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, Open-label, Long-term Safety Study of H 199/18 40 mg in Subjects with Healed Erosive Esophagitis.

Investigator(s): Multicenter

Study Center(s): 131 investigator sites initiated (64 from Study 173, 67 from Study 174); 111 investigator sites enrolled patients (56 from Study 173, 55 from Study 174)

Publication (reference): N/A

Studied Period (years): (date first drug dispensed) 11 November 1997 (date last patient completed) 16 March 1999	**Phase of Development:** Phase III

Objectives:

Primary Objective

To evaluate the safety and tolerability of long-term treatment with H 199/18 40 mg administered once daily in patients with healed erosive esophagitis (EE).

Secondary Objective

To describe the efficacy of open-label H 199/18 40 mg qd in the maintenance of healing of EE.

Methodology: This was a multicenter, open-label, long-term (12-month), noncomparative safety study in patients with healed EE. Patients whose EE was healed in Study 173 or Study 174 were eligible for enrollment in this study (Study 179). The final visit data from Study 173 and Study 174 served as baseline data for this study. Clinical assessments were performed at Months 1, 3, 6, 9, and 12 (final). Standard safety variables, including adverse events (AEs), clinical laboratory tests, vital signs, and concomitant medications were assessed at all visits. Esophagogastroduodenoscopy (EGD) was done at baseline (final visit of Study 173 and Study 174), Month 6, and at Month 12. Gastric biopsies were done at Month 12 to be compared to gastric biopsies collected at the baseline of Study 173 and Study 174. Patients whose EE recurred during Study 179 were kept in the study, at the investigator's discretion, until the end of Month 12.

[Study 173 assessed the efficacy and safety of H 199/18 40 mg qd in comparison with omeprazole 20 mg qd after 4 weeks or 8 weeks of treatment in patients with erosive esophagitis. Study 174 assessed the efficacy and safety of H 199/18 20 mg qd in comparison to omeprazole 20 mg qd after 4 weeks or 8 weeks of treatment in patients with erosive esophagitis.]

Number of Patients (Planned and Analyzed):

	H40
Number of Patients Planned	600
Number of Patients Enrolled	808
Number of Patients Analyzed	
Efficacy: Intent-to-Treat	808
Safety	807

Diagnosis and Main Criteria for Inclusion: Patients from Study 173 or Study 174 whose EE was reported as healed (Los Angeles Classification Grade = Not Present) on the final EGD in Study 173 or Study 174, and who were negative for *H. pylori* (by histology) at baseline of Study 173 or Study 174.

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Test Product, Dose and Mode of Administration, Batch or Lot Number:
H 199/18 capsules 40 mg - Lots H1222-04-01-04, H1222-04-01-05, H1222-04-01-06, and H1222-04-01-07

Duration of Treatment: Up to 12 months.

Reference Therapy, Dose and Mode of Administration, Batch or Lot Number: None

Criteria for Evaluation:

Efficacy: An EGD was completed at Month 6 and at Month 12 to evaluate maintenance of healing of esophageal erosions (ie, LA Classification = Not Present, no erosions present) through Month 12. EGD results from the final visit of Study 173 and Study 174 were used as the baseline confirmation of healing in this study, and EGD results from the baseline of Study 173 and Study 174, which were prior to healing treatment, were used for a subgroup summary.

Safety: Adverse events were recorded at each visit. Fasting clinical laboratory samples were collected at all visits. Clinical laboratory tests included standard serum chemistry, special serum chemistry (serum iron, gastrin, and B_{12}), hematology, and urinalysis (dipstick). Vital signs were recorded at each visit and a physical examination was done at the baseline, Month 6, and final (Month 12) visits. Biopsy samples taken at baseline of Study 173 or Study 174, and at the final visit in Study 179, were evaluated for chronic inflammation, intestinal metaplasia, and atrophy by the updated Sydney System of classification, atrophic gastritis, as well as for enterochromaffin-like (ECL) cell hyperplasia (ECL cell classification system) and *H. pylori*. In addition, biopsy samples with intestinal metaplasia or atrophy graded greater than Mild were evaluated for atrophic gastritis.

Statistical Methods: Safety was the primary objective of this study. Because this study was noncomparative, only descriptive statistics were used. All enrolled patients who received at least one dose of study drug were included in the assessment of safety. Summaries of adverse events, and incidence rates for adverse events by body system and preferred term, were tabulated over the entire study period (through Week 52; Month 12), and for events occurring through the end of Week 4 (Month 1), Week 13 (Month 3), Week 26 (Month 6), and Week 39 (Month 9). Laboratory test results were summarized using descriptive statistics for each test by visit, and for the change from baseline in each test by visit, as well as across all visits. Frequencies of patients with values outside the predefined limits of change (identified as potentially clinically significant) were determined. Vital signs were summarized by visit and across all visits using descriptive statistics. Summaries of gastritis ratings (chronic inflammation, intestinal metaplasia, and atrophy) were tabulated for baseline (baseline of Study 173 or Study 174) and final (end of Study 179) biopsy data for antral sites, fundic sites, and all sites combined. Frequencies of patients with an increase (worsening) from baseline were determined for each rating at each location. Biopsy evaluations for atrophic gastritis were also tabulated for baseline and final biopsy data. Frequencies of ECL cell ratings at the baseline and final biopsies were tabulated, as were frequencies of patients who had an increase (worsening) in ECL cell rating.

For efficacy, the healing status (maintenance of EE defined as LA Classification = Not Present) of all patients was summarized at Month 6 and Month 12. Because patients who recurred at Month 6 could, at the investigator's discretion, remain in the study, a shift table of maintenance of healing of EE status at Month 12 by maintenance of healing status at Month 6 was done. Maintenance of healing status through the final visit was summarized by gender, age group, race, and LA Classification Grade at baseline of Study 173 or Study 174.

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SUMMARY

Efficacy Results: In the 808 patients previously healed in Study 173 or Study 174 and enrolled in this study, life-table estimates of the maintenance of healing of EE were 93.7% (CI = 92.0%, 95.5%) at Month 6 and 89.4% (CI = 87.0%, 91.7%) at Month 12. In addition, of 27 patients who had demonstrated a recurrence of EE at Month 6 and had a final EGD at Month 12, 22 (81.5%) were evaluated as maintained at Month 12, while 5 patients (18.5%) continued to demonstrate recurrence. The remaining 16 patients who demonstrated recurrence at Month 6 did not have an EGD after Month 6 (all were discontinued prior to completing 7 months of treatment, only 2 for lack of efficacy). There were no apparent effects of gender, age, race, or initial LA Classification on the maintenance of healing of EE.

Safety Results:

Clinical Adverse Events (AEs): Six hundred fifty-three (80.9%) of the 807 patients treated completed at least 6 months (26 weeks) of daily treatment and 565 patients (70.0%) completed daily treatment until their 12-month visit (at least 48 weeks of treatment). The mean duration of treatment was 297 days. The cumulative proportions of patients reporting at least one AE at Month 1, Month 6, and Month 12, were: 37.4%, 68.3%, and 78.2%, respectively. The percentage of patients with at least one AE that the investigator considered of Possible or Probable relationship to study treatment was 23.8%, most of which were gastrointestinal AEs. The most frequently reported AEs were respiratory infection (13.0%), headache (10.3%), sinusitis (9.8%), diarrhoea (9.4%), abdominal pain (9.3%), accident or injury (7.2%), gastritis (6.8%, an endoscopy finding), nausea (6.1%), and back pain (5.9%). The nature of the adverse events reported after 6 months and 12 months of treatment was similar to that reported after 1 month of treatment. One patient died 77 days post-study (pancreatic cancer) and there were no drug-related serious AEs. Forty-four patients (5.4%) had serious AEs. Sixty-one patients (7.5%) discontinued treatment due to AEs. The AEs most frequently associated with discontinuation were nausea, abdominal pain, and flatulence.

Laboratory Test Results: Mean changes in laboratory measurements were generally small and were not clinically meaningful. Individual changes from normal at baseline to outside normal limits at any time point after baseline were most frequently observed in serum gastrin, ALAT, hemoglobin, ASAT, white blood cell counts, serum B_{12}, and alkaline phosphatase. The largest mean changes were moderate treatment-related mean increases from baseline seen in serum gastrin (pg/mL): 44.90 (Month 1), 53.27 (Month 3), 21.59 (Month 6), 80.92 (Month 9), and 39.41 (Month 12). The fluctuations in mean gastrin increases may have been related to the fasting state of the patients. There were clinically meaningful individual changes in ALAT, ASAT, and hemoglobin in a small number of patients, and in white blood cell counts in 1 patient. However, no clinically meaningful mean nor individual changes were seen in any other laboratory parameter. Of the 6 patients discontinued due to abnormal laboratory findings, 5 patients were discontinued due to elevated liver function tests, 4 of whom had these elevations at baseline (end of Study 173 or Study 174), and 1 patient was discontinued due to a decreased white blood cell count at Month 6 (returned to within normal limits 7 days after treatment was discontinued).

Vital Signs and Physical Examinations: There were no clinically meaningful changes in vital signs (blood pressure and pulse rate) or physical examinations (including weight) over the course of the study.

Gastric Biopsy Results: Gastric biopsy evaluations revealed very few increases for chronic inflammation, atrophy, and intestinal metaplasia at either antral locations (2.6, 1.1, and 0.4%, respectively) or fundic locations (2.5, 1.0, and 0.6%, respectively). For all three gastritis characteristics, but especially for chronic inflammation, the number of patients with decreased (improved) ratings post-baseline was higher than the number of patients with increased (worsened) ratings. At the final biopsy, 2 patients had atrophic gastritis. These included 1 patient who had atrophic gastritis at baseline and 1 patient with treatment-emergent atrophic gastritis. The biopsy data available for these two patients was not sufficient to draw conclusions regarding the relationship of the atrophic gastritis to study treatment, prior *H. pylori* infections, or other possible contributing factors.

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Gastric Biopsy Results (Continued): ECL cell ratings showed that 1 patient had micronodular hyperplasia at the final biopsy (4 patients had micronodular hyperplasia at baseline); all other non-normal, post-baseline ECL cell ratings were either linear or simple hyperplasia. Increases (worsening) in ECL cell ratings were seen in 6.4% of the 601 patients who had both a baseline and final ECL cell evaluation. Maximum serum gastrin values for those patients with ECL cell increases tended to be higher than for patients without ECL cell increases.
Of the 16 patients who were *H. pylori* positive at their baseline biopsy, 3 were positive at their final biopsy, 4 were negative at their final biopsy, and 9 did not have evaluable final biopsies. One of the 16 patients had a non-normal ECL cell rating (simple hyperplasia at final biopsy). No patients who were *H. pylori* negative at baseline were *H. pylori* positive at their final biopsy.

Date of the Report: 27 August 1999