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-0034		
VERSION NO.	01		
STUDY CODE	SH-QBE-0034		
DATE	10 February, 1999		

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

STUDY CENTRE

Single-centre study

STUDY PERIOD

- **DATE OF FIRST ENROLMENT** 2 December, 1997
- **DATE OF LAST COMPLETED** 31 March, 1998

PHASE OF DEVELOPMENT

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OBJECTIVES

The objectives of the study were to investigate possible pharmacokinetic interactions between 40 mg H 199/18 o.m., 1 g amoxicillin b.i.d. and 500 mg clarithromycin b.i.d. after repeated administration to healthy male and female subjects and 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

MAIN CRITERIA FOR INCLUSION

Healthy male and female subjects.

TEST PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

H 199/18 capsule 40 mg o.m. orally, batch nos. H 1222-04-01-04, H 1222-04-01-05
Amoxicillin 1 g b.i.d. orally, batch no. H 1034-02-01-03

Clarithromycin 500 mg (Bremon®) b.i.d. orally, batch no. H 1031-04-01-02
Triple combination (H 199/18 capsule 40 mg o.m. orally, amoxicillin 1 g b.i.d. orally and clarithromycin 500 mg b.i.d. orally)

DURATION OF TREATMENT

Four treatment periods 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 observed maximum drug concentration in plasma (C_{max}) and the elimination half-life ($t_{1/2}$) were estimated for H 199/18, amoxicillin, clarithromycin and 14-hydroxyclarithromycin.

STATISTICAL METHODS

The log-transformed AUC_τ, C_{max} and $t_{1/2}$ for each of the three drugs (H 199/18, amoxicillin and clarithromycin) and the metabolite 14-hydroxyclarithromycin were analysed using a mixed model ANOVA with fixed effects for sequence, period and treatment and a random effect for subjects within sequence. Each drug was analysed separately. The results 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 the drug alone and during combination treatments.

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 the drug alone and during combination treatments.

SUBJECTS

	Total
No. planned	20
No. randomised and treated	20
Males/Females	16/4
Mean age (range)	26.5 years (20-37)
No. analysed for pharmacokinetics	18 (H 199/18)
	17 (amoxicillin)
	18 (clarithromycin)
	18 (14-hydroxyclarithromycin)
No. analysed for safety	20
No. completed	17

SUMMARY

- PHARMACOKINETIC RESULTS

Ratios, 95% confidence intervals (CI) and p-values of AUC_τ , C_{max} and $t_{1/2}$ of H 199/18, amoxicillin, clarithromycin, 14-hydroxyclarithromycin and triple combination are presented in Table 1.

The AUC_τ of H 199/18 increased by 70% during the triple drug combination compared to when H 199/18 was given alone (22.69 µmol·h/L and 3.31µmol·h/L, respectively). C_{max} of H 199/18 was 18 % higher during the combination treatment than during treatment with H 199/18 alone (5.84 µmol/L and 4.94 µmol/L, respectively). The $t_{1/2}$ of H 199/18 was prolonged by 35% during triple drug combination compared to monotherapy (2.1 and 1.55 hours, respectively). The AUC_τ , C_{max} and $t_{1/2}$ of amoxicillin were similar during the triple drug combination (95.0 µmol·h/L, 32.4 µmol/L and 1.57 hours, respectively) to those during treatment with amoxicillin alone. For clarithromycin, the AUC_τ , C_{max} and $t_{1/2}$ were also similar during the combination treatment (24.63 µmol·h/L, 3.13 µmol/L and 5.60 hours, respectively) compared to when clarithromycin was given alone. AUC_τ for 14-hydroxyclarithromycin was 19 % higher during triple combination than during treatment with clarithromycin alone (10.72 µmol·h/L and 9.04 µmol·h/L, respectively). The C_{max} was 22% higher during the triple drug combination than during mono therapy (1.17 µmol/L and 0.96 µmol/L, respectively).

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 40 mg H 199/18 o.m.(H), 1 g amoxicillin b.i.d. (A), 500 mg clarithromycin b.i.d. (C) or a triple combination (40 mg H 199/18 o.m., 1 g amoxicillin b.i.d. and 500 mg clarithromycin b.i.d.) (HAC) to healthy subjects are presented.

	Ratio of estimated geometric mean	95% confidence interval		p-value
		lower	upper	
AUC_τ				
199/18 (HAC /H)	1.70	1.40	2.08	<0.001
Amoxicillin (HAC/A)	1.03	0.93	1.14	0.56
Clarithromycin (HAC/C)	1.03	0.87	1.23	0.70
14-hydroxyclarithromycin (HAC/C)	1.19	1.04	1.35	0.015
C_{max}				
199/18 (HAC /H)	1.18	1.00	1.40	0.050
Amoxicillin (HAC/A)	1.07	0.98	1.17	0.14
Clarithromycin (HAC/C)	1.12	0.91	1.37	0.25
14-hydroxyclarithromycin (HAC/C)	1.22	1.06	1.39	0.008
$t_{1/2}$				
199/18 (HAC /H)	1.35	1.19	1.54	<0.001
Amoxicillin (HAC/A)	1.02	0.91	1.14	0.68
Clarithromycin (HAC/C)	1.05	0.91	1.22	0.48
14-hydroxyclarithromycin (HAC/C)	0.82	0.65	1.04	0.087

The elimination phase for clarithromycin and 14-hydroxyclarithromycin was not complete on day 7 for subjects 1, 7, 9, 14 and 18. The estimated $t_{1/2}$ was therefore unreliable for these subjects and not included in the statistical analyses. The evaluation of the $t_{1/2}$ is thus based on data from only 13 subjects and should be interpreted with caution.

- **SAFETY RESULTS**

A total of 91 AEs was reported for the 20 subjects during the entire study (including wash-out periods). Diarrhoea, headache, flatulence and taste perversion were the most common AEs. These were most frequently reported during triple combination, amoxicillin and clarithromycin treatments and are wellknown side effects of antibiotics.

DATE OF THE REPORT

10 February, 1999