These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert in the country of prescription.

Sponsor / Company: sanofi-aventis **Drug substance(s):** alfuzosin	**Study Identifier:** NCT00629720 **Study code:** PKM6270 (ALFACHIP)
Title of the study: Four-week, open-label, multicenter, randomized, parallel-group study to investigate the pharmacokinetics, safety, tolerability and the effects on Leak Point Pressure (LPP) 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	
Study center(s): 6 active centers, 3 in Serbia and 3 in the United States of America	
Study period: Date first patient enrolled: 10-Jul-2006 Date last patient completed: 23-Feb-2007	
Phase of development: Phase III	
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 (≥40 cm H2O) 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	
Methodology: Multicenter, multinational, 4-week, open-label, randomized, parallel group, pharmacokinetic study	
Number of patients: Planned: 24 Randomized: 29 Treated: 29 Evaluated for phamacokinetics: 29 ; for pharmacodynamics: 28 ; for safety: 29	
Diagnosis and criteria for inclusion: • Children and adolescents of either gender 2 to 16 years-of-age with elevated detrusor LPP of neuropathic etiology • Detrusor LPP ≥40 cm H_2O	
Investigational product: alfuzosin Dose: The daily dose was adjusted by body weight. Alfuzosin, oral solution containing 0.2 mg/mL alfuzosin: Dose regimen for children 2 to 7 years: • 0.1 mg/kg/day divided into 3 doses given at breakfast, lunch, and dinner (0.1 mg/kg/day = 0.033 mg/kg 3 times daily [TID]); or • 0.2 mg/kg/day divided into 3 doses given at breakfast, lunch, and dinner (0.2 mg/kg/day = 0.066 mg/kg TID) Alfuzosin, tablets containing 1.5 mg alfuzosin: Dose regimen for children 8 to 16 years: • 0.1 mg/kg/day divided into 2 doses given at breakfast and dinner(0.1 mg/kg/day = 0.05 mg/kg twice daily [BID]); or • 0.2 mg/kg/day divided into 2 doses given at breakfast and dinner (0.2 mg/kg/day = 0.1 mg/kg BID) Administration: Oral	

Duration of treatment: 4 weeks

Duration of observation: 5 weeks

Criteria for evaluation:

Pharmacokinetics:

The following PK parameters were assessed: the plasma concentration observed before treatment administration during repeated dosing (C_{trough}), maximum concentration observed (C_{max}), area under the plasma concentration versus time curve from time 0 to 4 hours (AUC_{0-4}), area under the plasma concentration versus time curve from time 4 to 8 hours (AUC_{4-8}), area under the plasma concentration versus time curve from time 0 to 8 hours (AUC_{0-8}) (for the TID formulation), and area under the plasma concentration versus time curve from time 0 to 12 hours (AUC_{0-12}) (for the BID formulation). The accumulation ratio (R_{ac}) was also calculated and is displayed by formulation and dose group.

Pharmacodynamic:

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

Safety:

Safety was evaluated using physical examinations, vital signs monitoring (blood pressure [BP], heart rate [HR]), electrocardiogram (ECG) parameters, visual changes and alertness, adverse events (AEs), urinalysis, hematology, biochemistry, hormone analysis (testosterone, estradiol, thyroid function tests, prolactin, follicle stimulating hormone, and luteinizing hormone).

Pharmacokinetic sampling times:

Pharmacokinetic sampling times:

Blood sampling was done at Visit 2 (Day 1) and Visit 3 (Day 7 $\pm$2 days): for solution (TID) blood samples, 1 mL was collected before the morning dose (Time 0), then at 1, 2, 4 (before the noon dose), 5, 6, and 8 hours after dosing. For tablet (BID) blood samples, 1 mL was collected before the morning dose (Time 0) then at 3, 4, 8, and 12 hours after dosing.

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.

The study populations presented in this report are the:

- Pharmacokinetic population: all randomized patients with no major protocol deviations.
- Pharmacodynamic population: all randomized patients, with no protocol deviations that could impact the assessments of LPP, and who had a post-baseline assessment of LPP performed no more than 5 half-lives after the study drug intake (ie, 20 hours for solution, 40 hours for tablets), and who had a study drug exposure at the time of the post-baseline assessment of LPP at least equal to 3 days.
- Modified ITT population (mITT): all randomized and exposed patients who had a baseline and at least one post-baseline LPP assessment.
- Safety population: all randomized and exposed patients regardless of the amount of treatment administered.

All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 9.1. Treatment-emergent adverse events (TEAEs) were defined as AEs that developed or worsened or became serious during the on-treatment portion of the study or within 5 half-lives (2 days) following the last administration of alfuzosin. Treatment-emergent AEs were analyzed by preferred term, high-level term, high-level group term, and system organ class.

Summary:

Pharmacokinetic results:

With alfuzosin given as a solution to children 2 to 7 years-of-age, the accumulation ratios (AUC0-8 Day 7/AUC0-8 Day 1) were 1.02 at 0.1 mg/kg/day and 1.25 at 0.2 mg/kg/day.

With tablet administration to children and adolescents 8 to 16 years-of-age, the accumulation ratios (AUC0-12 Day 7/AUC0-12 Day 1) were 2.49 at 0.1 mg/kg/day and 1.67 at 0.2 mg/kg/day.

AUC0-8 on Day 7 in children 2 to 7 years-of-age who received the solution of alfuzosin at 0.2 mg/kg/day was 3.1-fold higher than that observed with 0.1 mg/kg/day versus a dose ratio of 2. A high total variability was also observed for both doses on Day 7 (56% at 0.2 mg/kg/day versus 37% at 0.1 mg/kg/day).

AUC0-12 on Day 7 in children and adolescents 8 to 16 years-of-age who received alfuzosin 0.2 mg/kg/day as tablets was 1.4-fold higher than that observed with 0.1 mg/kg/day versus a dose ratio of 2. A moderate total variability was observed for both doses on Day 7 (24% at 0.2 mg/kg/day versus 20% at 0.1 mg/kg/day).

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

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

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] N=6
Day 7 N=7 Rac	5.85±2.91 (50) [4.91]	3.00 (0.00-7.88)	56.5±11.4 (20) [55.5] N=5 [2.49]
		0.2 mg/kg/day	
Day 1 N=7	7.26±1.76 (24) [7.07]	3.93 (2.98-4.03)	50.0±15.4 (31) [48.0]
Day 7 N=7 Rac	12.4±2.85 (23) [12.1]	3.17 (2.98-4.02)	82.5±19.9 (24) [80.1] [1.67]

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

Pharmacokinetic results (cont'd):

Gender effect: ratio of geometric mean values of AUC0-8 for solution and of AUC0-12 for tablets

	Solution		Tablets	
	Female versus male		Female versus male	
	0.1 mg/kg/day	0.2 mg/kg/day	0.1 mg/kg/day	0.2 mg/kg/day
Day 1	1.08	0.71	1.15	1.21
Day 7	0.99	0.74	NC	0.83

NC: Not calculated since 1 male

With alfuzosin given as a solution to children 2 to 7 years-of-age, 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. With tablet administration to children and adolescents 8 to 16 years-of-age, the accumulation ratios (AUC_{0-12} Day 7/AUC_{0-12} Day 1) were 2.49 at 0.1 mg/kg/day and 1.67 at 0.2 mg/kg/day.

AUC_{0-8} on Day 7 in children 2 to 7 years-of-age who received the solution of alfuzosin at 0.2 mg/kg/day was 3.1-fold higher than that observed with 0.1 mg/kg/day versus a dose ratio of 2. A high total variability was also observed for both doses on Day 7 (56% at 0.2 mg/kg/day versus 37% at 0.1 mg/kg/day). AUC_{0-12} on Day 7 in children and adolescents 8 to 16 years-of-age who received alfuzosin 0.2 mg/kg/day as tablets was 1.4-fold higher than that observed with 0.1 mg/kg/day versus a dose ratio of 2. A moderate total variability was observed for both doses on Day 7 (24% at 0.2 mg/kg/day versus 20% at 0.1 mg/kg/day). The moderate deviation from dose proportionality for both formulations could be explained by the relative low number of subjects per dose and the variability of pharmacokinetics parameters.

No major gender effect was observed.

Pharmacodynamic results:

Pharmacodynamic results were too exploratory to draw reliable conclusion.

Safety results:

Both alfuzosin dose regimens were safe and well tolerated in both 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.

Issue date: 14-Mar-2008