alfuzosin in adults and was not to be exceeded. The tablets were administered to children and adolescents 8-16 years of age who were able to swallow tablets and had a body weight  $\geq 30\text{kg}$ . The daily dose was divided into 2 doses and administered as a BID regimen (0.2 mg/kg/day = 0.1 mg/kg BID).

#### *Outcomes/endpoints*

*Statistical methods:* As this was an exploratory, open-label, non-comparative study, no formal sample size calculation was done and all statistical analyses were descriptive.

#### Results

During the 12-week efficacy phase, 1 (8.3%) patient on solution in the 2-7 years age group had 1 major protocol violation resulting in exclusion from the efficacy analyses (missing post-baseline grading of hydronephrosis). During the whole study period, 3 (12.0%) patients had 1 major protocol violation resulting in exclusion from the efficacy analyses (2-7 years age group: 2 [16.7%] patients; 8-16 years age group: 1 [16.7%] patient). All major protocol violations were missing baseline/post-baseline gradings of hydronephrosis.

*Baseline data:* Of the 25 enrolled patients, 16 (64.0%) were female and 9 (36.0%) were male. The majority of patients were Caucasians (72.0%). According to the Tanner puberty score, 62.5% of the female patients and 77.8% of the male patients were pre-adolescent. The mean age of the patients was 7.9 years (range: 2-16 years) and the mean weight was 27.0 kg (range: 10.0-66.0 kg). The diagnosis of hydronephrosis had been known for a median of 1.3 years in the 2-7 years age group and 4.2 years in the 8-16 years age group. At baseline, the most commonly reported symptoms (in more than 50% of the patients) were wetting during the day (21/25 patients, 84.0%) and at night (21/25 patients, 84.0%) and constipation (14/25 patients, 56.0%). Six (24%) patients reported a history of symptomatic UTIs with 4 (16.0%) patients each reporting 1 cystitis episode and 1 (4.0%) patient each reporting a pyelonephritis episode and site of urinary tract unspecified within the last 3 months prior to the study. The mean grade  $\pm$ SD of

hydronephrosis at baseline was  $1.79 \pm 0.72$  in the 2-7 years age group and  $1.62 \pm 0.85$  in the 8-16 years age group. Sixteen (64%) patients had received previous treatments of neuropathic bladder dysfunction: 8 (66.7%) patients in the 2-7 years age group and 8 (61.5%) patients in the 8-16 years age group. Anticholinergics/ antimuscarinics were the most commonly used drugs (12 [48.0%] patients). Intermittent clean catheterization was applied in 15 (60%) patients.

**Efficacy results:** Positive clinical response was defined as a grade decrease in hydronephrosis from baseline to Week 12  $\geq 1$ . For patients with bilateral hydronephrosis at baseline, complete response was defined as positive clinical response for both kidneys. For patients with unilateral hydronephrosis at baseline, complete response was defined as positive clinical response for the affected kidney without worsening of the other kidney. For patients with bilateral hydronephrosis at baseline, partial response was defined as positive clinical response for the one kidney without worsening of the other kidney.

**Table 6.** Summary of complete and partial response rates at Week 12, ITT population

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

At Week 12, 10/25 patients reported complete response, defined as an improvement of hydronephrosis grading  $\geq 1$  in both kidneys. Of the 10 patients reporting complete response, 2 patients were in the 2-7 years age group and 8 patients were in the 8-16 years age group. These data must be put into perspective due to the small number of patients included in the study and the lack of a control group. Of all 20 patients with bilateral hydronephrosis at baseline, 5 patients reported an improvement of hydronephrosis grading  $\geq 1$  in both kidneys and 6 patients in one kidney only. All 5 patients with unilateral hydronephrosis at baseline reported an improvement of hydronephrosis grading  $\geq 1$ .

**Safety results:**

The overall median extent of exposure was 365.0 days (range: 10-372 days). Treatment exposures were comparable for the formulation and age groups. TEAEs were reported at similar frequencies in both age groups and in all formulation groups. In total, 19/25 (76.0%) patients experienced at least 1 TEAE (9 (75.0%) of patients in the 2-7 years age group; 10 (76.9%) in the 8-16 years age group). Four/25 (16.0%) patients reported serious TEAEs, with 2 patients in each age group. No deaths were reported and no patient discontinued due to a TEAE. The majority of patients reported TEAEs in the SOC of infections and infestations (13/25; 52.0%) followed by gastrointestinal disorders, respiratory, thoracic and mediastinal disorders, and injury, poisoning and procedural complications (reported by 4/25 [16.0%] patients each). The most commonly reported TEAEs in all age groups were reported for the SOC “infections and infestations” (2-7 years age group 50.0%; 8-16 years age 53.8%). The most frequently reported TEAEs were cystitis, nasopharyngitis, and pyrexia, all of which were reported by 4/25 (16.0%) patients each. Cystitis and nasopharyngitis were more frequently reported in the 2-7 years age group (25.0%)

while pyrexia was reported at similar frequencies among the age groups (2-7 years age group 16.7%; 8-16 years age 15.4%). The majority of TEAEs were reported in single patients. One patient in the 8-16 years age group reported a severe case of convulsion during the whole study period. All other TEAEs were assessed by the Investigator as either mild or moderate in intensity.

*Assessors comment: The complete response rates by formulation did not differ between the formulations at Week 12. A difference between the age groups was observed at Week 12: Two patients reported a complete response in the 2-7 years age group and 8 patients in the older age group. A difference between the sexes was observed at Week 12 (7 female patients and 3 male patients reported complete response). Because of the small size of the study and the difference in subgroups, results should be interpreted with caution. Safety data from this exploratory study evokes no concerns. The efficacy results merit further investigation.*

Study **EFC5722 (ALFACHIN)** was a 12-week, multicenter, double-blind, randomized, placebo-controlled, parallel-group study to investigate the efficacy, pharmacodynamic and safety of two doses of alfuzosin (0.1 mg/kg/day; 0.2 mg/kg/day) in the treatment of children and adolescents 2-16 years of age with elevated detrusor leak point pressure of neuropathic etiology followed by a 40-week open-label extension.

## Methods

*Objectives:* The *primary objective* of the study was to evaluate the efficacy of alfuzosin in comparison to placebo on the detrusor leak point pressure (LPP) in children and adolescents 2-16 years of age with elevated detrusor LPP of neuropathic etiology and detrusor LPP  $\geq 40$  cm H<sub>2</sub>O. *Secondary objectives* were:

- a) To investigate the safety and tolerability of 2 different dose regimens of alfuzosin in comparison to placebo in children and adolescents 2-16 years of age;
- b) To evaluate the effects of the 2 doses of alfuzosin in comparison to placebo on:
  - Detrusor compliance;
  - Urinary tract infection (UTI) episodes during the treatment period (symptomatic and documented by urine culture);
- c) To assess the pharmacokinetics (population pharmacokinetics) after open label extension period; d) To evaluate the 12-month long-term safety of alfuzosin 0.1 mg/kg/day and 0.2 mg/kg/day.

*Study design:* This was a phase 3 double-blind randomised multicenter study carried out in 49 study centers in 15 countries during the period October 2007 to December 2009.

*Study population /Sample size:* Children and adolescents of either gender 2-16 years of age presenting with elevated detrusor LPP of neuropathic etiology and detrusor LPP  $\geq 40$  cm H<sub>2</sub>O and  $< 100$  cm H<sub>2</sub>O. The study was planned to include 150 patients; 172 patients were randomised and treated (placebo: 57; alfuzosin 0.1 mg/kg/day: 57; alfuzosin 0.2 mg/kg/day: 58). The *ITT population* consisted of 172 patients, the *PP population* of 149 patients (placebo: 50; alfuzosin 0.1 mg/kg/day: 49; alfuzosin 0.2 mg/kg/day: 50). The *safety population* was 172 patients, the population evaluated for pharmacokinetic was 140 patients (placebo: 54; alfuzosin 0.1 mg/kg/day: 47; alfuzosin 0.2 mg/kg/day: 39).

*Treatments:* Treatment was given with an oral solution containing 0.2 mg/mL alfuzosin was given either: 0.1 mg/kg/day or 0.2 mg/kg/day divided in 3 doses given at breakfast/lunch/dinner

(0.1 mg/kg/day = 0.033 mg/kg TID); or orally as tablets containing 1.5 mg alfuzosin given either 0.1 mg/kg/day or 0.2 mg/kg/day divided in 2 doses. The daily dose was adjusted to body weight.

**Statistical Methods:** The study was planned and sized to demonstrate the superiority over placebo of at least one of the 2 doses of alfuzosin 0.1 mg/kg and 0.2 mg/kg. Comparison between each alfuzosin dose and placebo related to the primary criterion was conducted with a Fisher's exact test using the Hochberg procedure method of adjustment of p-values. Safety and tolerance data were summarized by dose group and by age and formulation within each dose group using descriptive statistics. Potentially clinically significant abnormalities (PCSAs) in clinical laboratory test results, vital signs, and ECG were flagged and analyzed.

## Results

*Recruitment/ Number analysed:*

**Table 7.** Summary of patient disposition, double-blind phase

	Placebo (N=57)	Alfuzosin (mg/kg/day)	
		0.1 (N=57)	0.2 (N=58)
Randomized patients	57 (100%)	57 (100%)	58 (100%)
Exposed patients	57 (100%)	57 (100%)	58 (100%)
Completed study treatment period	56 (98.2%)	55 (96.5%)	56 (96.6%)
Continue in open label phase	54 (94.7%)	54 (94.7%)	55 (94.8%)
Discontinued study treatment period	1 (1.8%)	2 (3.5%)	2 (3.4%)
<b>Reason for treatment discontinuation</b>			
Adverse event	1 (1.8%)	1 (1.8%)	2 (3.4%)
Lack of efficacy	0	0	0
Poor compliance to protocol	0	0	0
Subject lost to follow-up	0	0	0
Other reason:			
Too many & too much blood draws. Child is not better with treatment.	0	1 (1.8%)	0

Patients receiving placebo and who had completed the 12-week double-blind efficacy study phase and continued into the 40-week open-label safety extension study were switched to alfuzosin with a dose corresponding to their randomization dose group.

**Baseline data:** Of the 172 randomized patients, 85 were female and 87 were male. The majority of patients were Caucasians (79.7%). According to the Tanner puberty score, 51/85 of the female patients and 56/87 of the male patients were pre-adolescent. The mean age of the patients was 8.3 years (range: 2 - 17 years) and the mean weight was 29.9 kg (range: 10.0 - 89.0 kg). Throughout the 3-month prior to the study, a higher percentage of urinary tract infections (UTIs) were reported in the alfuzosin 0.2 mg/kg/day group (31.0%) compared to the alfuzosin 0.1 mg/kg/day group (12.3%), and the placebo group (15.8%). This difference between groups was mostly due to an increased reporting of cystitis in the alfuzosin 0.2 mg/kg/day group. The most common underlying diseases of neuropathic bladder ongoing at randomization were spina bifida (49.4%), hydrocephalus (34.9%) neuronal tube defect (36.6%), and meningocele (32.6%). The treatment groups were balanced in terms of voiding history, ie, urgency, frequency, wetting during day and night. Overall, 116/172 patients had received previous treatments of neuropathic bladder dysfunction. Anticholinergics/antimuscarinics were the most commonly used drugs (91/172 patients). Intermittent clean catheterization was applied in 94/172 patients. Only few patients applied lower urinary tract rehabilitation measurements such as pelvic floor muscle exercise, electrostimulation or biofeedback. No patients in the alfuzosin groups and 2/57 patients in the placebo group were considered noncompliant.

**Efficacy results:** 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 cm H<sub>2</sub>O (placebo: 23/57 patients; alfuzosin 0.1 mg/kg/day: 23/57 patients; alfuzosin 0.2 mg/kg/day: 28/58 patients). The difference in response versus placebo was 0% [95% CI -17.5; 17.5] for the alfuzosin 0.1 mg/kg/day group and +7.9% [95% CI -10.0; 25.1] for the alfuzosin 0.2 mg/kg/day group.

**Table 8.** Detrusor leak point pressure (LPP; cm H<sub>2</sub>O): Number (%) of patients with LPP <40 cm H<sub>2</sub>O at endpoint, double-blind phase; ITT population

	Placebo (N=57)	Alfuzosin (mg/kg/day)	
		0.1 (N=57)	0.2 (N=58)
LPP			
< 40 cmH <sub>2</sub> O	23 (40.4%)	23 (40.4%)	28 (48.3%)
≥ 40 cmH <sub>2</sub> O 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

Analyses using the PP population confirmed the results of the ITT analysis on the proportion of patients with detrusor LPP <40 cm H<sub>2</sub>O at Week 12.

Subgroup analyses showed that in patients 2–7 years of age, a slightly higher proportion of patients in both alfuzosin treatment groups reported LPP <40 cm H<sub>2</sub>O 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). The difference in response versus placebo was 21.4% for the alfuzosin 0.1 mg/kg/day group and 14.3% for the alfuzosin 0.2 mg/kg/day group. 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 cm H<sub>2</sub>O at the end of the 12-week double-blind study phase (placebo: 14/29 patients; alfuzosin 0.1 mg/kg/day: 8/29 patients; alfuzosin 0.2 mg/kg/day: 15/30 patients). The difference in response versus placebo was -20.7% [95% CI -42.3; 4.1] for the alfuzosin 0.1 mg/kg/day group and +1.7% [95% CI -22.4; 25.6] for the alfuzosin 0.2 mg/kg/day group. All 95% CIs for the respective odds ratios included 1 indicating no statistically significant difference between the alfuzosin dose groups and placebo. Analyses stratified by age using the PP population confirmed the results of the ITT analysis on the proportion of patients with detrusor LPP <40 cm H<sub>2</sub>O at Week 12.

#### *LPP responder by anticholinergic and/or antimuscarinic drugs*

Analyses stratified by pre-existing medication with anticholinergic and/or antimuscarinic drugs were consistent with the results of the primary analysis. The odds ratios by anticholinergic/antimuscarinic use for each alfuzosin group versus placebo were close to 1 with large 95% CIs All 95% CIs included 1, indicating no statistically significant difference between the alfuzosin dose groups and placebo. One patient in the alfuzosin 0.1 mg/kg/day group with LPP <40 cm H<sub>2</sub>O at endpoint started treatment with an alpha-blocking agent or anticholinergic/antimuscarinic agent after randomization.

### LPP responder by formulation used, gender and geographic area

There was no significant difference between the alfuzosin dose groups and the placebo group for the LPP responder rate in the subgroups defined by formulation used, gender or geographic area.

### Absolute change in detrusor LPP at the end of the double-blind treatment period

At the end of the 12-week double-blind study phase, a numerically larger decrease from baseline to endpoint in mean LPP was observed in both alfuzosin groups compared to the placebo group (LS mean change: placebo -5.4; alfuzosin 0.1 mg/kg/day -11.7; alfuzosin 0.2 mg/kg/day -12.5). However, the difference was not statistically significant (adjusted p=0.1040 for both alfuzosin groups). The decrease from baseline to endpoint in median LPP (ie, median at endpoint – median at baseline) was comparable between the treatment groups (median change: placebo -9.5; alfuzosin mg/kg/day -7.0; alfuzosin 0.2 mg/kg/day -8.5). Analyses using the PP population confirmed the results of the ITT analysis on the mean and median change from baseline in detrusor LPP. Since the changes in LPP from baseline (median versus mean) are not consistent, ie the distribution of LPP is not normally distributed, a rank-based ANCOVA relaxing the normality assumption was run on changes from baseline to corroborate the results of the parametric ANCOVAs. The rank-based ANCOVA confirmed the results of the parametric ANCOVAs.

**Table 9.** Detrusor leak point pressure (%): rank analysis of ANCOVA on percent change from baseline, ITT population

	Placebo (N=57)	Alfuzosin mg/kg/day	
		0.1 (N=57)	0.2 (N=58)
Mean relative change from baseline at endpoint	-9.33	-20.21	-21.92
Number	54	53	56
Point estimate of treatment effect (SE) [a]		-0.05 (0.055)	-0.09 (0.053)
95% CI		(-0.16 to 0.05)	(-0.20 to 0.01)
p-values vs Placebo [b]		0.3305	0.0876
Adjusted p-values vs Placebo [c]		0.3305	0.1752

Note : [a] point estimate of the treatment effect on baseline adjusted ranks (residuals obtained from covariance analysis using rank of baseline LPP as covariate; negative values correspond to a beneficial effect of alfuzosin)

In patients 2–7 years of age, a larger decrease of LPP was found in both alfuzosin dose groups as compared to the placebo group (LS mean change: placebo +1.6, alfuzosin 0.1 mg/kg/day -14.0, alfuzosin 0.2 mg/kg/day -10.9). In patients 8–16 years of age, mean change of LPP was comparable between the alfuzosin treatment groups and the placebo group (LS mean change: placebo -11.9, alfuzosin 0.1 mg/kg/day -8.3; alfuzosin 0.2 mg/kg/day -13.9). The analyses with regard to the use of anticholinergic and/or antimuscarinic drugs revealed no considerable difference in the mean change of LPP between the treatment groups.

At the end of the 12-week double-blind study phase, a comparable change from baseline to endpoint in mean detrusor compliance was observed in both alfuzosin groups compared to the placebo group (LS mean change: placebo 1.5; alfuzosin 0.1 mg/kg/day 2.0; alfuzosin 0.2 mg/kg/day 2.5).

With respect to the relative (%) change in detrusor compliance, a comparable LS mean change at endpoint compared to baseline was found across the treatment groups (LS mean change: placebo 113.6; alfuzosin 0.1 mg/kg/day 126.6, adjusted p=0.7889; alfuzosin 0.2 mg/kg/day 98.6, adjusted p=0.7889). A rank-based ANCOVA relaxing the normality assumption was run on percent changes from baseline and confirmed the results of the parametric ANCOVAs.

At endpoint, no notable difference in number of patients reporting detrusor compliance < 9 mL/cm H<sub>2</sub>O was found between the alfuzosin groups and placebo.

There was no evidence for a difference in the frequency of number of patients reporting symptomatic UTIs and number of UTI episodes during the study between the alfuzosin groups and placebo. However, there was an imbalance in the frequency of UTIs in the 3 months prior to the study since a higher percentage of symptomatic UTIs were reported in the alfuzosin 0.2 mg/kg/day group (31.0%) as compared to the alfuzosin mg/kg/day group (12.3%) and the placebo group (15.8%).

The LPP response was analyzed in the subgroup of patients with baseline LPP in the range of 41-45 cm H<sub>2</sub>O to evaluate small changes in LPP around 40 cmH<sub>2</sub>O.

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.

*Assessors comment: No significant positive effect on the detrusor leak point pressure was demonstrated in a paediatric population with detrusor LPP, due to neurologic factors,  $\geq 40$  cm H<sub>2</sub>O.*

**Safety results:** The overall median exposure was 359.0 days (range: 28-410 days). Treatment exposures were comparable for the dose groups.

**Table 10.** Overview of TEAEs, whole study period, Safety population

	<b>Alfuzosin (mg/kg/day)</b>	
	<b>0.1</b>	<b>0.2</b>
	<b>(N=83)</b>	<b>(N=86)</b>
Patients with any TEAE	57 (68.7%)	61 (70.9%)
Patients with any serious TEAEs	10 (12.0%)	7 (8.1%)
Patients with any TEAE leading to death	0	0
Patients permanently discontinued treatment due to TEAE	3 (3.6%)	3 (3.5%)

Note: TEAE: Treatment emergent adverse event

Severe TEAEs were reported in 17/169 patients during the study period. All severe TEAEs occurred in single patients:

- Alfuzosin 0.1 mg/kg/day: pneumonia, arthritis infective, lobar pneumonia, malnutrition, epilepsy, tethered cord syndrome, respiratory failure, renal impairment, irritability, and procedural pain.
- Alfuzosin 0.2 mg/kg/day: pyelonephritis, pneumonia, asymptomatic bacteriuria, tethered cord syndrome, diarrhoea, decubitus ulcer, and femur fracture.

Possibly related TEAEs were reported at similar frequencies between the alfuzosin dose groups (0.1 mg/kg/day 10/83, 12.0%; 0.2 mg/kg/day 10/86, 11.6%). Somnolence was reported in 3 (3.5%) alfuzosin 0.2 mg/kg/day patients. Diarrhoea was reported in 2 patients in each dose group (0.1 mg/kg/day 2/83, 2.4%; 0.2 mg/kg/day 2/86, 2.3%). All other possibly related TEAEs occurred in single patients. There were no relevant differences between the alfuzosin dose groups in the frequencies of any individual possibly related TEAEs.

**SAEs and deaths during the whole study period:** Serious TEAEs were reported for 17/169 patients with 10 (12.0%) patients in the 0.1 mg/kg/day group and 7 (8.1%) patients in the 0.2 mg/kg/day group. Epilepsy was reported in 2 (2.4%) alfuzosin 0.1 mg/kg/day patients and decubitus ulcer in 2 (2.3%) alfuzosin 0.2 mg/kg/day patients. Pneumonia, tethered cord syndrome and ventriculoperitoneal shunt malfunction were reported in 1 patients in each dose group (0.1 mg/kg/day 1/83, 1.2%; 0.2 mg/kg/day 1/86, 1.2%). All other serious TEAEs occurred in single patients. No serious TEAE was considered possibly related to study treatment by the Investigator. No deaths occurred in this study.

**Table 11.** Number (%) of patients experiencing serious TEAE(s) presented by primary system organ class and preferred term, whole study period, Double-blind phase, Safety population

Primary System Organ Class Preferred Term	Placebo (N=57)	Alfuzosin (mg/kg/day)	
		0.1 (N=57)	0.2 (N=58)
Any serious TEAE	1 (1.8%)	2 (3.5%)	0
Nervous system disorders	0	1 (1.8%)	0
Epilepsy	0	1 (1.8%)	0
Investigations	1 (1.8%)	0	0
Weight decreased	1 (1.8%)	0	0
Injury, poisoning and procedural complications	0	1 (1.8%)	0
Shunt malfunction	0	1 (1.8%)	0

n(%) = number and percentage of patients with at least one TEAE  
MedDRA version: 12.0

Note : Table sorted by SOC internationally agreed order and decreasing frequency of preferred terms in Alfuzosin 0.2 group

*Assessors comment: Alfuzosin treatment was well tolerated in this paediatric study population.*

### 3. Discussion on clinical aspects

Pharmacokinetics and safety of the two paediatric formulations were first evaluated in Study ALFACHIP and a population pharmacokinetic analysis was conducted using pooled PK data from the three clinical studies. There was no adult group included for comparison in the PK study and no comparison with adult historical PK data has been made. The data indicated a slight deviation from dose proportionality especially in the younger age group. No indications of a time dependency in the pharmacokinetics were observed after 7 days dosing. There appeared to be no major gender effect in either age group, however, the numbers in each group were small. The variability in PK parameters was relatively high, as also observed previously in adults.

The safety of alfuzosin 0.1 mg/kg/day and 0.2 mg/kg/day during up to 40 weeks of treatment in a paediatric population aged 2 -16 years and with elevated detrusor leak point pressure was satisfactory.

After 12 – 40 weeks of treatment, no significant efficacy of alfuzosin 0.1 mg/kg/day and 0.2 mg/kg/day was shown on detrusor LPP in an adequately sized performed study in paediatric and adolescent patients 2-16 years of age with detrusor LPP  $\geq 40$  cm H<sub>2</sub>O of neuropathic etiology.

## V. OVERALL CONCLUSION AND RECOMMENDATION

### ➤ Overall conclusion

The preclinical model used to study juvenile endpoints of alfuzosin is considered adequate. The margin of exposure was calculated and compared to the highest exposure detected in children. At 10 mg/kg/day, the exposure in terms of C<sub>max</sub> was at least 5-fold higher in animals compared to children. The AUC in animals was comparable to that in children.

A detailed assessment of the paediatric pharmacokinetic clinical data has not been made in this assessment report, since the overall clinical results are not considered supportive of a paediatric indication by the sponsor. Thus, pharmacokinetic data will not be used to support a posology in paediatric patients and no questions were posed.

The efficacy of alfuzosin in the treatment of children with children and adolescents 2-16 years of age with elevated detrusor leak point pressure of neuropathic etiology could not be established in clinical studies performed on this indication. No safety concerns occurred in the paediatric population in these clinical studies.

In line with the intentions of articles 45 and 46, it was concluded that some information on the performed studies should be amended in section 5.1.

➤ **Comments from member states**

In the first round of the procedure, supportive comments were received from 2 member states, while a third member state agreed with the overall conclusion of the AR but suggested to also include some additional information.

The updated draft PDAR circulated 2010-12-16 maintained the initial view of the Rapporteur. One member state gave a supportive comment on D 115, while another member state was in principle positive but maintained a slight disagreement with regard to details of what data should be included in the SPC amendment.

➤ **Recommendation**

Based on preclinical and clinical studies, the MAH's suggestion to amend the SPC section 4.2 for Xatral with pediatric information, is adequate and the suggested wording for this section is supported by the Rapporteur. As clinical study results were negative and no paediatric indication is suggested, the information added to section 5.1 of the SPC should be as follows:

**Section 4.2**

*Paediatric population:*

Efficacy of alfuzosin has not been demonstrated in children aged 2 to 16 years (see section 5.1). Therefore, alfuzosin is not indicated for use in paediatric population.

**Section 5.1**

*Paediatric population*

Alfuzosin is not indicated for use in the paediatric population (see section 4.2).

Efficacy of alfuzosin hydrochloride was not demonstrated in the two studies conducted in 197 patients 2 to 16 years of age with elevated detrusor leak point pressure (LPP $\geq$ 40 cm H<sub>2</sub>O) of neurologic origin. Patients were treated with alfuzosin hydrochloride 0.1 mg/kg/day or 0.2 mg/kg/day using adapted paediatric formulations.

The MAH should also implement corresponding text in the PL.

The MAH should submit a type IB variation to implement the SPC amendments agreed in this procedure and should also implement corresponding text in the PL.