ASTRA
ASTRA HÄSSLE

DRUG PRODUCT	**H 199/18 capsule**	**Synopsis**	(FOR NATIONAL AUTHORITY USE ONLY)
DRUG SUBSTANCE	**H 199/18 capsule**	REFERRING TO PART OF THE DOSSIER	
DOCUMENT NO.	**SH-QBE-0009**		
VERSION NO.	**01**		
STUDY CODE	**SH-QBE-0009**		
DATE	12 May, 1999		

A Dose-finding/efficacy and safety study of H 199/18 vs. omeprazole management of patients with gastroesophageal reflux symptoms without macroscopic esophagitis - A multicenter study

STUDY CENTRE(S)

Multicentre study including 41 centres in Canada and 98 centres in UK and Republic of Ireland.

PUBLICATION (REFERENCE)

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STUDY PERIOD		**PHASE OF DEVELOPMENT**
- DATE OF FIRST ENROLMENT	September 29, 1997	IIIA
- DATE OF LAST COMPLETED	July 13, 1998	

OBJECTIVES

Primary:

- To compare the efficacy of 4 weeks' (visit 3) treatment with H 199/18 40 mg o.m. versus omeprazole 20 mg o.m. and H 199/18 20 mg o.m. versus omeprazole 20 mg o.m., on complete resolution of heartburn as assessed by the investigator.

Secondary:

- To compare the efficacy of 4 weeks' treatment with the two different doses of H 199/18 on complete resolution of heartburn as assessed by the investigator.
- To compare the efficacy of 2 weeks' (visit 2) treatment with H 199/18 40 mg o.m. versus omeprazole 20 mg o.m. and H 199/18 20 mg o.m. versus omeprazole 20 mg o.m., on complete resolution of heartburn as assessed by the investigator.

- To compare the efficacy of 4 weeks' treatment with H 199/18 40 mg o.m. versus omeprazole 20 mg o.m. and H 199/18 20 mg o.m. versus omeprazole 20 mg o.m., on relief of heartburn as assessed by the patient with a diary card.
- To compare the treatment groups with regard to Overall Treatment Evaluation (OTE).
- To compare the treatment groups with regard to other Gastroesophageal reflux disease (GERD) symptoms.
- To evaluate the safety and tolerability of H 199/18.

STUDY DESIGN

Double-blind, randomised and parallel group study. Balanced groups 1:1:1 with H 199/18 40 mg: H 199/18 20 mg: omeprazole 20 mg, respectively.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

Presence of heartburn as main symptom with normal endoscopy, at least 6 months' history of episodes of heartburn, female or male 18-80 years of age, signed informed consent.

TEST PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

H 199/18, 40 mg capsule, once daily, batch numbers: H 1222-04-01-04, H 1222-04-01-05
H 199/18, 20 mg capsule, once daily, batch numbers: H 1189-04-01-03, H 1189-04-01-04

COMPARATOR PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Omeprazole, 20 mg capsule, once daily, batch number: H 0431-13-05-06

DURATION OF TREATMENT

Four weeks of double-blind treatment

MAIN VARIABLE(S):

- EFFICACY

The primary variable was complete resolution of heartburn defined as no days with heartburn episodes during the last 7 days prior to visit 3. Secondary variables were complete resolution of heartburn at visit 2 and adequate control of heartburn at visit 3. Further secondary variables were relief of heartburn as assessed by diary cards, OTE and relief of other GERD symptoms.

- SAFETY

Adverse events (AE), laboratory assessments and vital signs.

STATISTICAL METHODS

The three treatment groups are compared regarding the primary variable using a Mantel-Haenszel Chi-Square test with stratification based on countries. The significance level is adjusted for two comparisons (H 199/18 40 mg versus omeprazole 20 mg, and H 199/18 20 mg versus omeprazole 20 mg).

Dichotomised secondary variables are analysed by a Mantel-Haenszel Chi-Square test stratified by country (complete resolution of heartburn, adequate control of heartburn) or by baseline score (regurgitation, dysphagia). The number of days until the first day without heartburn and the number of days until the first 7-day period without heartburn were analysed by a log rank test. The percentage of time without heartburn during the study period was analysed by a one way ANOVA. The score of the OTE questionnaire was analysed by a Mann-Whitney test.

The primary variable is analysed using both an intention totreat (ITT) and a per protocol (PP) approach. Secondary variables are analysed using an ITT approach only. An "All patients randomised" analysis was also performed and the results of this analysis are presented in Section 14.4 in the body of the report.

PATIENTS

	H 199/18 40 mg	H 199/18 20 mg	Ome 20 mg	Total
No. planned	**400**	**400**	**400**	**1200**
No. randomised and treated	**425**	**423**	**434**	**1282**[*)]
Males/Females	**183/242**	**183/240**	**187/247**	**553/729**
Mean age (range)	**48.4 (19-79)**	**48.0 (18-80)**	**48.3 (19-78)**	**48.2 (18-80)**
No. analysed for efficacy	**425**	**423**	**434**	**1282**
No. analysed for safety	**424**	**418**	**435**	**1277**
No. completed	**407**	**401**	**399**	**1207**

* 1295 patients were randomised. Thirteen patients were randomised but not treated.

SUMMARY

- EFFICACY RESULTS

The proportion of patients with complete resolution of heartburn after four weeks is shown in Table 1. The difference between the treatment groups is not statistically significant, as shown in Table 2.

Table 1. Proportion of patients with complete resolution of heartburn, defined as no heartburn during the last 7 days preceding visit 3, estimates and 95% exact confidence intervals.

Treatment	Estimate	Lower limit	Upper limit
ITT			
H 40	56.7% (241/425)	51.8%	61.5%
H 20	60.5% (256/423)	55.7%	65.2%
O 20	58.1% (252/434)	53.3%	62.8%
PP			
H 40	59.3% (198/334)	53.8%	64.6%
H 20	63.5% (216/340)	58.2%	68.7%
O 20	60.5% (207/342)	55.1%	65.7%

Table 2. Difference between H 199/18 and omeprazole 20 mg in proportion of patients with complete resolution of heartburn at visit 3, estimates, 95% confidence intervals and Mantel-Haenszel test stratified by country.

	Estimate	Lower limit	Upper limit	M-H Chi-Square	p-value
ITT					
H 40 - O 20	-1.4%	-8.0%	5.3%	0.20	0.656
H 20 - O 20	2.5%	-4.1%	9.0%	0.53	0.466
PP					
H 40 - O 20	-1.2%	-8.6%	6.1%	0.16	0.693
H 20 - O 20	3.0%	-4.3%	10.3%	0.64	0.425

- SAFETY RESULTS

All the three treatment regimens were safe and well tolerated. It was a trend of more patients reporting AEs, in the elderly group (≥ 65 years) in the H 199/18 40 mg group and the omeprazole 20 mg group. There was also a trend of more patients reporting headache in the H 199/18 40 mg treatment group than in the other two treatments groups. The laboratory profile were very similar for the three treatments with only small deviation during the study.

DATE OF THE REPORT

12 May, 1999