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-0037		
VERSION NO.	01		
STUDY CODE	SH-QBE-0037		
DATE	9 February, 1999		

A pharmacokinetic study of H 199/18 in elderly male and female subjects

STUDY CENTRE

Single centre study

STUDY PERIOD **PHASE OF DEVELOPMENT**

- **DATE OF FIRST ENROLMENT** 21 November, 1997 I
- **DATE OF LAST COMPLETED** 19 December, 1997

OBJECTIVES

The primary objective was to study the pharmacokinetics of H 199/18 and its main metabolites in elderly male and female subjects.

The secondary objective was to evaluate the tolerability of H 199/18 in elderly subjects.

STUDY DESIGN

Open one-way study

MAIN CRITERIA FOR INCLUSION

Elderly male and female subjects aged between 70 and 80 years.

TEST PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

H 199/18 capsule 40 mg o.m. orally, batch no. H 1222-04-01-04

COMPARATOR PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

There was no comparator product in this study.

DURATION OF TREATMENT

Five days (single dose daily for 5 days).

MAIN VARIABLES:

- PHARMACOKINETICS

The total area under the plasma concentration vs time curve (AUC), the area under the plasma concentration versus time curve up to the last quantifiable concentration (AUC_t), the observed maximum concentration (C_{max}), the elimination half-life ($t_{1/2}$) and the time of maximum plasma concentration (t_{max}).

STATISTICAL METHODS

Descriptive statistics were calculated for the pharmacokinetic parameters from day 1 and day 5. Also, 95% confidence intervals were calculated for the true geometric mean of AUC and $C_{max.}$

SUBJECTS

	Total
No. planned	14
No. randomised and treated	14
Males/Females	6/8
Mean age (range)	74.2 years (71-80)
No. analysed for pharmacokinetics	14 (study day 1) 13 (study day 5)
No. analysed for safety	14
No. completed	13

SUMMARY

- PHARMACOKINETIC RESULTS

Geometric means and 95% confidence intervals (CI) of AUC and C_{max} for H 199/18, the sulphone and the hydroxy metabolites on days 1 and 5 are presented in Tables 1-2. AUC and C_{max} for H 199/18 increased by 94% and 52%, respectively, on day 5 compared to those on day 1.

The values of AUC and C_{max} on day 5 in this study were compared with those from an earlier study in GERD patients with a mean age of 45.2 years (range 29-58) treated with H 199/18 40 mg daily for five days. The ratio of the AUC values in the present study to that in GERD patients was 1.25 (CI; 0.94 to 1.67). The ratio for C_{max} was 1.18 (CI; 0.91 to 1.52). The differences in AUC and C_{max} were not statistically significant.

Table 1. Geometric means for *AUC (µmol·h/L)* of H 199/18, the sulphone metabolite and the hydroxy metabolite following oral doses of 40 mg of H 199/18 on day 1 (n=14) and on day 5 (n=13) to elderly subjects. Estimates and limits of 95% CI are presented.

	Geometric mean	95% confidence interval	
		lower	upper
Day 1			
H 199/18	8.25	5.73	11.88
Sulphone metabolite	10.77	6.78	17.13
Hydroxy metabolite	0.76	0.64	0.90
Day 5			
H 199/18	15.98	12.79	19.97
Sulphone metabolite	27.36	20.55	36.41
Hydroxy metabolite	0.78	0.71	0.87

Table 2. Geometric means for C_{max} *(µmol/L)* of H 199/18, the sulphone metabolite and the hydroxy metabolite following oral doses of 40 mg of H 199/18 on day 1 (n=14) and on day 5 (n=13) to elderly subjects. Estimates and limits of 95% CI are presented.

	Geometric mean	95% confidence interval	
		lower	upper
Day 1			
H 199/18	3.67	2.90	4.66
Sulphone metabolite	1.32	1.08	1.62
Hydroxy metabolite	0.28	0.24	0.32
Day 5			
H 199/18	5.57	4.71	6.58
Sulphone metabolite	2.16	1.83	2.55
Hydroxy metabolite	0.21	0.19	0.24

- **SAFETY RESULTS**

Eighteen Adverse Events (AEs) were reported for 9 of the 14 subjects during active treatment with H 199/18. The AEs reported were of mild to moderate intensity and of a kind commonly seen in a study population of healthy subjects e.g. headache.

DATE OF THE REPORT

9 February, 1999