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, H 199/18 40 mg and Omeprazole 20 mg in Study Subjects with Erosive Esophagitis

Investigator(s): Multicenter

Study Center(s): 150 investigator sites initiated; 140 investigator sites enrolled patients

Publication (reference): N/A

Studied Period (years): < 1 (date first drug dispensed) 29 September 1997 (date last patient completed) 18 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) and H 199/18 20 mg qd (H20) compared to O20 by Week 8 of treatment in patients with erosive esophagitis (EE).

Secondary Objectives

1. To assess the healing efficacy of H40 compared to O20 and H20 compared to O20 at Week 4 of treatment.
2. To assess complete resolution and relief of GERD symptoms by H40 compared to O20 and H20 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 and H20 compared to O20.
4. To assess the healing efficacy of H40 compared to H20 at Week 4 and Week 8 of treatment.
5. To assess safety and tolerability of H40 compared to O20 and 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 three treatment groups, H40, H20 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 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 maintenance study, until the maintenance study was fully enrolled.

Number of Patients (Planned and Analyzed):

	H 199/18 40 qd	H 199/18 20 qd	Omeprazole 20 qd
Number of Patients Planned	560	560	560
Number of Patients Enrolled	654	656	650
Number of Patients Analyzed			
Efficacy ITT	654	656	650
Efficacy PP	536	550	534
Safety Analysis	653	655	649

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 H-1222-04-01-03 and H-1222-04-01-05
H 199/18 capsules 20 mg	-	Lots H-1189-04-01-02 and H-1189-04-01-04

Duration of Treatment: Up to 8 weeks

Reference Therapy, Dose and Mode of Administration, Batch or Lot Number:

Omeprazole capsules 20 mg	-	Lot H-0431-13-05-06
GELUSIL® Antacid tablets	-	Lots AM-173 and 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 to be completed 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 Hochberg procedure was used to correct for multiple comparisons. 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 three 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 94.1% (95% CI: 92.2% to 96.0%), 89.9% (95% CI: 87.5% to 92.3%) and 86.9% (95% CI: 84.2% to 89.6%) of patients by Week 8 for treatment with H40, H20, and O20, respectively (cumulative life table estimates – ITT population). There were statistically significant differences between treatments in the analysis of the primary efficacy parameter, healing of EE by Week 8, favoring H40 over O20 using both the log-rank test and the Wilcoxon test. There was a statistically significant difference between H20 and O20 in the analysis of healing of EE by Week 8 for the log-rank test. At Week 4, cumulative life table estimates of healing rates were 75.9, 70.5 and 64.7% for H40, H20, and O20, respectively. 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 was a significant difference in the percentage of patients exhibiting resolution of the investigator-recorded GERD symptom of heartburn at Week 4 favoring H40 (64.7%) over O20 (57.2%). The difference between H20 (61.0%) and O20 was not significant. There were no significant differences in the percentage of patients exhibiting resolution of the other investigator-recorded symptoms of GERD (acid regurgitation, dysphagia, epigastric pain) at Week 4 (comparison of either H 199/18 treatment to O20). There were no significant differences for any of the investigator-recorded GERD symptoms for relief of the symptom.

There were significant differences favoring H40 over O20 in diary-recorded time to first resolution of heartburn and in time to sustained resolution of heartburn. There were significant differences favoring H40 over O20 in percentage of heartburn free days (24 hours) and in percentage of heartburn free nights. There was a significant difference favoring H20 over O20 in percentage of heartburn free nights.

Safety Results:

Clinical Adverse Events The incidence of patients reporting any AE was 43.3, 44.7 and 41.0% for treatment with H40, H20, and O20, respectively. One patient died during the study (myocardial infarction, H20: 051/029). Six (0.9%), eight (1.2%) and six (0.9%) patients who received H40, H20 and O20, respectively, had clinical AEs that were considered serious. There were 13 (2.0%), 17 (2.6%) and 13 (2.0%) patients, respectively, who discontinued treatment due to clinical AEs. The most frequently reported AE was headache, which occurred in 8.6% of patients treated with H40, in 8.7% of patients treated with H20 and in 6.9% of patients treated with O20. The most frequently reported gastrointestinal AEs were diarrhoea, abdominal pain, nausea, flatulence, and gastritis. These side effects were reported at similar rates in all treatment groups.

Laboratory Safety The laboratory measurements which were most frequently outside predefined limits were SGPT (ALAT) where 7 H40 (1.2%), 3 H20 (0.5%), and 5 O20 (0.8%) patients were elevated (> 144 U/L) and hemoglobin where 5 H40 (0.8%), 7 H20 (1.2%), and 3 O20 (0.5%) were below the limit (< 9.5 g/dL in females and < 11.5 g/dL in males). Potassium exceeded the predefined limit (6.0 mEq/L) in 3 H40 (0.5%), 3 H20 (0.5%), and 4 O20 (0.7%) patients. The percent increase in the mean gastrin levels for patients treated with H 199/18 40 mg qd (134%) was larger than the increase for H 199/18 20 mg qd (105%) or for omeprazole 20 mg qd (83%). Other laboratory values were less frequently observed above or below the predefined limits. Mean changes in these laboratory measures from baseline were small and were generally comparable for the three treatment groups.

Date of the Report: 20 May 1999