ASTRA
ASTRA HÄSSLE

DRUG PRODUCT		**Synopsis**	(FOR NATIONAL AUTHORITY USE ONLY)
DRUG SUBSTANCE	H 199/18	REFERRING TO PART OF THE DOSSIER	
DOCUMENT NO.	SH-QBE-0040		
VERSION NO.	01		
STUDY CODE	SH-QBE-0040		
DATE	10 February, 1999		

An interaction study between H 199/18 b.i.d., amoxicillin b.i.d. and clarithromycin b.i.d. in healthy male and female subjects.

STUDY CENTRE

Single centre study

STUDY PERIOD

- **DATE OF FIRST PATIENT ENROLLED** 23 January, 1998
- **DATE OF LAST PATIENT COMPLETED** 14 May, 1998

PHASE OF DEVELOPMENT

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OBJECTIVES

The primary objective of this study was to investigate the presence of any pharmacokinetic interactions between H 199/18 20 mg b.i.d., amoxicillin 1 g b.i.d. and clarithromycin 500 mg b.i.d. after repeated administration to healthy male and female subjects.

The secondary objective was to evaluate the safety of H 199/18 alone and in combination with amoxicillin and clarithromycin.

STUDY DESIGN

Open, randomised, four-way cross-over study

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

Healthy male and female subjects

TEST PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

H 199/18 capsule 20 mg, batch no. H 1189-04-01-04, oral dose of 20 mg b.i.d.
Clarithromycin tablets 250 mg (Bremon®), batch no. H 1031-04-01-02, oral dose of 500 mg b.i.d.
Amoxicillin tablets 1 g (Clamoxyl®), batch no. H 1035-03-01-05, oral dose of 1 g b.i.d.
Triple combination (H 199/18 capsule 20 mg b.i.d. orally, amoxicillin 1 g b.i.d. orally and clarithromycin 500 mg b.i.d. orally), batch numbers as above.

DURATION OF TREATMENT

Four study periods, each consisting of seven days, separated by wash-out periods of 14-28 days.

MAIN VARIABLES:

- PHARMACOKINETICS

The area under the plasma concentration vs time curve during the dosing interval (AUC_τ), the maximum observed plasma concentration (C_{max}) and the elimination half-life ($t_{1/2}$) of the parent drugs and their metabolites.

STATISTICAL METHODS

The log-transformed AUC_τ, C_{max} and $t_{1/2}$ of each of the three parent drugs (H199/18, amoxicillin and clarithromycin) and measured metabolites, were analysed using a mixed model ANOVA (Analyses of Variance) with fixed effects for sequence, period and treatment and a random effect for subjects within sequence. Each drug was analysed separately.
The results were finally anti-logarithmized and stated as:
a) Estimates (geometric means) of AUC_τ, C_{max} and $t_{1/2}$ and 95% confidence intervals for the true geometric means during treatment with each drug alone and with the combination.
b) Estimates of the ratios for combination treatment to drug alone for AUC_τ, C_{max} and $t_{1/2}$, 95% confidence intervals for the true ratios and p-values for tests of equal geometric means during treatment with each drug alone and during treatment with the combination.

SUBJECTS

	Total
No. planned	20
No. randomised and treated	20
Males/Females	11/9
Mean age (range)	28.2 years (22-44)
No. analysed for pharmacokinetics	19
No. analysed for safety	20
No. completed	19

SUMMARY

- PHARMACOKINETIC RESULTS

Ratios of estimated geometric means, 95% confidence intervals (CI) and p-values of AUC_τ, C_{max} and $t_{1/2}$ for H 199/18, amoxicillin, clarithromycin and triple combination are presented in Table 1.

For H 199/18, there was a more than two-fold higher AUC_τ, during the triple combination compared to monotherapy (11.29 and 4.97 µmol·h/L, respectively). For C_{max}, there was a 39% increase during the triple combination compared to monotherapy (3.23 and 2.33 µmol/L, respectively). The $t_{1/2}$ was prolonged by 50% during the triple combination compared to monotherapy (1.63 and 1.09 hours, respectively).

The AUC_τ and C_{max} for amoxicillin during the triple combination (90.28 µmol·h/L and 32.92 µmol/L, respectively) were similar to those observed in treatment with amoxicillin alone. The $t_{1/2}$ was slightly but statistically significantly prolonged by 12% when amoxicillin was given in the triple combination compared to monotherapy (1.63 and 1.46 hours, respectively).

The AUC_τ, C_{max}, and $t_{1/2}$ for clarithromycin were not significantly changed during triple combination treatment (23.35 µmol·h/L, 3.10 µmol/L, 4.55 hours, respectively) as compared to monotherapy.

Table 1. Ratios, limits for 95% CI and p-values for tests of equal geometric means of AUC_τ (µmol·h/L), C_{max} (µmol/L) and $t_{1/2}$ (h) following repeated oral administration of H 199/18 20 mg b.i.d. (H), amoxicillin 1 g b.i.d. (A), clarithromycin 500 mg b.i.d. (C) or a triple combination (H199/18 20 mg b.i.d., amoxicillin 1 g b.i.d. and clarithromycin 500 mg b.i.d.;HAC) to healthy subjects.

	Ratio of estimated geometric mean	95% confidence interval lower	upper	p-value
AUC_t				
H 199/18 (HAC/H)	2.27	2.00	2.58	<0.001
Amoxicillin (HAC/A)	1.01	0.90	1.14	0.85
Clarithromycin (HAC/C)	1.14	0.99	1.30	0.060
C_{max}				
H 199/18 (HAC/H)	1.39	1.24	1.55	<0.001
Amoxicillin (HAC/A)	1.14	0.96	1.35	0.12
Clarithromycin (HAC/C)	1.16	0.98	1.38	0.086
$t_{1/2}$				
H 199/18 (HAC/H)	1.50	1.39	1.61	<0.001
Amoxicillin (HAC/A)	1.12	1.03	1.22	0.008
Clarithromycin (HAC/C)	0.88	0.77	1.01	0.059

For 14-hydroxyclarithromycin, both the AUC_τ and C_{max} were 53% higher during treatment with the triple combination (13.18 µmol·h/L and 1.43 µmol/L, respectively) than during monotherapy. The $t_{1/2}$ for the metabolites was approximately 8.2 hours after both treatment arms.

The AUC_τ values for the sulphone, hydroxy and desmethyl metabolites of H 199/18 were 7.55, 0.46, and 0.32 µmol·h/L, respectively, during monotherapy. The corresponding values during the triple combination treatment were 6.18. 0.48 and 0.46 µmol·h/L, respectively.

- **SAFETY RESULTS**

A total of 60 AEs were reported for the 20 subjects during the entire study (including wash-out periods). Most AEs were reported during the triple combination. Headache, diarrhoea, flatulence and taste perversion were the most common AEs. Diarrhoea and taste perversion, which are well known side effects of antibiotics, were most frequently reported during the triple combination, amoxicillin and clarithromy cin treatments.

DATE OF THE REPORT

10 February, 1999