AstraZeneca

DRUG PRODUCT		**Synopsis**	(FOR NATIONAL AUTHORITY USE ONLY)
DRUG SUBSTANCE	H 199/18	REFERRING TO PART OF THE DOSSIER	
DOCUMENT NO.	SH-QBE-0056		
VERSION NO.	1		
STUDY CODE	SH-QBE-0056		
DATE	26 October, 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 dose administration under fed conditions in healthy male and female subjects

STUDY CENTRE(S)

Single centre study

STUDY PERIOD

- DATE OF FIRST SUBJECT ENROLLED 5 March, 1999
- DATE OF LAST SUBJECT COMPLETED 8 July, 1999

PHASE OF DEVELOPMENT

Phase I

OBJECTIVES

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

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, single oral dose of 40 mg

COMPARATOR PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

H 199/18 phase III capsule 40 mg, batch no. H 1222-04-01-08, single oral dose of 40 mg

DURATION OF TREATMENT

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

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.

An interim analysis was done after the first 38 randomised subjects completed the study. If the 94% confidence intervals for the ratio of market capsule to phase III capsule regarding the geometric means of AUC and AUC_t were in the interval 0.80-1.25, and the corresponding confidence interval for C_{max} was contained in the interval 0.70-1.43, then the trial would be stopped and the two treatments would be considered bioequivalent for single dose administration under fed conditions. As the results of the interim analysis did not fulfil these criteria, the study continued with an additional 38 healthy subjects and new estimates and confidence intervals, based on all available data, were calculated and the same criteria for bioequivalence were applied.

SUBJECTS

	Total
No. planned	76
No. randomised and treated	76
Males/Females	40/36
Mean age (range)	26 (20-44)
No. analysed for pharmacokinetics	76
No. analysed for safety	76
No. completed	76

SUMMARY

- PHARMACOKINETIC RESULTS

As shown in Table 1, the ratio (market capsule/phase III capsule) of the geometric means for AUC, AUC_t and C_{max} and the 94% confidence intervals for the ratio were 1.16 (0.99-1.35), 1.26 (1.05-1.51) and 1.28 (1.04-1.59), respectively.

A mean plasma elimination half-life ($t_{1/2}$) of approximately 1 hour was found for both the market and the phase III capsules. The median time to the maximum plasma concentration (t_{max}) was 5.5 hours for both capsule 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 single oral dose administration of H 199/18 market capsule or phase III capsule to healthy males and females under fed conditions. Estimates, limits for 94% CI and p-values for tests of equal geometric means are presented.

	Estimated geometric mean	94 % confidence interval lower	upper	p-value
AUC (n=68*)				
Market	2.68	2.22	3.23	
Phase III	2.32	1.92	2.79	
Market/Phase III	1.16	0.99	1.35	0.077
AUC_t (n=76)				
Market	2.42	1.98	2.96	
Phase III	1.91	1.57	2.34	
Market/Phase III	1.26	1.05	1.51	0.016
C_{max} (n=76)				
Market	0.93	0.77	1.13	
Phase III	0.73	0.60	0.88	
Market/Phase III	1.28	1.04	1.59	0.027

* Subjects 9, 13, 35, 37, 47, 58, 66 and 74 are excluded from the analysis, due to unreliable estimates of AUC.

- SAFETY RESULTS

Nineteen adverse events were reported for 15 of the 76 subjects when given H 199/18 as a market capsule and 15 adverse events were reported for 11 of the 76 subjects when given H 199/18 as a phase III capsule formulation.

DATE OF THE REPORT

1999-10-26