

The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

Study No: 558	
Title: An open, randomised, four-part crossover study to investigate the relative bioavailability of three new pharmacokinetically enhanced (PE) formulations of <i>Augmentin</i> in comparison to the standard immediate release (IR) formulation of <i>Augmentin</i> in healthy volunteers.	
Rationale: In this study, the pharmacokinetics of amoxicillin and clavulanate in three novel formulations were compared in order to select a formulation for further development. The aim of the new formulation was to provide more effective therapy against organisms of increasing resistance by increasing plasma concentration of amoxicillin over a longer period of time and ensuring susceptibility levels for <i>S. pneumoniae</i> close to 100%.	
Phase: I	
Study Period: 03 August 1999 to 22 September 1999.	
Study Design: An open-label, randomised, four-part, crossover study.	
Centres: One centre in the UK.	
Indication: None.	
Treatment: Each subject received the reference (IR) formulation and two of the three novel (PE) formulations, and underwent four dosing sessions: A single dose of the reference formulation was taken on the first dosing session; a single dose of one of the three novel formulations was taken on the second dosing session and a single dose of another new formulation was taken on the third and fourth dosing sessions. For Formulations A to C, two tablets were administered each containing: Formulation A: 562.5 mg amoxicillin trihydrate and 62.5 mg clavulanate (IR), 437.5 mg crystalline sodium amoxicillin (PE) formulated with 2% xanthan gum and 78mg citric acid per tablet. Formulation B: 562.5 mg amoxicillin trihydrate and 62.5 mg clavulanate (IR), 437.5 mg crystalline sodium amoxicillin (PE) formulated with 78mg citric acid per tablet. Formulation C: 562.5 mg amoxicillin trihydrate and 62.5 mg clavulanate (IR), 437.5 mg amoxicillin trihydrate (PE) formulated with 2% xanthan gum and 78mg citric acid per tablet. Formulation D was the reference formulation and consisted of one 500/125 amoxicillin/clavulanate tablet and three 500mg amoxicillin tablets.	
Objectives: To assess amoxicillin and clavulanate pharmacokinetics of three new PE formulations of amoxicillin/clavulanate in comparison with standard IR amoxicillin and amoxicillin/clavulanate potassium tablet in healthy volunteers.	
Statistical Methods: Amoxicillin maximum plasma concentration (C_{max}), following \log_e -transformation, and the time above minimum inhibitory concentration ($T > MIC$) were separately analysed by fitting a mixed effects model, with fixed effects sequence, period and regimen (formulation A, B, C and D) and random effects subject (sequence). Point estimates for the least-square means were calculated for each formulation, with accompanying 95% confidence intervals (CIs). For \log_e -transformed C_{max} , estimates and associated CIs were exponentially back transformed to provide least square means and 95% CIs on the original scale. All subjects who received at least one dose of study medication were included in the evaluation of clinical safety and tolerability. PK was assessed for all subjects who provided blood samples and were included in the formal statistical analysis for the study periods in which they participated.	
Study Population: Healthy male or female subjects, aged between 18 and 60 years inclusive, who were not allergic to penicillin (or chemically related) antibiotics. Key exclusion criteria included use of any prescription or non-prescription medication, pregnancy, and positive hepatitis tests. Adequate contraceptive measures were required for females of child-bearing potential.	
Number of Subjects:	All Subjects
Planned N	12
Dosed N	12
Completed n (%)	11 (91.7)
Total Number Subjects Withdrawn n (%)	1 (8.3)
Withdrawn due to Adverse Events n (%)	0
Withdrawn due to Lack of Efficacy n (%)	Not applicable
Withdrawn for Other Reasons n (%)	1 (8.3)
Demographics	All Subjects
N (ITT)	12

Females: Males	8: 4			
Mean Age in Years (SD)	36 (9.6)			
Mean Weight in kg (SD)	70 (7.0)			
White n (%)	12 (100)			
Pharmacokinetic (PK) Results:				
PK parameter	Formulation A (n=7)	Formulation B (n=8)	Formulation C (n=8)	Formulation D (n=12)
Amoxicillin				
C _{max} (mcg/mL)				
Arithmetic Mean (SD)	17.4 (1.95)	17.4 (6.10)	20.5 (7.61)	23.8 (5.73)
Least square mean ^a (95% CI)	17.7 (14.3, 22.0)	15.7 (12.8, 19.3)	18.9 (15.4, 23.1)	23.1 (19.0, 28.0)
T _{max} (hours)				
Median (range)	1.75 (1.00 to 2.02)	1.52 (1.25 to 3.00)	2.13 (0.98 to 5.07)	1.50 (1.00 to 2.03)
AUC _(0 to infinity) (mcg.h/mL)				
Arithmetic Mean (SD)	75.6 (18.7)	70.7 (25.4)	71.4 (22.8)	69.5 (15.6)
T _{1/2} (hours)				
Arithmetic Mean (SD)	1.32 (0.25)	1.25 (0.15)	1.21 (0.09)	1.33 (0.16)
T>MIC (hours)				
Arithmetic Mean (SD)	6.0 (1.3)	5.9 (1.3)	5.1 (1.0)	4.9 (1.0)
Least square mean ^b (95% CI)	5.9 (5.0, 6.8)	6.2 (5.3, 7.1)	5.0 (4.1, 5.8)	4.9 (4.1, 5.7)
T>MIC (%)				
Arithmetic Mean (SD)	50 (11)	49 (10)	42 (9)	41 (8)
Clavulanate				
C _{max} (mcg/mL)				
Arithmetic Mean (SD)	1.99 (0.58)	1.88 (0.58)	2.27 (0.32)	1.00 (0.38)
T _{max} (hours)				
Median (range)	1.02 (1.00 to 3.00)	1.66 (1.25 to 3.00)	1.40 (0.98 to 2.00)	1.26 (1.00 to 2.00)
AUC _(0 to infinity) (mcg.h/mL)				
Arithmetic Mean (SD)	5.43 (1.24)	5.18 (1.49)	5.84 (0.89)	2.47 (0.89)
AUC _(0 to t)				
Arithmetic Mean (SD)	5.32 (1.22)	5.07 (1.50)	5.70 (0.91)	2.37 (0.91)
T _{1/2} (hours)				
Arithmetic Mean (SD)	1.06 (0.143)	1.03 (0.079)	1.00 (0.10)	1.06 (0.07)
a represents adjusted geometric means. b represents adjusted arithmetic means. AUC _(0 to infinity) Area under the plasma concentration-time curve extrapolated to infinity; AUC _(0 to t) Area under the plasma concentration-time curve from time zero to the last quantifiable plasma concentration; T _{1/2} Terminal elimination half-life; T _{max} Time to reach maximum plasma concentration.				
Safety Results: Safety Population -Adverse event (AE) data were collected from 0.5 hours pre-dose, 12 hours post-dose on each dosing day and at follow-up (within 15 days of the last dose of the study). AEs spontaneously reported by the subject were also recorded.				
Adverse Events:	Formulation A	Formulation B	Formulation C	Formulation D
N (ITT)	8	8	8	12
No. subjects with AEs n (%)	4 (50.0)	3 (37.5)	3 (37.5)	5 (41.7)
Most Frequent AEs				
Headache	1 (12.5)	2 (25.0)	2 (25.0)	2 (16.7)
Diarrhoea	1 (12.5)	1 (12.5)	2 (25.0)	0
Upper respiratory tract infection	2 (25.0)	0	0	0
Serious Adverse Events, n (%) [n considered by the investigator to be related to study medication]:				
N	8	8	8	12
No. subjects with SAEs, n (%) [related] -includes fatal and non-fatal events	0	0	0	0

Publications:
No Publication

Date Updated: 10-Oct-05