AstraZeneca

DRUG PRODUCT		**Synopsis**	(FOR NATIONAL AUTHORITY USE ONLY)
DRUG SUBSTANCE	H 199/18	REFERRING TO PART OF THE DOSSIER	
DOCUMENT NO.	SH-QBE-0057		
VERSION NO.	1		
STUDY CODE	SH-QBE-0057		
DATE	30 August, 1999		

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

STUDY CENTRE

Single centre study

STUDY PERIOD

- **DATE OF FIRST SUBJECT ENROLLED** 3 March, 1999
- **DATE OF LAST SUBJECT COMPLETED** 2 June, 1999

PHASE OF DEVELOPMENT

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OBJECTIVES

To investigate if the market capsule and the phase III capsule of 20 mg H 199/18 are bioequivalent following single dose administration under fasting conditions.

STUDY DESIGN

Open, randomised, two-way cross-over study

TEST PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

H 199/18 market capsule 20 mg, batch no. H 1189-06-01-05, single oral dose of 20 mg

COMPARATOR PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

H 199/18 phase III capsule 20 mg, batch no. H 1189-04-01-05, single oral dose of 20 mg

DURATION OF TREATMENT

Two single doses separated by a wash-out period of at least six days.

MAIN AND 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}).

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 and a random effect for subject within sequence.

A group sequential method in two steps, with an equal number of subjects in each step, was applied. If 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} after the first step were all contained in the interval (0.80 to 1.25), then the trial would be stopped and the treatments would be considered bioequivalent for single dose administration under fasting conditions. However, the confidence interval for C_{max} after the first step was not contained in the pre-determined interval, and therefore the study continued and new estimates and confidence intervals, based on all available data, were calculated and the same criteria for bioequivalence were applied.

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

SUBJECTS

	Total
No. planned	72 (36 in the first step)
No. randomised and treated	72
Males/Females	49/23
Mean age (range)	27.4 years (20-46)
No. analysed for pharmacokinetics	72
No. analysed for safety	72
No. completed	72

SUMMARY

- **PHARMACOKINETIC RESULTS**

As shown in Table 1, the 94% confidence intervals for the ratios (market capsule/phase III capsule) of AUC, AUC_t and C_{max} for H 199/18 were all within the interval of 0.80 to 1.25.

The geometric mean of $t_{1/2}$ was approximately 0.70 hours and the mean t_{max} was approximately 2 hours for both formulations.

Table 1 Geometric means of AUC (µmol·h/L), AUC_t (µmol·h/L) and C_{max} (µmol/L) of H 199/18 and the ratio of the geometric means following a single oral dose of H 199/18 market capsule 20 mg or phase III capsule 20 mg to healthy males and females under fasting conditions. Estimates, limits for 94% CI and p-values for tests of equal geometric means are presented.

	Estimate	94 % confidence interval		p-value
		lower	upper	
AUC (n=71*)				
Market capsule	1.64	1.41	1.91	
Phase III capsule	1.56	1.34	1.82	
Market capsule/Phase III capsule	1.05	1.00	1.11	0.081
AUC_t (n=72)				
Market capsule	1.57	1.34	1.84	
Phase III capsule	1.49	1.27	1.74	
Market capsule/Phase III capsule	1.06	1.00	1.12	0.074
C_{max} (n=72)				
Market capsule	1.09	0.95	1.25	
Phase III capsule	0.98	0.85	1.12	
Market capsule/Phase III capsule	1.12	1.01	1.23	0.035

* Subject no. 26 is excluded from the analysis, due to unreliable estimate of AUC.

- **SAFETY RESULTS**

Twelve adverse events were reported for 12 of the 72 subjects when given H 199/18 as a phase III capsule formulation and 14 AEs were reported for 13 subjects when given H 199/18 as the market formulation.

DATE OF THE REPORT

30 August, 1999