AstraZeneca

Drug product	NEXIUM® 40 mg capsules	**SYNOPSIS**	
Drug substance(s)	Esomeprazole		
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A Multicenter, Randomized, Double-Blind, Double-Dummy, Parallel-Group Efficacy Study Comparing 8 Weeks of Treatment with Esomeprazole Magnesium (40 mg qd) to Lansoprazole (30 mg qd) for the Healing of Erosive Esophagitis in Patients with Moderate or Severe Erosive Esophagitis

Study center(s)

This study was conducted at 163 study centers in the US.

Publications

None at the time of writing this report.

Study dates		**Phase of development**
First patient enrolled	18 December 2002	Therapeutic use (IV)
Last patient completed	8 August 2003	

Objectives

Primary objective: To compare the difference in healing rates of erosive esophagitis (EE) between esomeprazole 40 mg qd (E40) and lansoprazole 30 mg qd (L30) in patients with moderate or severe EE, defined as Grade C or D in the Los Angeles (LA) Classification scale.

Secondary objectives:

1. To compare the difference in the resolution of, and relief of, the investigator evaluated gastroesophageal reflux disease (GERD) symptoms of heartburn, acid regurgitation, dysphagia, and epigastric pain between E40 and L30 at Week 4 of treatment in patients with moderate or severe EE

2. To compare the difference between E40 and L30 in the occurrence of heartburn symptoms as reported in the patient's daily diary

3. To evaluate the safety and tolerability of E40 compared to that of L30 in patients with moderate or severe EE.

Study design

This was a multicenter, randomized, double-blind, double-dummy, parallel-group, up to 8-week comparative efficacy and safety study of esomeprazole 40 mg and lansoprazole 30 mg in patients with moderate or severe EE. Patients healed in this study were eligible to enter a separate study of maintenance of EE healing (Study 325).

Target patient population and sample size

Male and female patients between 18 and 75 years of age with moderate or severe EE as defined by Grade C or D in the LA Classification scale.

It was estimated that a sample size of 474 patients per treatment group (948 patients in total) would be needed to detect a 10% difference in healing rate (85% for E40 vs 75% for L30) with a 5% significance level and 95% power, allowing for a dropout rate of up to 10%.

Investigational product and comparator(s): dosage, mode of administration, and batch numbers

E40: -Esomeprazole magnesium 40 mg once daily
(40 mg oral capsule, batch number H1222-04-01-10) &
-Placebo (to match the lansoprazole 30 mg capsule) once daily
(batch number H0995-06-01-05)

L30: -Lansoprazole 30 mg once daily
(30 mg oral capsule, batch number H1481-01-01-01) &
-Placebo (to match the esomeprazole 40 mg capsule) once daily
(batch number H0459-06-03-10)

GELUSIL® tablets were provided as a rescue medication for relief of GERD symptoms.

Duration of treatment

Up to 8 weeks.

Criteria for evaluation (main variables)

Efficacy

- Primary variable: EE status (healed/not healed) through Week 8. 'Healed' was defined in the LA Classification scale as EE 'Not Present.'

- Secondary variables:

  - EE status through Week 4.

  - Resolution of GERD symptoms as evaluated by the investigator. 'Resolution' was defined as None (no symptom) on a 4-point scale (None, Mild, Moderate, and Severe) for the 7 days prior to the Week 4 or Week 8 visit.

  - Relief of GERD symptoms as evaluated by the investigator. 'Relief' was defined as No or Mild symptoms on the 4-point scale for the 7 days prior to the Week 4 or Week 8 visit.

  - Time to first resolution of heartburn from the patient's daily diary; ie, time to first day on which the patient reported no symptoms of heartburn

  - Time to sustained resolution of heartburn from the patient's daily diary; ie, time to the first day of the first 7-consecutive day period during which the patient reported no symptoms of heartburn

  - Percent heartburn-free days from patient's daily diary through Week 4

  - Percent heartburn-free nights from patient's daily diary through Week 4.

Safety

Standard safety assessments included adverse event (AE) reports, clinical laboratory tests, physical examinations, and vital signs.

Statistical methods

The efficacy endpoints were analyzed using an 'intention-to-treat' (ITT) population, which included all randomized patients with EE of Grade C or D at baseline, who took at least one dose of study medication. The primary efficacy endpoint was also analyzed using a 'per-protocol' (PP) patient population, which was a subset of the ITT population, created by excluding, in a blinded fashion, those patients who met pre-defined criteria for non-evaluability. All safety evaluations were made using a safety population, which comprised all randomized patients who took at least one dose of study medication.

The primary analysis was made using a log-rank test to compare E40 and L30 with respect to EE healing rate through Week 8, where the healing rate was estimated by the Kaplan Meier method. The estimated rates were also calculated through Week 4. In addition, the observed

healing rates were compared at Weeks 4 and 8 using a Cochran-Mantel-Haenszel (CMH) test stratified by baseline grade of EE.

Resolution (severity 'None') and relief (severity 'None' or 'Mild') of GERD symptoms assessed by the investigator were analyzed using a CMH test stratified by the baseline severity of each symptom.

'Time to' first resolution and 'time to' sustained resolution of heartburn from the patients' assessment in the daily diary through Week 4 were analyzed using a log-rank test. The percent of heartburn-free days and percent of heartburn-free nights were compared between treatment groups using an ANOVA model.

All safety parameters were summarized descriptively. No formal comparisons were made.

Patient population

As shown in Table S1 below, the treatment groups were generally well balanced in terms of demographics, baseline characteristics, dropouts, and eligibility for the ITT and PP populations. Overall, 93.8% of the patients completed the study. The most common reasons for discontinuation were 'lost to follow-up' and 'other' for the E40 group, and 'adverse event' and 'lost to follow-up' for the L30 group.

Table S1 Patient population and disposition

		E40	L30	Total
Patient disposition				
N randomized (N planned)		499 (474)	502 (474)	1001 (948)
Completed study: n (%)		467 (93.6%)	472 (94.0%)	939 (93.8%)
Discontinued: n (%)		32 (6.4%)	30 (6.0%)	62 (6.2%)
N analyzed for safety [a]		498 (99.8%)	501 (99.8%)	999 (99.8%)
N analyzed for efficacy (ITT)[a]		498 (99.8%)	501 (99.8%)	999 (99.8%)
N analyzed for efficacy (PP)[b]		458 (91.8%)	450 (89.6%)	908 (90.7%)
Demographic characteristics (ITT)				
Gender: n (%)	Male	327 (65.7%)	333 (66.5%)	660 (66.1%)
	Female	171 (34.3%)	168 (33.5%)	339 (33.9%)
Age in years:	Mean (SD)	47.3 (13.2)	47.1 (12.9)	47.2 (13.1)
	Range	19 to 78	19 to 75	19 to 78
Race: n (%)	Caucasian	411 (82.5%)	411 (82.0%)	822 (82.3%)
	Black	20 (4.0%)	27 (5.4%)	47 (4.7%)
	Oriental	3 (0.6%)	2 (0.4%)	5 (0.5%)
	Other	64 (12.9%)	61 (12.2%)	125 (12.5%)
Baseline characteristics (ITT)				
LA Grade: n (%)	C	390 (78.3%)	403 (80.4%)	793 (79.4%)
	D	108 (21.7%)	98 (19.6%)	206 (20.6%)
GERD history: n (%)	<1 year	38 (7.6%)	27 (5.4%)	65 (6.5%)
	1-5 years	204 (41.0%)	203 (40.5%)	407 (40.7%)
	>5 years	256 (51.4%)	271 (54.1%)	527 (52.8%)
EE history: n (%)	Yes	166 (33.3%)	158 (31.5%)	324 (32.4%)
	No	332 (66.7%)	343 (68.5%)	675 (67.6%)
H. pylori serology: n (%)	Positive	54 (10.8%)	34 (6.8%)	88 (8.8%)
	Negative	437 (87.8%)	466 (93.0%)	903 (90.4%)

[a] Number of patients who took at least 1 dose of study treatment and had EE of LA Grade C or D at baseline.
[b] Number of patients who met predefined criteria for evaluability.
E40 = esomeprazole 40 mg qd; L30 = lansoprazole 30 mg qd
ITT = Intention to treat; PP = Per-protocol

Efficacy results

As shown in the Table S2 below, the E40 treatment group was associated with a significantly higher estimated cumulative healing rate through Week 8 than the L30 treatment group (primary outcome measure). The data for the secondary outcome measures provided further

evidence of the relative efficacy of E40 compared to L30. E40 healing rates were consistently higher than L30 rates, with a significant difference in observed rates at Week 4. E40 was also associated with a significantly higher resolution rate for investigator-assessed heartburn at Week 4. There were no other significant treatment differences in either investigator- or patient-assessed symptom control.

Table S2 Summary of efficacy results (ITT population)

	E40		L30		p-value
	N	Result	N	Result	(E40 vs L30)
Estimated cumulative % of patients with EE healed through Week 4 (from EGD)[a]	498	58.6%	501	49.4%	--
Estimated % of patients with EE healed through Week 8 (from EGD)[a]	498	82.4%	501	77.5%	0.007
Observed % of patients with EE healed at Week 4 (from EGD)[b]	498	55.8%	501	47.5%	0.005
Observed cumulative % of patients with EE healed at Week 8 (from EGD)[b]	498	77.5%	501	73.3%	0.099
% of patients with resolution of GERD symptoms at Week 4 (per investigator)[c]:					
Heartburn	478	72.0%	483	63.6%	0.005
Acid regurgitaion	478	79.5%	483	76.2%	0.203
Dysphagia	478	93.1%	483	93.8%	0.614
Epigastric pain	478	83.1%	483	82.6%	0.831
% of patients with relief of GERD symptoms at Week 4 (per investigator)[d]:					
Heartburn	478	89.3%	483	87.8%	--
Acid regurgitaion	478	91.0%	483	93.2%	--
Dysphagia	478	98.1%	483	98.1%	--
Epigastric pain	478	94.1%	483	93.6%	--
Median number of days to first resolution of heartburn (from patient's daily diary)[e]	476	2.0	474	2.0	0.436
Median number of days to sustained resolution of heartburn (from patient's daily diary)[f]	476	6.0	474	6.0	0.076
% heartburn-free days in first 4 weeks (from patient's daily diary)[g]	476	74.6%	474	72.7%	0.303
% heartburn-free nights in first 4 weeks (from patient's daily diary)[g]	480	86.0%	477	84.7%	0.263

[a] Healed = EE not present; p-value is from log-rank test on Kaplan-Meier estimates.
[b] p-value is from CMH test on observed values stratified by baseline grade of EE.
[c] Resolution = No symptom; p-value is from CMH test stratified by baseline severity of each symptom.
[d] Relief = No or mild symptom; p-value is from CMH test stratified by baseline severity of each symptom.
[e] p-value is from log-rank test.
[f] Sustained resolution = no symptom for 7 consecutive days; p-value is from log-rank test.
[g] p-value is from ANOVA.
E40 = esomeprazole 40 mg qd; L30 = lansoprazole 30 mg qd
ITT Intention to treat; EGD = esophagogastroduodenoscopy

Safety results

Both treatments were well tolerated and were generally similar with respect to the frequency, type, intensity, and duration of AEs (see Table S3 and Table S4). There were no notable trends within or between treatments with respect to clinical laboratory tests, vital signs, or physical examinations. Among the most commonly reported events, the observed incidence of diarrhea was higher in the L30 treatment group (22 patients vs 10 in the E40 group).

Table S3 Number (%) of patients who had at least 1 adverse event in any category, and total numbers of adverse events (safety population)

Category of adverse event	E40 (N=498)	L30 (N=501)	Overall (N=999)
	Number (%) of patients who had an adverse event in each category[a], Weeks 0-8		
Any adverse events	165 (33.1%)	185 (36.9%)	350 (35.0%)
Serious adverse events			
Serious adverse events leading to death	0	0	0
Serious adverse events not leading to death	2 (0.4%)	4 (0.8%)	6 (0.6%)
Discontinuations of study treatment due to adverse events	5 (1.0%)	9 (1.8%)	14 (1.4%)
Treatment-related adverse events	31 (6.2%)	37 (7.4%)	68 (6.8%)
	Total number of adverse events		
Adverse events[b]	275	348	623
Serious adverse events[b]	2	6	8
Adverse events leading to discontinuation[b]	7	9	16
Treatment-related adverse events[b]	44	47	91

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

[b] Events are counted by preferred term; ie, for patients with multiple events falling under the same preferred term, only 1 occurrence of the event is counted.

E40 = esomeprazole 40 mg qd; L30 = lansoprazole 30 mg qd

Table S4 Number (%) of patients with the most commonly reported[a] adverse events, sorted by decreasing order of frequency as summarized over all treatment groups (safety population)

Adverse event (preferred term)	Number (%) of patients who had an adverse event, Weeks 0-8		
	E40 (N=498)	L30 (N=501)	Overall (N=999)
Barrett's esophagus	14 (2.8%)	19 (3.8%)	33 (3.3%)
Gastritis NOS	19 (3.8%)	14 (2.8%)	33 (3.3%)
Diarrhea NOS	10 (2.0%)	22 (4.4%)	32 (3.2%)
Headache	16 (3.2%)	15 (3.0%)	31 (3.1%)

[a] Events with a total frequency of ≥2% in either treatment group are included in this table.
E40 = esomeprazole 40 mg qd; L30 = lansoprazole 30 mg qd

Date of the report

23 January 2004