AstraZeneca

DRUG PRODUCT	MUPS	**Synopsis**	(FOR NATIONAL AUTHORITY USE ONLY)
DRUG SUBSTANCE	H 199/18	REFERRING TO PART OF THE DOSSIER	
DOCUMENT NO.	DC-QBE-0002		
VERSION NO.	01		
STUDY CODE	DC-QBE-0002		
DATE	17 May, 1999		

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

INVESTIGATOR

STUDY CENTRE

Single centre study at
Quintiles AB, Phase I Services
Islandsgatan 2
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STUDY PERIOD, PART ONE

- DATE OF FIRST SUBJECT ENROLLED 10 June, 1998
- DATE OF LAST SUBJECT COMPLETED 11 July, 1998

PHASE OF DEVELOPMENT

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STUDY PERIOD, PART TWO

- DATE OF FIRST SUBJECT ENROLLED 17 September, 1998
- DATE OF LAST SUBJECT COMPLETED 22 October, 1998

OBJECTIVES

To investigate if a Phase III capsule formulation and a MUPS tablet formulation of 40 mg H 199/18 are bioequivalent under non-fasting conditions during single and repeated dose administration.

STUDY DESIGN

The study was an open, randomised, two-way cross-over trial.

MAIN CRITERIA FOR INCLUSION

Healthy adult male and female subjects of normal weight.

TEST PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

H 199/18 MUPS tablets, 40 mg, batch no. H 1365-01-01-01, were given orally once daily immediately following breakfast.

COMPARATOR PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

H 199/18 capsule with enteric coated pellets, 40 mg, batch no. H 1222-04-01-05, were given orally once daily immediately following breakfast.

DURATION OF TREATMENT

Two periods of five days each, separated by a wash-out period of at least 13 days.

MAIN VARIABLES

- PHARMACOKINETIC

  The total area under the plasma concentration versus time curve (AUC), area under the plasma concentration versus time curve up to the last quantifiable concentration (AUC_t) and the observed maximum concentration of H 199/18 in plasma (C_{max}) were calculated for days 1 and 5 in each period.

STATISTICAL METHODS

Data from day 1 and day 5 were analysed separately. Analysis of variance (ANOVA) was performed on log-transformed values of AUC, AUC_t and C_{max}. By applying the antilogarithm transformation, the 94% CI (corresponds to 90% CI, adjusted for interim analysis) for the geometric mean of each parameter and formulation and the 94% CIs for the ratios (Test/Comparator) of the geometric means were obtained. The estimated geometric means and CIs and the estimated ratios and CIs were corrected for the content of H 199/18 in the formulations. The study was performed in two steps with an interim analysis in between. The 90 % confidence intervals for the ratios of the geometric means for AUC and AUC_t and the ratios of the geometric means for C_{max} in the interim analysis and final analysis should be within 0.80 – 1.25 in order to be able to establish bioequivalence. Analyses of variance (ANOVA) were performed on the elimination rate constant (λ), $t_{½}$ as well as t_{max}. The laboratory results and adverse events were presented descriptively.

SUBJECTS

	Total
No. planned	82 in total with 40 in the first step and 42 in the second step
No. randomised and treated	82
Males/Females	51/31
Mean age (range)	25 years (20-45)
Baseline values	
No. analysed for pharmacokinetics	76
No. analysed for pharmacodynamics	
No. analysed for safety	82
No. completed	76

SUMMARY - CONCLUSIONS

- PHARMACOKINETIC RESULTS

As the interim analysis performed after the first part of the study showed case scenario 3, (i.e. all confidence intervals for AUCs and estimates for C_{max} were inside the relaxed bioequivalence range of 0.70 to 1.43 but at least one of them was not inside the bioequivalence range 0.80 to 1.25) the study was continued with 42 more subjects in order to get 36 more evaluable subjects. The geometric mean with 94 % CI for each main variable and formulation and the ratios of the geometric means (MUPS tablet/capsule) with 94% CIs for day 1 and day 5 are shown in Tables 1 and 2, respectively.

The CIs for the ratios of the geometric means for AUC and AUC_t, expressing extent of absorption, and the ratio of the geometric means for C_{max}, expressing both extent and rate of absorption, were outside the range of bioequivalence (0.80 – 1.25) both for day 1 and day 5.

Table 1. Geometric least square means and ratios for *AUC (µmol· h/L*; n=69), *AUC_t (µmol· h/L*; n= 76) and *C_{max} (µmol/L*; n=76) for H 199/18 following a single oral administration of 40 mg as a MUPS tablet or as a capsule to healthy subjects under non-fasting condition. Drug potency corrected estimates, 94 % CIs and p-values for test of equal geometric means are presented.

Day 1	Geometric mean	94 % confidence interval		p-value
		Lower	upper	
AUC[a]				
MUPS	3.60	3.35	3.86	
Capsule	2.83	2.63	3.03	
MUPS/Capsule	1.27	1.15	1.41	0.0001
AUC_t				
MUPS	3.09	2.84	3.36	
Capsule	2.43	2.24	2.64	
MUPS/Capsule	1.27	1.13	1.43	0.0002
C_{max}				
MUPS	1.30	1.18	1.43	
Capsule	1.05	0.95	1.15	
MUPS/Capsule	1.24	1.09	1.42	0.0037

[a] The AUC values for the MUPS tablet and/or the capsule estimated for subjects 37,45,47,57,63,64 and 80 were regarded as uncertain (less than three plasma concentrations after C_{max} or an AUC_{extr} exceeding 20%). These subjects were therefore excluded from the calculation of the geometric least square means of AUC.

Table 2. Geometric least square means and ratios for *AUC (µmol· h/L*; n = 76), *AUC_t (µmol· h/L*; n = 76) and *C_{max} (µmol/L*; n = 76) for H 199/18 following oral o.d. administration of 40 mg for five days as MUPS tablets or as capsules to healthy subjects under non-fasting condition. Drug potency corrected estimates, 94 % CIs and p-values for test of equal geometric means are presented.

Day 5	Geometric mean	94 % confidence interval		p-value
		lower	upper	
AUC				
MUPS	9.58	9.10	10.08	
Capsule	6.94	6.59	7.30	
MUPS/Capsule	1.38	1.28	1.48	0.0001
AUC_t				
MUPS	9.47	8.98	9.97	
Capsule	6.83	6.48	7.19	
MUPS/Capsule	1.39	1.29	1.49	0.0001
C_{max}				
MUPS	2.89	2.71	3.09	
Capsule	2.24	2.10	2.40	
MUPS/Capsule	1.29	1.18	1.42	0.0001

On study day 1, the median time for reaching maximum plasma concentrations was 4.5 hours for both formulations. The mean half-lives ($t_{1/2}$) were 1.2 and 1.3 hours for the tablet and the capsule, respectively. On study day 5, the median t_{max} was 3.5 and 4.5 hours for the tablet and the capsule, respectively. The mean $t_{1/2}$ was 1.4 and 1.3 hours for the tablet and the capsule, respectively.

- SAFETY RESULTS

In total, 224 AEs were reported. There were no serious adverse events (SAEs) and the adverse events (AEs) reported were mostly mild to moderate. Three AEs were reported as severe; one respiratory infection and an intense attack of dysmenorrhea with syncope. The AEs were of a kind usually seen in a group of healthy volunteers.

- CONCLUSION

The Phase III capsule formulation and the MUPS tablet formulation of 40 mg H 199/18 were not bioequivalent with respect to AUC, AUC_t and C_{max} under non-fasting conditions, neither during single nor repeated dose administration. Repeated doses of H 199/18 were well tolerated in this study.

DATE OF THE REPORT

17 May, 1999