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 20 mg and Omeprazole 20 mg in Study Subjects with Erosive Esophagitis

Investigator(s): Multicenter

Study Center(s): 83 investigator sites initiated; 80 investigator sites enrolled patients

Publication (reference): N/A

Studied Period (years): < 1 (date first drug dispensed) 14 October 1997 (date last patient completed) 27 May 1998	**Phase of development:** Phase III

Objectives:

Primary Objective

1. To assess the healing efficacy of H 199/18 20 mg qd (H20) compared to omeprazole 20 mg qd (O20) at Week 8 of treatment in patients with erosive esophagitis (EE).

Secondary Objectives

1. To assess the healing efficacy of H20 compared to O20 at Week 4 of treatment.
2. To assess complete resolution and relief of GERD symptoms by H20 compared to O20 at Week 4 and Week 8 of treatment.
3. To assess time to resolution and relief of heartburn by H20 compared to O20.
4. To assess safety and tolerability of H20 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, H20 or O20, for up to 8 weeks of therapy. All patients were to be re-evaluated by EGD at Week 4 of treatment and, if unhealed, return at Week 8 of treatment for their final close-out 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 study, until the long-term study was fully enrolled.

Number of Patients (Planned and Analyzed):

	H20	O20
Number of Subjects Planned	500	500
Number of Subjects Enrolled	588	588
Number of Subjects Analyzed		
Efficacy Intention to Treat	588	588
Efficacy Per-Protocol	499	486
Safety Analysis	585	588

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

Test Product, Dose and Mode of Administration, Batch or Lot Number:
H 199/18 capsules 20 mg - Lots H1189-04-01-02, H1189-04-01-04

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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 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. Fasting clinical laboratory evaluations were completed on 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 the percentage of patients with healed 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 mean changes from baseline.

SUMMARY

EFFICACY RESULTS: Healing of EE occurred in 90.6% (95% CI: 88.1 to 93.0%) and 88.3% (95% CI: 85.5 to 91.0%) of patients by Week 8 for treatment with H20 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. At Week 4, the life table estimates of healing rates were 68.7% (H20) and 69.5% (O20). There were no meaningful differences between population subsets (gender, age, race or *H. pylori* status) in the proportion of patients with healing of EE by treatment, although a trend toward improved healing was observed in women.

There was a significant difference in the percentage of patients exhibiting resolution of the investigator-recorded GERD symptom of dysphagia at Week 4 favoring O20 (94.3%) over H20 (90.6%). There were no significant differences in the percentage of patients exhibiting resolution of the other investigator-recorded symptoms of GERD (heartburn, acid regurgitation, epigastric pain) at Week 4. There were no significant differences for any of the investigator-recorded GERD symptoms (heartburn, acid regurgitation, dysphagia and epigastric pain) for relief of the symptom.

There were no significant differences between H20 and O20 in diary-recorded time to first resolution of heartburn or in time to start of sustained resolution of heartburn. There were no significant differences between H20 and O20 in percentage of heartburn free days (24 hours) or in percentage of heartburn free nights.

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SAFETY RESULTS:

Clinical Adverse Events The incidence of patients reporting any AE was 44.1% and 42.9% for H20 and O20, respectively. One patient (multiple myeloma, O20: 761/016) died 161 days post study. One (0.2%) and 6 (1.0%) patients who received H20 and O20, respectively, had clinical AEs that were considered serious. There were 9 patients (1.5%) and 10 (1.7%), respectively, who discontinued treatment due to clinical AEs. The most frequently reported AE was headache, which occurred in 9.9% of patients treated with H20 and in 6.3% of patients treated with O20. The most frequently reported gastrointestinal AEs were diarrhoea, gastritis, flatulence, nausea and abdominal pain. These side effects were reported at similar rates in both treatment groups.

Laboratory Safety The laboratory measurements which were most frequently outside predefined limits were SGPT (ALAT) where 5 H20 (0.9%) and 7 O20 (1.3%) patients were elevated (> 144 U/L) and SGOT (ASAT) where 4 H20 (0.7%) and 3 O20 (0.5%) were above the limit (> 126 U/L). The percent increase from baseline in the mean gastrin levels for patients treated with H20 (102%) was larger than the increase for patients treated with O20 (76%). Other laboratory values were less frequently observed above or below the predefined limits. Mean changes in laboratory measures from baseline were small and were generally comparable for the two treatment groups.

Date of the Report: 20 May 1999