2.0 SYNOPSIS

Name of Company: Astra Pharmaceuticals, L.P.	**Individual Study Table Referring to Item of the Submission:** N/A	**(For National Authority Use only)**
Name of Finished Product:	**Volume:** N/A	
Name of Active Ingredient: H 199/18	**Page:** N/A	

Title of Study: A Multicenter, Randomized, Double-blind, Eight Week Comparative Efficacy and Safety Study of H 199/18 40 mg and Omeprazole 20 mg in Study Subjects with Erosive Esophagitis

Investigator(s): Multicenter

Study Center(s): 79 investigator sites initiated; 72 investigator sites enrolled patients

Publication (reference): N/A

Studied Period (years): < 1 (date first drug dispensed) 14 October 1997 (date last patient completed) 11 May 1998	**Phase of development:** Phase III

Objectives:

Primary Objective

1. To assess the healing efficacy of H 199/18 40 mg qd (H40) compared to omeprazole 20 mg qd (O20) at Week 8 of treatment in patients with erosive esophagitis.

Secondary Objectives

1. To assess the healing efficacy of H40 compared to O20 at Week 4 of treatment.
2. To assess complete resolution and relief of GERD symptoms by H40 compared to O20 at Week 4 and Week 8 of treatment.
3. To assess time to resolution and relief of heartburn by H40 compared to O20.
4. To assess safety and tolerability of H40 compared to O20.

Methodology: This was a multicenter, randomized, double-blind study to evaluate the healing efficacy and safety of H 199/18 in patients with erosive esophagitis. Patients with EGD verified erosive esophagitis (graded according to the Los Angeles Classification) were randomized into one of two treatment groups, H40 or O20, for up to 8 weeks of therapy. All patients were to be reevaluated by EGD at Week 4 of treatment and, if unhealed, return at Week 8 of treatment for their final closeout visit and EGD evaluation. Patients healed at Week 4 were considered to have completed the study as treatment successes. The need for additional visits was left to the clinical judgment of the investigator. Patients who were healed (ie, disappearance of all mucosal breaks) were given the opportunity to participate in a separate long term safety study, until that study was fully enrolled.

Number of Patients (Planned and Analyzed):

	H40	**O20**
Number of Subjects Planned	500	500
Number of Subjects Enrolled	576	572
Number of Subjects Analyzed		
Efficacy Intention to Treat	576	572
Efficacy Per-Protocol	487	486
Safety Analysis	576	571

Diagnosis and Main Criteria for Inclusion: EGD verified erosive esophagitis (Los Angeles Classification)

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Test Product, Dose and Mode of Administration, Batch or Lot Number:
H 199/18 capsules 40 mg - Lots H1222-04-01-03, H1222-04-01-05

Duration of Treatment: Up to 8 weeks

Reference Therapy, Dose and Mode of Administration, Batch or Lot Number:
omeprazole capsules 20 mg - Lot H0431-13-05-06
GELUSIL® Antacid tablets - Lots AM-173, AM-130

Criteria for Evaluation:

Efficacy: The primary efficacy parameter was the percentage of patients who exhibit healing of esophageal erosions on EGD evaluation (ie, LA Classification "Not Present", no erosions present) by Week 8 of treatment. Secondary efficacy parameters were: 1) the percentage of patients who healed on EGD evaluation at Week 4 of treatment, 2) complete resolution and relief of GERD symptoms, ie, heartburn, acid regurgitation, dysphagia, and epigastric pain symptoms assessed by the investigator at Week 4 and Week 8 of treatment (relief defined as a recorded symptom of "None" or "Mild), and 3) time to first resolution and sustained resolution of heartburn using diary card information (resolution defined as heartburn recorded as "None" and sustained resolution defined as seven consecutive days with heartburn recorded as "None").

Safety: All randomized patients who received at least one dose of study drug were included in the assessment of AEs. Assessments were made at each post-treatment visit. Clinical laboratory evaluations were to be completed on fasting patients at baseline and at the final visit. Clinical laboratory tests included serum chemistry, urinalysis and hematology. Vital signs were recorded at each visit.

Statistical Methods: Primary healing efficacy data were analyzed for intent-to-treat (ITT) and per-protocol (PP) populations. Definitions of the PP and ITT populations were set prior to unblinding the data. Definition of the ITT population was changed after unblinding of data at the request of FDA to include all randomized patients. For percentage of patients with healed erosive esophagitis (EE) by Week 8 (primary efficacy parameter), a log-rank test was used to assess differences between treatment groups. The primary efficacy parameter was also analyzed using a Cochran-Mantel-Haenszel (CMH) test with stratification on baseline severity and a Wilcoxon test. For investigator-recorded symptoms, CMH tests stratified on baseline severity of each symptom were used to assess differences between treatment groups for resolution and relief. Diary card data were used to compare treatment groups regarding the number of days until the first resolution of heartburn (log-rank test), the number of days until sustained resolution of heartburn (log-rank test) and percentage of heartburn-free days and heartburn-free nights (analysis of variance).

Laboratory, AE, and vital signs data were tabulated to evaluate tolerability profiles between the two treatment groups. Laboratory measurements were summarized according to predefined limits of change and the changes from baseline.

SUMMARY

Efficacy Results: Healing of EE occurred in 92.2% (95% CI: 89.9% to 94.5%) and 89.8% (95% CI: 87.2% to 92.4%) of patients by Week 8 for treatment with H40 and O20, respectively (cumulative life table estimates - ITT population). There were no statistically significant differences between treatments in the analysis of healing of EE by Week 8. Breslow-Day analysis led to the conclusion that treatment differences favoring H40 over O20 at Week 8 (88.4% and 77.5%, $p = 0.007$; cumulative healing rates – CMH test) existed in patients with baseline LA Grade C and D. There were no significant differences observed between these two treatments (86.3% and 89.3% respectively, $p = 0.189$) in patients with baseline LA Grade A and B. At Week 4, life table estimates of healing rates were 71.5% (H40) and 68.6% (O20). There were no meaningful differences between population subsets (gender, age, race or *H. pylori* status) in the proportion of patients healed by treatment.

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Efficacy Results: (Continued)

There were no significant differences between H40 and O20 in the percentage of patients exhibiting resolution or relief of the investigator-recorded GERD symptoms of heartburn, acid regurgitation, dysphagia, and epigastric pain at Week 4.

There were no significant differences between H40 and O20 in diary-recorded time to first resolution of heartburn and in time to start of sustained resolution of heartburn. There were no significant differences between H40 and O20 in percentage of heartburn free days (24 hours) and in percentage of heartburn free nights.

Safety Results:

Clinical Adverse Events The incidence of patients reporting any AE was 49.1% with H40 and 45.0% with O20. No patients died during the study. Seven patients (1.2%) who received H40 and eight (1.4%) who received O20 had clinical AEs that were considered serious. There were 18 patients (3.1%) who received H40 and 10 (1.8%) who received O20 who discontinued treatment due to clinical AEs. The most frequently reported AE was headache, which occurred in 10.2% of patients treated with H40 and in 6.8% of patients treated with O20. The most frequently reported gastrointestinal AEs were diarrhoea, nausea, gastritis, abdominal pain and flatulence. These side effects were reported at similar rates in both treatment groups.

Laboratory Safety The laboratory measurement which was most frequently outside predefined limits was ALAT (SGPT), where 4 H40 (0.7%) and 4 O20 (0.7%) patients were elevated (> 144 U/L). Hemoglobin was below the predefined lower limit (9.5 g/dL for females and 11.5 g/dL for males) in 4 H40 (0.7%) and 2 O20 (0.4%) patients. Other laboratory values were less frequently observed above or below the predefined limits. Changes from baseline were small and were generally comparable for the two treatment groups.

Date of the Report: 20 May 1999