AstraZeneca

DRUG PRODUCT		**Synopsis**	(FOR NATIONAL AUTHORITY USE ONLY)
DRUG SUBSTANCE(S)	H199/18	REFERRING TO PART	
DOCUMENT NO.	DC-QBE-0004	OF THE DOSSIER	
VERSION NO.	01		
STUDY CODE	DC-QBE-0004		
DATE	27 August, 1999		

A comparison study of the pharmacodynamic effect of a 40 mg H199/18 MUPS™ tablet formulation versus a capsule formulation in patients with gastroesophageal reflux symptoms

STUDY CENTRE(S)

Single centre study at LAB Pharmacological Research Intl. Inc., 1000 Saint-Charles, Vaudreuil, QC J7V 8P5

STUDY PERIOD		PHASE OF DEVELOPMENT
GROUP 1		
- **DATE OF FIRST PATIENT ENROLLED**	25 January, 1999	II
- **DATE OF LAST PATIENT COMPLETED**	20 April, 1999	
GROUP 2		
- **DATE OF FIRST PATIENT ENROLLED**	10 March, 1999	II
- **DATE OF LAST PATIENT COMPLETED**	20 April, 1999	

OBJECTIVES

The primary objectives were to compare the effect on 24-hour intragastric pH of H 199/18 40 mg capsule formulation and H199/18 40 mg MUPS™ tablet formulation when given together with food on Days 1 and 5.

STUDY DESIGN

Open, randomised, two-way cross-over study

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION

Patients with symptomatic GERD

TEST PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

H199/18 40 mg MUPS™ tablet formulation, batch no. H1365-01-01-01, oral dose of 40 mg once daily

COMPARATOR PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

H199/18 40 mg Phase III capsule formulation, batch no. H1222-04-01-06, oral dose of 40 mg once daily

DURATION OF TREATMENT

Two periods of 5 days, separated by a wash-out period of at least 14 days

MAIN VARIABLE(S):

The percentage of time over a 24-hour period with intragastric pH > 4

STATISTICAL METHODS

For the comparison of the two formulations, the log-transformed percentage of time with pH > 4 was analysed using a mixed model ANOVA (Analysis of Variance) 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 as well as for Day 5.

Descriptive statistics were provided for the percentage of time with pH > 4 during the 24-hour period, 24-hour median pH, and for adverse events.

Patients

	Total
No. planned	48
No. randomised and treated	48
Males/Females	33/15
Mean age (range)	38.1 years (21-57)
No. analysed for pharmacodynamics	Day 1 - 42 Day 5 - 34
No. analysed for safety	48
No. completed	42

SUMMARY

- PHARMACODYNAMIC RESULTS

Table 1. Geometric means of percentage of time with pH > 4 (%) and ratios of geometric means following daily oral doses of H199/18 taken either as a MUPS™ tablet or as a capsule to symptomatic gastroesophageal reflux disease patients. Estimates, limits for 95% confidence intervals of geometric means, and 90% confidence intervals for the ratio of geometric means, and p-values for test of equal geometric means are presented.

	Estimated	Confidence Interval		p-value
	Mean	Lower	upper	
Day 1 (n = 42)				
MUPS™ formulation	38.65	36.40	40.90	-
Capsule formulation	29.89	27.64	32.14	-
MUPS™/ Capsule	1.29	1.00	1.67	0.1013
Day 5 (n = 34)				
MUPS™ formulation	66.41	64.31	68.50	-
Capsule formulation	68.20	66.10	70.29	-
MUPS™/Capsule	0.98	0.90	1.05	0.5466

The ratio of geometric means for percentage time with pH > 4 of H199/18 MUPS™ tablet 40 mg and H199/18 capsule 40 mg on Day 1 was 1.29, and the confidence interval was outside the 0.80 to 1.25 range accepted for bioequivalence. The ratio of geometric means for percentage time pH > 4 of H199/18 MUPS™ tablet 40 mg and H199/18 capsule 40 mg on Day 5 was 0.98, and the confidence interval was within the 0.80 to 1.25 range for equivalence.

- **SAFETY RESULTS**

A total of 84 adverse events was reported during the study. Headaches were the most common adverse event reported during this study. One patient reported two serious adverse events (gastro-enteritis and pneumonia). All the adverse events were mild to moderate in intensity (93% and 7% of total adverse events, respectively).

DATE OF THE REPORT

27 August 1999