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-0035		
VERSION NO.	01		
STUDY CODE	SH-QBE-0035		
DATE	7 May, 1999		

A bioequivalence study with 40 mg H 199/18 comparing a new tablet formulation with a capsule formulation in healthy subjects

STUDY CENTRE

Single centre study

STUDY PERIOD

- **DATE OF FIRST ENROLMENT** 27 February, 1998
- **DATE OF LAST COMPLETED** 14 May, 1998

PHASE OF DEVELOPMENT

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OBJECTIVE

To investigate if a 40 mg MUPS tablet formulation of H 199/18 is bioequivalent to the phase III capsule formulation during single and multiple dosing regimens

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 MUPS tablet 40 mg, batch no. H 1365-01-01-01, once daily dose of 40 mg for five days

COMPARATOR PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

H 199/18 phase III capsule 40 mg, batch no. H 1222-04-01-05, once daily dose of 40 mg for five days.

DURATION OF TREATMENT

Two periods of five days separated by at least 13 days.

MAIN VARIABLES:

- **PHARMACOKINETICS**

The main pharmacokinetic variables were the total area under the plasma concentration versus time curve (AUC), the area under the plasma concentration versus time curve up to the last quantifiable concentration (AUC_t) and the observed maximum plasma concentration (C_{max}) following treatments on day 1 and day 5.

STATISTICAL METHODS

The log-transformed variables AUC, AUC_t, and C_{max} were analysed using a mixed model ANOVA (analysis of variance) with fixed effects for sequence, period and treatment (MUPS tablet or capsule) and a random effect for subjects within sequence. Data from day 1 and day 5 were analysed separately.

An interim analysis was to be performed after 36 evaluable subjects. If the ratio (MUPS tablet/capsule) of geometric means for C_{max} as well as the 94% confidence intervals for the ratio of geometric means for AUC and AUC_t on day 1 and day 5 were all contained in the interval of 0.80-1.25, then the trial was to be stopped and the capsule and the MUPS tablet were to be considered bioequivalent. Otherwise, the study was to continue with an additional 36 subjects and new estimates and confidence intervals, based on all available data, were to be calculated and the same criteria for bioequivalence were to be applied.

The confidence levels were adjusted in order to compensate for the interim analysis.

SUBJECTS

	Total
No. planned	72 (36 in the first step)
No. randomised and treated	40
Males/Females	29/11
Mean age (range)	26.8 years (20-46)
No. analysed for pharmacokinetics	36
No. analysed for safety	40
No. completed	36

SUMMARY

- PHARMACOKINETIC RESULTS

As the interim analysis showed that the stated criteria of bioequivalence had been fullfilled, the study was stopped after completion of the first step.

The estimates of the true geometric means with 94% confidence intervals for AUC, AUC_t and C_{max} are shown in Tables 1-3.

The plasma elimination half-life ($t_{1/2}$) was similar for the two formulations during both single (approximately 1 hour) and multiple(approximately 1.25 hours) dosing regimens. The time to the maximum plasma concentration (t_{max}) was almost 2 hours for both formulations both during single and multiple dosing regimens.

Table 1. Geometric means and the ratio of geometric means for *AUC (µmol·h/L)* on day 1 and day 5 following administration of daily doses of 40 mg H 199/18 as a MUPS tablet or a phase III capsule. Estimates, limits for 94% CI and a p-value for the test of equal geometric means are presented (n=36).

Day		Estimated geometric mean	94% confidence interval lower	upper	p-value
1	H 199/18 Capsule (A)	5.06	3.93	6.51	
	H 199/18 MUPS tablet (B)	4.95	3.85	6.37	
	B/A	0.98	0.88	1.08	0.68
5	H 199/18 Capsule (A)	11.19	9.60	13.03	
	H 199/18 MUPS tablet (B)	10.82	9.29	12.60	
	B/A	0.97	0.89	1.05	0.42

Table 2. Geometric means and the ratio of geometric means for *AUC_t (µmol·h /L)* on day 1 and day 5 following administration of daily doses of 40 mg H 199/18 as a MUPS tablet or a phase III capsule. Estimates, limits for 94% CI and a p-value for the test of equal geometric means are presented (n=36).

Day		Estimated geometric mean	94% confidence interval lower	upper	p-value
1	H 199/18 Capsule (A)	4.99	3.87	6.42	
	H 199/18 MUPS tablet (B)	4.87	3.79	6.27	
	B/A	0.98	0.88	1.08	0.67
5	H 199/18 Capsule (A)	11.04	9.48	12.86	
	H 199/18 MUPS tablet (B)	10.69	9.18	12.45	
	B/A	0.97	0.89	1.05	0.43

Table 3. Geometric means and the ratio of geometric means for C_{max} *(µmol/L)* on day 1 and day 5 following administration of daily doses of 40 mg H 199/18 as a MUPS tablet or a phase III capsule. Estimates, limits for 94% CI and a p-value for the test of equal geometric means are presented (n=36).

Day		Estimated geometric mean	94% confidence interval lower	upper	p-value
1	H 199/18 Capsule (A)	2.64	2.18	3.21	
	H 199/18 MUPS tablet (B)	2.62	2.15	3.18	
	B/A	0.99	0.85	1.15	0.89
5	H 199/18 Capsule (A)	4.71	4.17	5.34	
	H 199/18 MUPS tablet (B)	4.43	3.91	5.01	
	B/A	0.94	0.86	1.03	0.20

- **SAFETY RESULTS**

A total of 57 AEs was reported for 29 of the 40 subjects during the entire study (including wash-out periods). Fourteen AEs were reported for 12 subjects during active treatment with H 199/18 capsule 40 mg and 30 AEs were reported for 18 subjects during active treatment with H 199/18 MUPS tablet 40 mg.

Headache was the most commonly reported AE during the active treatment periods.

The results from the ECG measurements do not indicate any effect of H 199/18 on the electrophysiology of the heart.

DATE OF THE REPORT

7 May, 1999