



Clinical Study Synopsis for Public Disclosure

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Name of company: Boehringer Ingelheim		Tabulated Trial Report		 Boehringer Ingelheim Synopsis No.:
Name of finished product: Alna®		EudraCT No.: 2007-005310-39		
Name of active ingredient: Tamsulosin		Page: 1 of 4		
Module:		Volume:		
Report date: 29 APR 2009	Trial No. / U No.: 527.79 / U09-1398-01	Date of trial: 29 SEP 2008 – 08 DEC 2008	Date of revision (if applicable):	
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Title of trial:		An open label randomized two-way crossover study to investigate the effect of paroxetine mediated CYP2D6 inhibition on the single oral dose pharmacokinetics of tamsulosin in healthy male volunteers (CYP2D6 extensive metabolizers).		
Principal/Coordinating Investigator:		[REDACTED]		
Trial sites:		Human Pharmacology Centre, Boehringer Ingelheim Pharma GmbH & Co. KG, Germany		
Publication (reference):		None		
Clinical phase:		I		
Objectives:		To investigate the effect of CYP2D6 inhibition by paroxetine on the single oral dose pharmacokinetics of tamsulosin and to investigate the effect on safety and tolerability		
Methodology:		Open label randomized two-way crossover study in healthy male volunteers.		
No. of subjects:		planned: Entered: 24 (each treatment) actual: Entered: 24 (each treatment), Treated: 24 (each treatment), Analysed for primary endpoints: 24		
Diagnosis and main criteria for inclusion:		Healthy male, age ≥ 21 and ≤ 50 years, BMI range: ≥ 18.5 and ≤ 29.9 kg/m ²		
Test product:		Tamsulosin (Alna®) 0.4 mg MR capsule and paroxetine (Tagonis®)		
dose:		Tamsulosin: 0.4 mg q.d. on day 1 Paroxetine: 20 mg q.d. on days -7 to 2 10 mg q.d. on days -10 to -8 and 3 to 5		
mode of admin.:		Oral administration with 240 mL water		
batch no.:		not applicable		

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Reference therapy:	Tamsulosin 0.4 mg MR capsule			
dose:	0.4 mg			
mode of admin.:	Oral administration with 240 mL water			
batch no.:	not applicable			
Duration of treatment:	Tamsulosin: 1 day for both treatments, separated by at least 14 days Paroxetine: 15 days for the combination treatment			
Criteria for evaluation:	Pharmacokinetics:			
Efficacy / clinical pharmacology:	Primary endpoints: <ul style="list-style-type: none"> • Tamsulosin HCl pharmacokinetic parameters: C_{max} and $AUC_{0-\infty}$ Secondary endpoints: <ul style="list-style-type: none"> • Tamsulosin HCl pharmacokinetic parameters: AUC_{0-tz}, t_{max}, λ_z, $t_{1/2}$, MRT_{po}, CL/F, V_z/F $RC_{max,T/R}$, $RAUC_{0-\infty,T/R}$			
Safety:	Physical examination, vital signs (BP and PR supine and standing), 12-lead ECG, laboratory tests, adverse events, assessment of tolerability by investigator			
Statistical methods:	For the primary analyses, point estimators (geometric means) of the median intra-subject ratios of $AUC_{0-\infty}$, C_{max} , AUC_{0-tz} and their two-sided 90% confidence intervals (CIs) were derived. For the secondary analyses, descriptive statistics and tabular and graphical displays were used to summarize and evaluate the secondary endpoints.			

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SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results: After multiple administrations of 20 mg q.d. paroxetine (10 mg from days -10 to -8 followed by 20 mg from days -7 to 2 and 10 mg from days 3 to 5) with a single dose of tamsulosin HCl, the gMean plasma concentration-time profile of paroxetine reached the peak (14.9 ng/mL at 5 hours post dose) before the t_{max} (at 8 hours post dose) of tamsulosin HCl. The paroxetine steady-state trough concentrations on the day of tamsulosin administration ranged from 0.0817 to 17.7 ng/mL and suggest that the paroxetine dosing regimen adopted in this trial could adequately inhibit the metabolism of tamsulosin by CYP2D6.

In vitro results indicate that CYP3A4 and CYP2D6 are mainly involved in the metabolism of tamsulosin as well as some minor participation of other CYP isoenzymes [P99-00533][P96-8235]. Co-administration of 20 mg q.d. paroxetine with a single dose of 0.4 mg tamsulosin HCl increased the gMean values of C_{max} and $AUC_{0-\infty}$ of tamsulosin HCl by factors of approximately 1.3 and 1.6, respectively. With co-administration of 20 mg q.d. paroxetine, the apparent clearance (CL/F) of tamsulosin HCl was decreased by approximately 39% and the terminal half life of tamsulosin HCl was increased from 11.4 hours to 15.3 hours. These results suggest that paroxetine reduced the metabolic clearance of tamsulosin HCl via inhibition of CYP2D6 resulting in an increased exposure and a prolonged terminal half-life.

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Safety results:	<p>Twenty-two from 24 subjects experienced AEs during this study. All AEs were mild to moderate in intensity and fully reversible. Most of the AEs were due to the administration and co-administration of paroxetine. Typically, paroxetine related AEs are prominent in this study (agitation, insomnia, restlessness, headache, somnolence, tremor, diarrhoea, dizziness, and others). No deaths and no serious AEs occurred. No findings of clinical laboratory parameters, vital signs, or ECG were considered clinically relevant. Tolerability was assessed as good for 23 subjects and assessed as not satisfactory in one case. One subject experienced an orthostasis related AE, which was postural dizziness on the study day when paroxetine and tamsulosin HCl were co-administered. However this subject had no changes in blood pressure or pulse rate when measured instantaneous upon report. During orthostatic testing, no changes in blood pressure or pulse rate of clinical relevance were reported.</p> <p>Although, plasma levels of tamsulosin were higher in treatment B compared to treatment A, the co-administration of a single dose of 0.4 mg tamsulosin HCl to the strong CYP2D6 inhibitor paroxetine at steady state (after multiple doses of 20 mg) did not show any effect on vital signs that were of clinical significance. Overall, the combination treatment was safe and well tolerated.</p>
Conclusions:	<p>The co-administration of multiple oral doses of 20 mg paroxetine with a single oral dose of 0.4 mg tamsulosin HCl was safe and well tolerated. Compared to the administration of tamsulosin HCl alone, there was no change in vital parameters like blood pressure and pulse rate of clinical significance, although one subject reported postural dizziness. However, C_{max} and $AUC_{0-\infty}$ of tamsulosin HCl increased approximately 1.3 fold and 1.6 fold with co-administration of paroxetine. Therefore, FLOMAX® capsules should be used with caution in combination with strong inhibitors of CYP2D6, at doses higher than 0.4 mg q.d. (e.g. 0.8 mg q.d.).</p>