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-0044		
VERSION NO.	01		
STUDY CODE	SH-QBE-0044		
DATE	7 May, 1999		

A food interaction study regarding pharmacokinetics and effect on intragastric pH following treatment with H 199/18 capsules in healthy male and female subjects

STUDY CENTRE

Single centre study

STUDY PERIOD

- **DATE OF FIRST ENROLMENT** 18 May, 1998
- **DATE OF LAST COMPLETED** 1 July, 1998

PHASE OF DEVELOPMENT

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OBJECTIVES

The primary objectives were to compare the pharmacokinetics and the effect on 24-hour intragastric pH of H 199/18 capsule 40 mg when given together with food and under fasting conditions on days 1 and 5.

The secondary objectives were to compare the pharmacokinetics and the effect on 24-hour intragastric pH in males and females and to assess the safety and tolerability of H 199/18.

STUDY DESIGN

Open, randomised, two-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, batch no. H 1222-04-01-05, oral dose of 40 mg o.m.

COMPARATOR PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

None

DURATION OF TREATMENT

Two periods of 5 days separated by 14 days

MAIN VARIABLES:

The total area under the plasma concentration versus time curve (AUC), the observed maximum plasma concentration (C_{max}) and the percentage of time with intragastric pH>4.

STATISTICAL METHODS

For the evaluation of a potential food interaction, the log-transformed variables AUC and C_{max} and the percentage of time with intragastric pH>4 were analysed using a mixed model ANOVA (Analysis of Variance) with fixed effects for sequence, period and treatment and a random effect for subject within sequence. Comparisons of the treatments, under fed and fasting conditions, were made for day 1 as well as for day 5.

The differences between males and females in log-transformed AUC_t, AUC and C_{max} and for the percentage of time with pH>4 were analysed with a two sample t-test. This was done for each treatment separately. For both treatments, the analyses were performed for day 1 as well as for day 5.

SUBJECTS

	Total
No. planned	24
No. randomised and treated	24
Males/Females	12/12
Mean age (range)	29.8 years (23-42)
	Males: 28.9 years (23.8-35)
	Females: 31.8 years (23.1-42.1)
No. analysed for clinical pharmacology	23
No. analysed for safety	24
No. completed	23

SUMMARY

- **CLINICAL PHARMACOLOGY RESULTS**

Food intake resulted in delayed and decreased absorption of H 199/18 (Table 1). On day 1 the estimated geometric mean for AUC decreased (53%) from 4.0 to 1.9 μmol·h/L and for C_{max} it decreased (79%) from 2.8 to 0.6 μmol/L. The decrease in AUC and C_{max} was less pronounced on day 5 (43 and 61%, respectively). The mean t_{max}, on both days 1 and 5, was approximately 1.5 hours under fasting conditions and 4-5 hours after food intake. Despite these differences in pharmacokinetic food interaction, there were only minor changes in time with intragastric pH>4 when comparing fed and fasting conditions. The difference in percentage of time with intragastric pH>4 between fed and fasting conditions was -3.7% (CI: -10.6% to 3.1%) on day 1 and -2.2% (CI: -8.5% to 4.1%) on day 5.

Under fasting conditions, there were no statistically significant differences between males and females regarding AUC, C_{max} or time with pH>4. However, after food intake, the AUC and C_{max} values on day 1 were 41% and 57% lower in females as compared to males. On day 5, the differences were not statistically significant. Also, the time with pH>4 after food intake was longer in males than in females, however, statistically significant only on day 5.

Table 1. Ratios of geometric means of AUC and C_{max} of H 199/18 after food intake and under fasting conditions following daily oral doses of H 199/18 capsule 40 mg to healthy subjects. Estimates, limits for 90% CI and p-values for tests of equal geometric means are presented (n=23).

Day		Estimated geometric mean	90% confidence interval lower	upper	p-value
1	**AUC** (n=20)*				
	After food/Fasting	0.47	0.36	0.60	<0.001
	C_{max}				
	After food/Fasting	0.21	0.14	0.30	<0.001
5	**AUC**				
	After food/Fasting	0.57	0.50	0.65	<0.001
	C_{max}				
	A/fter food/Fasting	0.39	0.33	0.45	<0.001

*AUC was not calculated for subject 107, 209 and 211 on day 1 due to high residual areas (AUC_{extr} 29-61%)

Table 2. Means of percentage of time with pH>4 (%) and the difference of the means after food intake and under fasting conditions following daily oral doses of H 199/18 capsule 40 mg to healthy subjects. Estimates, limits for 95% CI and p-values for tests of equal means are presented (n=23).

	Estimated mean	95% confidence interval lower	upper	p-value
Day 1				
After food	22.6	16.8	28.5	
Fasting	26.4	20.5	32.2	
After food-Fasting	-3.7	-10.6	3.1	0.27
Day 5				
After food	56.1	49.7	62.4	
Fasting	58.3	51.9	64.6	
After food-Fasting	-2.2	-8.5	4.1	0.48

- **SAFETY RESULTS**

A total of 29 AEs were reported for 18 of the 24 subjects in the study. Flatulence and headache were the most common AEs and all AEs were reported as mild or moderate in intensity.

DATE OF THE REPORT

7 May, 1999