ASTRA
ASTRA HÄSSLE

DRUG PRODUCT	H 199/18	**Synopsis**	(FOR NATIONAL AUTHORITY USE ONLY)
DRUG SUBSTANCE(S)	H 199/18 capsule	REFERRING TO PART OF THE DOSSIER	
DOCUMENT NO.	SH-QBE-0011		
VERSION NO.	01		
STUDY CODE	SH-QBE-0011		
DATE	12 May, 1999		

An efficacy and safety study of H 199/18 40 mg vs. omeprazole in the management of patients with gastroesophageal reflux symptoms without macroscopic esophagitis - A multicentre study

STUDY CENTRES

Multicentre study including 72 centres in France, Germany and Switzerland.

PUBLICATION (REFERENCE)

STUDY PERIOD		**PHASE OF DEVELOPMENT**
- DATE OF FIRST ENROLMENT	September 25, 1997	IIIA
- DATE OF LAST COMPLETED	April 30, 1998	

OBJECTIVES

Primary:

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

Secondary:

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

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION

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 capsule, 40 mg once daily, batch numbers: H 1222-04-01-04 and H 1222-04-01-05.

COMPARATOR PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

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

DURATION OF TREATMENT

Four weeks of double-blind treatment

MAIN VARIABLES:

- 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 two treatment groups were compared regarding the primary variable using a Mantel-Haenszel Chi-Square test with stratification based on countries. (H 199/18 40 mg versus omeprazole 20 mg).

Dichotomised secondary variables were 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). Number of days until the first day without heartburn and number of days until the first 7 day period without heartburn were analysed by a log rank test. 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 was analysed using both an intention to treat (ITT) and a per protocol (PP) approach. Secondary variables were 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	Ome 20 mg	Total
No. planned	330	330	660
No. randomised and treated	354	354	708[1)]
Males/Females	154/193	156/190	310/383[2)]
Mean age (range)	50.6 (21-77)	50.0 (19-83)	50.3 (19-83)
No. analysed for efficacy	347	346	693
No. analysed for safety	346	343	689[3)]
No. completed	338	329	667

[1)] 716 patients were randomised (358/treatment group). Eight patient were randomised but not treated.
[2)] 12 patients were withdrawn from all analyses due to inability to confirm the quality and reliability of data.
[3)] 4 patients were not included in the safety analysis due that no post data was available.

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	70.3% (244/347)	65.2%	75.1%
O 20	67.9% (235/346)	62.7%	72.8%
PP			
H 40	70.6% (192/272)	64.8%	75.9%
O 20	72.4% (194/268)	66.6%	77.7%

Table 2. Difference between H 199/18 40 mg 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	2.4%	-4.5%	9.3%	0.54	0.464
PP					
H 40 - O 20	-1.8%	-9.4%	5.8%	0.13	0.714

- **SAFETY RESULTS**

Both treatments were safe and well tolerated with a low frequency of reported AEs and SAEs. The frequency and distribution of AEs during the study were similar for the two treatments H 199/18 40 mg and omeprazole 20 mg. The laboratory profiles were very similar for the two treatments with small deviations during the study period.

DATE OF THE REPORT

12 May, 1999