ASTRA
ASTRA HÄSSLE

DRUG PRODUCT		**Synopsis**	(FOR NATIONAL AUTHORITY USE ONLY)
DRUG SUBSTANCE(S)	H 199/18	REFERRING TO PART OF THE DOSSIER	
DOCUMENT NO.	SH-QBE-0033		
VERSION NO.	01		
STUDY CODE	SH-QBE-0033		
DATE	20 April, 1999		

A bioequivalence study with 20 mg H 199/18 comparing a new tablet formulation with a capsule formulation in healthy subjects.

STUDY CENTRE(S)

Single centre study

STUDY PERIOD

- **DATE OF FIRST PATIENT ENROLLED** 2 April, 1998
- **DATE OF LAST PATIENT COMPLETED** 11 June, 1998

PHASE OF DEVELOPMENT

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OBJECTIVES

To investigate if a phase III capsule formulation and a MUPS tablet formulation of 20 mg H 199/18 are bioequivalent during single and repeated dose administration.

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 20 mg, batch no. H 1370-01-01-01, once-daily dose of 20 mg for five days

COMPARATOR PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

H 199/18 phase III capsule 20 mg, batch no. H 1189-04-01-04, once-daily dose of 20 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}) on days 1 and 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 each 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 the geometric means for C_{max} and the 94% confidence intervals (CI) 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, 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	38
Males/Females	19/19
Mean age (range)	25.2 years (20-35)
No. analysed for pharmacokinetics	34
No. analysed for safety	38
No. completed	34

SUMMARY

- PHARMACOKINETIC RESULTS

As the interim analysis showed that the stated criteria for bioequivalence had been fulfilled, 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 elimination half-life ($t_{1/2}$) was similar for the two formulations during both single (approximately 0.8 hour) and multiple (approximately 1.1 hours) dosing regimens. The time to the maximum plasma concentration (t_{max}) was approximately 1.5 hours for both formulations after both single and multiple dosing.

Table 1. Geometric means of *AUC (µmol·h/L)* and the ratio for *AUC* on day 1 and day 5 following administration of once-daily doses of 20 mg H 199/18 as a MUPS tablet or phase III capsule. Estimates, limits for 94% CI and a p-value for the test of equal geometric means are presented (n=34).

Day		Estimated geometric mean	94% confidence interval lower	upper	p-value
1	H 199/18 MUPS tablet (A)	2.17	1.77	2.65	
	H 199/18 Capsule (B)	2.12	1.74	2.59	
	A/B	1.02	0.93	1.12	0.64
5	H 199/18 MUPS tablet (A)	4.77	4.06	5.61	
	H 199/18 Capsule (B)	4.73	4.02	5.56	
	A/B	1.01	0.93	1.10	0.85

Table 2. Geometric means of AUC_t (µmol·h /L) and the ratio for AUC_t on day 1 and day 5 following administration of once-daily doses of 20 mg H 199/18 as a MUPS tablet or phase III capsule. Estimates, limits for 94% CI and a p-value for the test of equal geometric means are presented (n=34).

Day		Estimated geometric mean	94% confidence interval lower	upper	p-value
1	H 199/18 MUPS tablet (A)	2.13	1.74	2.60	
	H 199/18 Capsule (B)	2.08	1.70	2.54	
	A/B	1.02	0.93	1.12	0.62
5	H 199/18 MUPS tablet (A)	4.70	4.00	5.53	
	H 199/18 Capsule (B)	4.67	3.97	5.49	
	A/B	1.01	0.93	1.10	0.85

Table 3. Geometric means of C_{max} (µmol/L) and the ratio for C_{max} on day 1 and day 5 following administration of once-daily doses of 20 mg H 199/18 as a MUPS tablet or phase III capsule. Estimates, limits for 94% CI and a p-value for the test of equal geometric means are presented (n=34).

Day		Estimated geometric mean	94% confidence interval lower	upper	p-value
1	H 199/18 MUPS tablet (A)	1.56	1.33	1.81	
	H 199/18 Capsule (B)	1.41	1.21	1.65	
	A/B	1.10	0.95	1.28	0.22
5	H 199/18 MUPS tablet (A)	2.47	2.22	2.75	
	H 199/18 Capsule (B)	2.41	2.17	2.69	
	A/B	1.02	0.93	1.12	0.62

- **SAFETY RESULTS**

A total of 57 AEs was reported for 29 of the 38 subjects during the entire study (including wash-out periods). Twenty-four AEs were reported for 17 subjects during active treatment with H 199/18 capsule 20 mg, and 32 AEs were reported for 20 subjects during active treatment with H 199/18 MUPS tablet 20 mg.

Headache, abdominal pain, rhinitis, diarrhoea and flatulence were the most common AEs. All AEs were reported as mild or moderate in intensity.

DATE OF THE REPORT

20 April, 1999