AstraZeneca

DRUG PRODUCT		**Synopsis**	(FOR NATIONAL AUTHORITY USE ONLY)
DRUG SUBSTANCE	H 199/18	REFERRING TO PART OF THE DOSSIER	
DOCUMENT NO.	SH-QBE-0051		
VERSION NO.	01		
STUDY CODE	SH-QBE-0051		
DATE	20 August, 1999		

A pharmacodynamic study comparing a 20 mg MUPS tablet with a 20 mg capsule of H 199/18 in patients with symptomatic gastroesophageal reflux disease

STUDY CENTRE

Single centre study

STUDY PERIOD

- DATE OF FIRST PATIENT ENROLLED 9 February, 1999
- DATE OF LAST PATIENT COMPLETED 7 May, 1999

PHASE OF DEVELOPMENT

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OBJECTIVES

The primary objective was to investigate whether H 199/18 capsule 20 mg and H 199/18 MUPS tablet 20 mg are bioequivalent regarding the effect on 24-hour intragastric pH under fed conditions on study day 5.

A secondary objective was to compare the H 199/18 capsule 20 mg and H 199/18 MUPS tablet 20 mg regarding the effect on 24-hour intragastric pH under fed conditions on study day 1.

Additional secondary objectives were to compare the effect on 24-hour intragastric pH of H 199/18 MUPS tablet 20 mg and H 199/18 capsule 20 mg, respectively, when given together with food and under fasting conditions.

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

STUDY DESIGN

Open, randomised, four-way cross-over study

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

Patients with symptomatic GERD

TEST PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

H 199/18 MUPS tablet 20 mg, batch no. H 1370-01-01-01, oral dose of 20 mg o.m.

COMPARATOR PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

H 199/18 capsule 20 mg, batch no. H 1189-04-01-04, oral dose of 20 mg o.m.

DURATION OF TREATMENT

Four periods of 5 days separated by wash-out periods for at least 14 days.

MAIN VARIABLE:

- PHARMACODYNAMIC

The percentage of time with intragastric pH>4 for 24 hours.

STATISTICAL METHODS

Primary evaluation:
For the evaluation of bioequivalence for the MUPS tablet and the capsule on day 5 under fed conditions, the log-transformed percentage of time with pH>4 was analysed using a mixed model ANOVA (Analysis of Variance) with fixed effects for period, sequence and treatment and a random effect for patient within sequence.

Secondary evaluations:
The comparison between the MUPS tablet and the capsule regarding the effect on 24-hour intragastric pH on day 1 was done as described for day 5.

To evaluate the influence of food intake, the percentage of time with pH>4 was analysed using a mixed model ANOVA with fixed effects for sequence, period and treatment and a random effect for patient within sequence. Comparisons of the treatments were done for day 1 and day 5.

If bioequivalence was already concluded after 30 evaluable subjects, the trial was to be stopped. Otherwise the second step was to be performed with 32 new patients, new estimates and confidence intervals based on all available data were to be calculated and the same bioequivalence criteria as above were used.

PATIENTS

	Total
No. planned	32 (64)
No. randomised and treated	34
Males/Females	14/20
Mean age (range)	25.4 years (20-34)
No. analysed for pharmacodynamic evaluation	30
No. analysed for safety	34
No. completed	30

SUMMARY

- PHARMACODYNAMIC RESULTS

The ratio between H 199/18 MUPS tablet 20 mg and H 199/18 capsule 20 mg on day 5 under fed conditions regarding geometric means for percentage of time with intragastric pH>4 was 0.99, and the confidence interval was within 0.80 to 1.25 (94% CI; 0.84 to 1.16). Thus, the criteria for bioequivalence was fulfilled. The corresponding ratio on day 1 was 1.03 (CI; 0.80 to 1.32).

After administration of H 199/18 MUPS tablet 20 mg, the difference in percentage of time with intragastric pH>4 on day 5 between fed and fasting conditions was 1.1% (CI; -4.0% to 6.1%). However, on day 1, the corresponding values were 6.2% (CI; 0.7% to 11.6%). This difference was statistically significant.

After administration of H 199/18 capsule 20 mg, the difference in percentage of time with intragastric pH>4 between fed and fasting conditions was 1.5% (CI; -3.4% to 6.4%) on day 5 and -0.9% (CI; -5.5% to 3.7%) on day 1. No statistically significant differences could be detected between fed and fasting conditions.

- SAFETY RESULTS

Sixty-five AEs were reported for the 34 patients included in the study. Headache was the most common AE. All AEs reported were of mild to moderate intensity. No SAE occurred during the study.

DATE OF THE REPORT

20 August, 1999