2.0 SYNOPSIS

Name of Company: AstraZeneca LP	**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: esomeprazole magnesium	**Page:** N/A	

Title of Study: A Comparative Efficacy Study of Esomeprazole Magnesium (40 mg qd) and Lansoprazole (30 mg qd) in Patients with Erosive Esophagitis

Study Center(s): 242 investigator sites initiated; 228 investigator sites enrolled patients

Publication (reference): N/A

Studied Period (years): < 1 year (date first drug dispensed) 11 July 2000 (date last patient completed) 09 March 2001	**Phase of development:** Phase III

Objectives:

Primary Objective

1. To assess the efficacy, as defined by complete healing of erosive esophagitis, of esomeprazole 40 mg qd (E40) compared to lansoprazole 30 mg qd (L30) through Week 8 of treatment in patients with erosive esophagitis.

Secondary Objectives

1. Efficacy, as defined by complete healing of erosive esophagitis, of E40 compared to that of L30 at Week 4 of treatment.
2. Complete resolution and relief of investigator-assessed GERD symptoms of heartburn, acid regurgitation, dysphagia, and epigastric pain by E40 compared to L30 at Week 4 of treatment.
3. Time to first resolution and to sustained resolution of heartburn (patient diary data) by E40 compared to L30.
4. Safety and tolerability of E40 compared to that of L30.

Methodology: This was a multicenter, randomized, double-blind, double-dummy, parallel-group study to compare the healing efficacy and safety of esomeprazole to that of lansoprazole 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, E40 or L30, for up to 8 weeks of therapy. All patients were reevaluated by EGD at Week 4 of treatment and, if unhealed, continued in the study and returned 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.

Number of Patients (Planned and Analyzed):

	E40	L30
Number of Patients Planned	2,500	2,500
Number of Patients Enrolled	2,624	2,617
Number of Patients Analyzed		
Efficacy: Intent-to-Treat	2,624	2,617
Efficacy: Per-Protocol	2,441	2,439
Safety	2,620	2,608

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

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Name of Finished Product:		
Name of Active Ingredient: Esomeprazole magnesium		

Test Product, Dose and Mode of Administration, Batch or Lot Number:

esomeprazole capsules 40 mg - Lot H-1222-06-01-08
esomeprazole capsules PLACEBO - Lot H-1321-01-01-01

Duration of Treatment: Up to 8 weeks

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

lansoprazole capsules 30 mg - Lot H-0995-06-01-02 and Lot H-0995-06-01-03
lansoprazole capsules PLACEBO - Lot H-1481-01-01-01
GELUSIL® Antacid tablets - Lots 04050B, 03660B, 03850B, 039N9B, and 040N9B

Criteria for Evaluation:

Efficacy: The primary efficacy parameter was the percentage of patients who exhibited complete healing of esophageal erosions on EGD evaluation (ie, LA Classification Grade = Not Present; no erosions present) by Week 8 of treatment. Secondary efficacy parameters were: (1) the percentage of patients with complete healing of esophageal erosions 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); (3) time to first resolution and to sustained resolution of heartburn using diary card information (resolution defined as heartburn recorded as None and sustained resolution defined as 7 consecutive days with heartburn recorded as None); and (4) the mean percentage of heartburn-free days and nights.

Safety: All randomized patients who received at least one dose of study drug were included in the safety population for analysis. Evaluations for adverse events were made at each post-baseline visit. Clinical laboratory evaluations were completed on fasting patients at baseline and at the final visit. Clinical laboratory tests included serum chemistry and hematology. Vital signs were recorded at each visit and body weight was recorded at baseline and at the final visit.

Statistical Methods: Primary healing efficacy data were analyzed for intent-to-treat (ITT) and per-protocol (PP) populations. Determinations of the PP and ITT populations were set prior to unblinding the data. Kaplan-Meier life-table estimates were used to determine the percentage of patients with healed erosive esophagitis (EE) by Week 8 (primary efficacy parameter), and a log-rank test was used to assess differences between treatment groups. Crude healing rates at Week 4 and Week 8 were analyzed using a Cochran-Mantel-Haenszel (CMH) test with stratification on baseline severity of EE (LA Classification Grade). 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), as well as the percentage of heartburn-free days and heartburn-free nights (analysis of variance).

Adverse events, laboratory results, vital signs, and body weight data were tabulated descriptively for each of the two treatment groups. Laboratory measurements were also summarized according to predefined limits of change and shifts from baseline.

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SUMMARY

Efficacy Results: For both the ITT and PP populations, the proportion of patients with healing of EE by Week 8 was significantly higher in the E40 group than in the L30 group ($p = 0.0001$; log-rank test). Cumulative life-table estimates of healing rates for the ITT population for the E40 and L30 groups were 79.4% and 75.1%, respectively, by Week 4, and 92.6% and 88.8%, respectively, by Week 8. For the PP population, cumulative life-table estimates of healing rates for the E40 and L30 groups were 80.7% and 76.0%, respectively, by Week 4, and 93.1% and 89.2%, respectively, by Week 8.

When baseline EE severity grade (LA Classification) was taken into account (CMH test), significant differences between treatments were again seen in the proportion of patients with healing of EE in both the ITT ($p < 0.01$) and PP populations ($p < 0.001$) by both Week 4 and Week 8. The difference in healing rates for EE by Week 8 in the ITT population for each baseline LA Grade (ie, the difference in the percentage of patients with healing of EE in the E40 group minus that in the L30 group) was 0.4%, 0.3%, 10.0%, and 17.6% for LA Grades A, B, C, and D, respectively.

No clinically meaningful differences were seen in summaries of healing of EE in predefined subsets of patients by gender, age, race, *H. pylori* status, nor investigator site, although no statistical analyses were performed on these data. The results of E40 treatment were significantly better than results for L30 treatment for three of the six secondary efficacy parameters related to symptoms: complete resolution of investigator-recorded symptoms of GERD (significant for heartburn), number of days to sustained resolution of heartburn (patient diary), and mean percent of heartburn-free nights (patient diary). Results for the other three secondary efficacy parameters related to symptoms (relief of investigator-recorded symptoms of GERD, number of days to first resolution of heartburn [patient diary], and mean percent of heartburn-free days[patient diary]) were generally higher for E40 than for L30, but the differences were not statistically significant.

Safety Results:

Clinical Adverse Events: The incidence of patients reporting any AE was 31.7% with E40 and 30.9% with L30. Two patients (1 in each treatment group) died. Both patients died after completing the study, and both deaths were considered by the investigator to be unrelated to study drug. Eighteen patients (0.7%) who received E40 and 14 (0.5%) who received L30 had AEs that were considered serious; 3 of which were related to study drug. There were 48 patients (1.8%) who received E40 and 49 (1.9%) who received L30 who were discontinued from the study due to an AE. The most frequently reported AE was headache, which occurred in 5.8% of the patients treated with E40 and 4.5% of the patients treated with L30. The most frequently reported gastrointestinal AEs were diarrhea, abdominal pain, flatulence, and nausea. These side effects were reported at similar rates in both treatment groups.

Laboratory Safety: Mean changes from baseline were small and were comparable between the two treatment groups. The laboratory measurement that was most frequently outside predefined limits (identified by the Sponsor as potentially clinically significant) was hemoglobin, for which 25 E40 (1.0%) and 15 L30 (0.6%) patients had values below the predefined lower limit (9.5 g/dL for females and 11.5 g/dL for males). Other laboratory values were less frequently observed above or below the predefined limits and there were no clinically meaningful differences between the treatment groups in the incidence of shifts from within normal limits to above or below normal limits in individual patients' values.

Vital Signs: There were no clinically meaningful changes in blood pressure or pulse rate and no differences between the two treatment groups.