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Study No: S3B10939				
Title: An open-label, single-dose, randomized, two-period cross-over trial to evaluate the effect of alosetron administration (1 mg PO) on the pharmacokinetics of ibuprofen (600 mg PO) administration in healthy subjects.				
Rationale: Subjects with irritable bowel syndrome (IBS) are likely to use ibuprofen concomitantly with alosetron, and thus, the potential for interaction between ibuprofen and alosetron is of interest. Metabolism by the cytochrome P450 (CYP) 2 C 9 isoenzyme is one of the routes of elimination for ibuprofen. Although <i>in vitro</i> data have demonstrated that alosetron has no effect on CYP 2C9 metabolism, the isoenzyme is a major contributor to alosetron metabolism. This study was conducted to confirm that concomitant administration of alosetron with ibuprofen does not affect the pharmacokinetic profile of ibuprofen.				
Phase: I				
Study Period: 25 October 1999 – 16 November 1999.				
Study Design: An open-label, single-dose, randomized, two-period cross-over study.				
Centre: One centre in the USA.				
Indication: None.				
Treatment: Subjects were randomized to receive: Treatment A: ibuprofen 600 mg (3 x 200 mg). Treatment B: ibuprofen 600 mg (3 x 200 mg) + alosetron 1 mg. A washout period for at least 2 days occurred between dosing periods.				
Objectives: To determine the effect of single-dose concomitant administration of alosetron 1 mg orally (PO) on the pharmacokinetics of ibuprofen 600 mg PO in healthy subjects.				
Statistical Methods: Comparisons for evaluation of a drug interaction were the S(+)-ibuprofen pharmacokinetic parameters AUC from time zero extrapolated to infinity (AUC_{∞}) and time to maximal observed plasma concentration (C_{max}) obtained following single-dose ibuprofen alone compared with ibuprofen plus alosetron. \log_e -transformed parameters were analyzed using analysis of variance, allowing for subject, sequence, treatment and period. For each treatment geometric means and 95% confidence intervals (CI) were constructed. The difference in least squares means (reference: ibuprofen alone) and the corresponding 90% CI were back-transformed. The safety and pharmacokinetic populations included all those subjects who had taken any study drug.				
Study Population: Healthy, non-smoking subjects, aged 18 – 50 years, without any predisposing condition that might interfere with the absorption, excretion, metabolism or distribution of drugs or any previous gastrointestinal surgery (other than appendectomy or cholecystectomy >3 months prior to the study) were recruited.				
Number of Subjects: Twelve subjects were planned for the study. One female subject was discontinued and replaced prior to study start due to an inability to swallow the study drug.				
Planned N	12			
Recruited N	13			
Dosed N	12			
Completed n (%)	12 (92)			
Total Number Subjects Withdrawn N (%)	1 (8)			
Withdrawn due to Adverse Events n (%)	0			
Withdrawn due to Lack of Efficacy n (%)	0			
Withdrawn for Other Reasons (prior to dosing) n (%)	1 (8)			
Demographics				
N (Safety)	12			
Females: Males	8: 4			
Mean Age in Years (SD)	34.8 (8.9)			
Mean Weight in kg (SD)	72.8 (10.9)			
White n (%)	9 (75)			
Pharmacokinetic Endpoints: The table below provides the geometric mean and 95% CI's for the pharmacokinetic (PK) parameters.				
PK parameter	Ibuprofen 600 mg (A)		Ibuprofen 600 mg + Alosetron 1 mg (B)	
AUC_{∞} ($\mu\text{g}\cdot\text{h}/\text{mL}$)	92.49	(78.13, 109.48)	95.37	(81.40, 111.74)
C_{max} ($\mu\text{g}/\text{mL}$)	23.89	(20.70, 27.57)	22.88	(19.86, 26.35)

t _{1/2} (h)	2.41	(2.16, 2.69)	2.19	(1.92, 2.51)
λ _z (1/h)	0.288	(0.258, 0.321)	0.316	(0.276, 0.361)
t _{max} (h)*	1.26 (1.00, 3.00)		1.50 (1.00, 4.00)	
* median and range				
A summary of the log _e -transformed analysis for assessment of drug interaction is presented below.				
PK Parameter	Ratio (B/A)	90% CI		
AUC(∞) (μg.h/mL)	1.03	(1.00, 1.06)		
C _{max} (μg/mL)	0.96	(0.87, 1.06)		
t _{1/2} (h)	0.91	(0.85, 0.97)		
λ _z (1/h)	1.10	(1.03, 1.18)		
t _{max} (h)*	0.50 (B-A)	(0.00, 1.00)		
Safety results: There were no clinically significant changes in vital signs or laboratory values.				
Adverse Events: Adverse events were monitored from consent until final discharge.				
N (Safety)	12			
	Ibuprofen 600 mg	Ibuprofen 600 mg + Alosetron 1 mg		
No. subjects with AEs n (%)	2 (17)	1 (8)		
Serious Adverse Events, n (%) [n considered by the investigator to be related, possibly related, or probably related to study medication]:				
No. subjects with SAEs, n(%) -includes fatal and non-fatal events	0	0		

Publications:
No Publication

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