AstraZeneca

DRUG PRODUCT		**Synopsis**	(FOR NATIONAL AUTHORITY USE ONLY)
DRUG SUBSTANCE	H 199/18	REFERRING TO PART OF THE DOSSIER	
DOCUMENT NO.	SH-QBE-0055		
VERSION NO.	1		
STUDY CODE	SH-QBE-0055		
DATE	30 August, 1999		

A bioequivalence study comparing a H 199/18 market capsule, 40 mg, with the H 199/18 phase III capsule, 40 mg, following single and repeated administration under fasting conditions in healthy male and female subjects.

STUDY CENTRE

Single centre study

STUDY PERIOD

- **DATE OF FIRST SUBJECT ENROLLED** 12 March, 1999
- **DATE OF LAST SUBJECT COMPLETED** 4 June, 1999

PHASE OF DEVELOPMENT

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OBJECTIVES

To investigate if the market capsule and the phase III capsule of 40 mg H 199/18 are bioequivalent following single and repeated administration under fasting conditions.

The safety and tolerability of H 199/18 were also assessed.

STUDY DESIGN

Open, randomised, two-way cross-over study.

TEST PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

H 199/18 market capsule 40 mg, batch no. H 1222-06-01-05, once daily oral 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 1222-04-01-08, once daily oral dose of 40 mg for five days.

DURATION OF TREATMENT

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

MAIN VARIABLES:

- **PHARMACOKINETIC**

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 dose 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 (market capsule or phase III capsule) and a random effect for subject within sequence. Data from day 1 and day 5 were analysed separately.

A group sequential method in two steps, with an equal number of subjects in each step, was determined. Based on the data obtained in the first step, a formalised rule would determine whether the trial would be stopped or if it would continue to include more subjects.

An interim analysis was to be made when 36 evaluable subjects had completed both periods. If, after the first step, the confidence intervals for the ratios of market capsule to phase III capsule regarding geometric means for AUC, AUC_t as well as for C_{max}, for both day 1 and day 5, were all contained in the interval (0.80, 1.25), then the trial was to be stopped and the formulations were considered bioequivalent for both single and repeated dose administration. Otherwise, the study would continue and new estimates and confidence intervals, based on all available data, were to be calculated and the same criteria for bioequivalence was to be applied.

The confidence levels were adjusted in order to compensate for the interim analysis. The confidence levels were set to 94% in each step.

The results of separate analyses are presented for the 51 subjects who completed the study and analysed according to the Intention To Treat (ITT) approach and for the 37 subjects who

completed the study according to protocol and thus analysed according to the Per Protocol (PP) approach.

SUBJECTS

	Total
No. planned	76 (38 in the first step)
No. randomised and treated	57
Males/Females	40/17
Mean age (range)	25.5 (20-41)
No. analysed for clinical pharmacology	ITT 51 / PP 37
No. analysed for safety	57
No. completed	51

SUMMARY

- PHARMACOKINETIC RESULTS

As shown in Tables 1-3, the ratios (market capsule/phase III capsule) of AUC, AUC_t and C_{max} were all within the interval 0.80 – 1.25 for both day 1 and day 5 after the first step and thus the study could be stopped.

The mean elimination half-life ($t_{1/2}$) was similar for the market capsule and the phase III capsule both on day 1 (0.8 and 0.9 hours, respectively) and on day 5 (1.3 and 1.3 hours, respectively). The mean time to the maximum plasma concentration (t_{max}) was approximately 2 hours for both formulations on day 1 and approximately 1.8 hours for both formulations on day 5.

Table 1 **Geometric means of *AUC (µmol·h/L)* and the ratio of geometric means for AUC on day 1 and day 5 following administration of once daily doses of 40 mg H 199/18 as a market or phase III capsule. Estimates, limits for 94% CI and a p-value for test of equal geometric means are presented (PP-analysis, n=37).**

	Estimated geometric mean	94 % confidence interval lower	upper	p-value
Day 1				
Market capsule	4.35	3.60	5.25	
Phase III capsule	4.21	3.48	5.08	
Market/Phase III	1.03	0.93	1.15	0.54
Day 5*				
Market capsule	11.09	9.81	12.54	
Phase III capsule	11.19	9.89	12.65	
Market/Phase III	0.99	0.93	1.06	0.80

* n = 36 (subject no. 19 excluded from the analysis due to late absorption of H 199/18, see Section 11.1)

Table 2 **Geometric means of AUC_t *(µmol·h/L)* and the ratio of geomtric means for AUC_t on day 1 and day 5 following administration of once daily doses of 40 mg H 199/18 as a market or phase III capsule. Estimates, limits for 94% CI and a p-value for test of equal geometric means are presented (PP-analysis, n=37).**

	Estimated geometric mean	94 % confidence interval lower	upper	p-value
Day 1				
Market capsule	4.29	3.55	5.19	
Phase III capsule	4.14	3.42	5.01	
Market/Phase III	1.04	0.93	1.15	0.51
Day 5*				
Market capsule	10.98	9.71	12.42	
Phase III capsule	11.07	9.79	12.52	
Market/Phase III	0.99	0.93	1.06	0.82

* n = 36 (subject no. 19 excluded from the analysis due to late absorption of H 199/18, see Section 11.1)

Table 3 Geometric means of C_{max} *(µmol/L)* and the ratio of geometric means for C_{max} on day 1 and day 5 following administration of once daily doses of 40 mg H 199/18 as a market or phase III capsule. Estimates, limits for 94% CI and a p-value for test of equal geometric means are presented (PP-analysis, n=37).

	Estimated geometric mean	94 % confidence interval lower	upper	p-value
Day 1				
Market capsule	2.64	2.27	3.07	
Phase III capsule	2.41	2.07	2.81	
Market/Phase III	1.09	0.97	1.23	0.15
Day 5*				
Market capsule	4.55	4.09	5.05	
Phase III capsule	4.57	4.12	5.08	
Market/Phase III	0.99	0.90	1.10	0.91

* n = 36 (subject no. 19 excluded from the analysis due to late absorption of H 199/18, see Section 11.1)

- **SAFETY RESULTS**

Twenty-two adverse events were reported for 18 of the 56 subjects receiving H 199/18 as a phase III capsule formulation and 29 AEs were reported for 21 of the 54 subjects receiving H 199/18 as the market formulation. Headache was the most common AE. One subject discontinued the study due to unintended pregnancy and two subjects discontinued the study due to gastroenteritis. No SAE:s were reported.

H 199/18 40 mg, given in two different formulations in this study was well tolerated.

DATE OF THE REPORT

30 August, 1999