AstraZeneca

Drug product:	NEXIUM®	**SYNOPSIS**	
Drug substance(s):	esomeprazole magnesium		
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A Multi-Centered, Phase IV, Post-Marketing, Prospective, Randomized, Double-Blind Study Comparing Esomeprazole Magnesium 40 mg Once Daily versus Lansoprazole 30 mg Twice Daily in Symptom Control of Subjects with Persistent Symptoms of Gastroesophageal Reflux Disease While on 30 mg Once Daily Lansoprazole Therapy

Study center(s)

This study was conducted at 52 study sites in the U.S.

Publications

None at the time of writing this report.

Study dates		**Phase of development**
First patient enrolled	28 June 2002	Therapeutic use (IV)
Last patient completed	12 February 2003	

Objectives

The primary objective of this study was to compare the clinical efficacy of esomeprazole magnesium 40 mg qd versus lansoprazole 30 mg bid in symptom control of heartburn in patients with persistent heartburn symptoms while on to 30 mg once daily therapy of lansoprazole.

Secondary objectives were: (1) to compare the clinical efficacy of esomeprazole magnesium 40 mg qd versus lansoprazole 30 mg bid in symptom control of acid regurgitation, epigastric pain, and night-time heartburn in patients with GERD-associated symptoms resistant to 30 mg once daily therapy of lansoprazole, (2) to evaluate the use of supplemental antacids (as heartburn rescue therapy) in patients treated with esomeprazole magnesium 40 mg qd versus lansoprazole 30 mg bid, and (3) to assess tolerability of esomeprazole magnesium 40 mg qd versus lansoprazole 30 mg bid.

Study design

This was a multi-centered, Phase IV, post-marketing, prospective, randomized, double-blind comparative study of esomeprazole magnesium (NEXIUM®) 40 mg once daily and lansoprazole 30 mg twice daily to evaluate the symptom control of patients with gastroesophageal reflux disease (GERD) with continued heartburn symptoms with a course of therapy of at least 30 days of 30 mg once daily lansoprazole. All patients completed a daily symptom diary throughout the 8-week treatment period. The investigator assessment of heartburn symptoms was performed at randomization and after 4 weeks and 8 weeks of treatment.

Target patient population and sample size

Male and female patients over the age of 18 years with no current or historical evidence of esophageal ulcers or strictures, gastric or duodenal ulcers, or any other significant gastric or esophageal pathology judged to be clinically significant by the investigator, and with a reported history of heartburn symptoms of any severity on an average of at least 2 days per week during the 30 days prior to screening while on lansoprazole 30 mg qd.

The sample size calculation was based on the confidence interval approach for a non-inferiority trial. The 2 treatments were considered clinically equivalent if the lower limit of the 90% confidence interval for the difference was greater than the pre-specified equivalence value δ.

The primary endpoint in this study was the percentage of heartburn-free days from Day 8 to the end of study treatment, which is defined as:

$$\frac{\text{Number of days with no heartburn post-Day 7}}{\text{Total number of days treated (post-Day 7)}} \times 100$$

The study was designed to rule out differences between esomeprazole and lansoprazole (esomeprazole - lansoprazole) of -10 or more. For this study, a mean difference of 10 or less was considered to be equally effective in symptom control of patients with persistent heartburn symptoms while on lansoprazole 30 mg qd. To test this hypothesis using a 1-sided test while maintaining an alpha level of 0.05, it was estimated that 248 evaluable patients (124 in each arm) would provide at least 80% power. This calculation assumed that the true difference between the 2 treatments was in fact zero and that the common standard deviation was 30.5.

To allow for a drop-out rate of 17% during treatment, it was planned to randomize approximately 300 patients. To allow for the approximately 25% of patients failing to meet the inclusion/exclusion criteria, it was planned to enroll (screen) approximately 400 patients.

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

Drug	Dosage	Mode of Administration	Batch Number
Esomeprazole	40 mg qd	oral	AM-631
Lansoprazole	30 mg bid	oral	AM-631

Duration of treatment

A 2-week (14- to 17-day) baseline symptom assessment period, followed by an 8-week treatment period. Symptoms occurring prior to Day 8 were not analyzed; Days 1 through 7 were considered a washout period for the previously administered lansoprazole 30 mg qd.

Criteria for evaluation (main variables)

Efficacy

Primary variable: Percentage of heartburn-free days (defined as a day in which heartburn was absent during an entire 24-hour period) as recorded on the daily diary from Day 8 to the end of treatment.

Secondary variables:

- Percentage of symptom-free days (as recorded in the daily diary) for GERD-associated symptoms including acid regurgitation and epigastric pain from Day 8 to the end of treatment.
- Percentage of night-time heartburn-free days from Day 8 to the end of treatment.
- Percentage of patients with symptom improvement based on weekly symptom score from baseline (mean weekly score of 2-week baseline period) compared to last week of study drug treatment. Improvement is defined as any decrease in weekly symptom score from baseline.
- Average weekly score for heartburn, acid regurgitation, and epigastric pain from Day 8 to the end of treatment.
- Investigator assessment of symptoms at Week 4 and Week 8.
- Mean GELUSIL tablet consumption in each group from Day 8 to the end of treatment.

Safety

Standard safety assessments included medical history, physical examination, review of adverse events (AEs), clinical laboratory evaluations, and vital signs.

Statistical methods

The primary analysis was based on the ITT population, although analysis was also performed on the PP population to assess the robustness of the results. The primary efficacy variable was the percentage of heartburn-free days (defined as a day in which heartburn was absent during an entire 24-hour period) as recorded on the daily diary from Day 8 to the end of treatment. The study was designed to test the hypothesis that esomeprazole 40 mg qd is equally effective as lansoprazole 30 mg bid in symptom control in patients who had persistent heartburn symptoms while taking lansoprazole 30 mg qd. For this study, a mean difference of 10 or less was considered to be equally effective. Therefore, the statistical test that was employed needed to rule out differences of 10 or more in favor of lansoprazole. This was accomplished by the following procedure. First the endpoint was analyzed using analysis of covariance (ANCOVA). The ANCOVA model included center and treatment group as factors, and the patients' average baseline severity score as the covariate. Next, a 90% confidence interval of the difference in the least square means between the 2 treatments (esomeprazole - lansoprazole) was constructed. If the lower end of the 90% confidence interval for the difference of esomeprazole – lansoprazole was above the pre-specified equivalence limit of -10, then esomeprazole 40 mg qd was considered at least as effective as lansoprazole 30 mg bid at an alpha level of <0.05.

The percentage of symptom-free days for the other diary heartburn symptoms (ie, acid regurgitation, epigastric pain, and night-time heartburn) was evaluated using a similar analysis; however, since there were no pre-specified equivalence limits for these secondary endpoints, nominal p-values testing for treatment differences were also displayed.

The percentage of patients with symptom improvement was compared between treatment groups using Fisher's Exact Test. Weekly average GERD symptoms were analyzed using a repeated-measures model. Baseline scores were included in the model as a covariate, as well as terms for center, time, and treatment. Mean antacid consumption was analyzed with an ANOVA model. The model included center and treatment. The Cochran-Mantel-Haenszel statistics were used to assess the investigator-recorded GERD symptoms. The baseline severity was used as a stratifying variable for this analysis.

Additional descriptive and graphical displays were generated to support and supplement the analyses being performed. No inferential statistical methods were used for the safety or demographic data. Descriptive statistics were provided. All statistical tests performed were 2-tailed, unless otherwise specified, and all p-values were rounded to 3 decimal places. No adjustments for multiplicity were made.

Patient population

In total, 420 patients were screened at the study sites and 328 were randomized to study treatment. Three patient populations were analyzed: the intent-to-treat (ITT) population, the per-protocol (PP) population, and the safety population. All decisions on the inclusion or exclusion of patients from analysis populations were made while the treatments were still blinded. The ITT analysis population was considered the primary analysis group.

Table S1 Disposition of all randomized patients

	Esomeprazole 40 mg qd		Lansoprazole 30 mg bid		Total	
Disposition	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Randomized	160	(100.0)	168	(100.0)	328	(100.0)
Evaluable for ITT	138	(86.3)	144	(85.7)	282	(86.0)
Not evaluable for ITT	22	(13.8)	24	(14.3)	46	(14.0)
Evaluable for PP	130	(81.3)	139	(82.7)	269	(82.0)
Not evaluable for PP	30	(18.8)	29	(17.3)	59	(18.0)
Withdrawals	24	(15.0)	23	(13.7)	47	(14.3)
Completed protocol	136	(85.0)	145	(86.3)	281	(85.7)

Table S2 Summary of demographic characteristics (intent-to-treat population)

Demographic characteristics		Esomeprazole 40 mg qd (n=138)		Lansoprazole 30 mg bid (n=144)		Total (n=282)	
Gender, n (%)	Male	56	(40.6)	66	(45.8)	122	(43.3)
	Female	82	(59.4)	78	(54.2)	160	(56.7)
Age, years	Mean (SD)	49.0	(12.5)	48.3	(13.6)	48.7	(13.1)
	Range	20 to 78		19 to 76		19 to 78	
Race, n (%)	Caucasian	114	(82.6)	122	(84.7)	236	(83.7)
	Black	18	(13.0)	12	(8.3)	30	(10.6)
	Hispanic	5	(3.6)	8	(5.6)	13	(4.6)
	Asian	1	(0.7)	1	(0.7)	2	(0.7)
	Indian	0	(0.0)	1	(0.7)	1	(0.4)

Table S3 Summary of baseline characteristics (intent-to-treat population)

Baseline characteristic		Esomeprazole 40 mg qd (n=138)		Lansoprazole 30 mg bid (n=144)		Total (n=282)	
Height (cm), n (%)	Mean (SD)	168.2	(11.2)	169.2	(10.1)	168.7	(10.6)
	Range	132.1 to 189.2		147.3 to 188.0		132.1 to 189.2	
Weight (kg), n (%)	Mean (SD)	86.9	(19.7)	87.5	(19.2)	87.2	(19.4)
	Range	50.8 to 172.4		47.6 to 145.1		47.6 to 172.4	
Body mass index (kg/m^2), n (%)	Mean (SD)	30.8	(6.3)	30.6	(6.7)	30.7	(6.5)
	Range	17.5 to 53.8		19.4 to 49.7		17.5 to 53.8	
H. pylori serology	Positive	2	(1.4)	1	(0.7)	3	(1.1)
	Negative	136	(98.6)	143	(99.3)	279	(98.9)
Investigator assessment-Heartburn	None	2	(1.4)	0	(0.0)	2	(0.7)
	Mild	43	(31.2)	48	(33.3)	91	(32.2)
	Moderate	65	(47.1)	71	(49.3)	136	(48.2)
	Severe	22	(15.9)	18	(12.5)	40	(14.2)
	Unknown	6	(4.3)	7	(4.9)	13	(4.6)
Investigator assessment-Acid regurgitation	None	10	(7.2)	19	(13.2)	29	(10.3)
	Mild	54	(39.1)	53	(36.8)	107	(37.9)
	Moderate	49	(35.5)	49	(34.0)	98	(34.8)
	Severe	19	(13.8)	16	(11.1)	35	(12.4)
	Unknown	6	(4.3)	7	(4.9)	13	(4.6)
Investigator assessment-Epigastric pain	None	26	(18.8)	35	(24.3)	61	(21.6)
	Mild	54	(39.1)	47	(32.6)	101	(35.8)
	Moderate	40	(29.0)	40	(27.8)	80	(28.4)
	Severe	12	(8.7)	15	(10.4)	27	(9.6)
	Unknown	6	(4.3)	7	(4.9)	13	(4.6)

There were no clinically significant differences between treatment groups in demographic or baseline characteristics. Over half of the patients in this study (62.4%) had moderate or severe heartburn at study entry. Moderate acid regurgitation was reported by 34.8% of the patients at baseline. At baseline, 35.8% of the patients reported mild epigastric pain; 28.4% of the patients reported moderate epigastric pain. No meaningful differences were observed between treatment groups in concomitant medication use.

Efficacy results

The study was designed to test the hypothesis that esomeprazole 40 mg qd is equally clinically effective as lansoprazole 30 mg bid in symptom control of patients who had persistent heartburn symptoms while taking lansoprazole 30 mg qd for at least 30 days. For this study, a pre-specified difference of 10 or less was used to define equally effective. Therefore, the statistical test employed needed to rule out differences of 10 or more in favor of lansoprazole.

The primary hypothesis that esomeprazole 40 mg qd is equally clinically effective as lansoprazole 30 mg bid using patient-recorded heartburn-free days as the primary endpoint, in a population of patients who had persistent heartburn symptoms while taking lansoprazole 30 mg qd, was proven ($p<0.05$), since the lower end of the 90% confidence interval for the difference of esomeprazole – lansoprazole was above the pre-specified equivalence limit. The mean percentage of heartburn-free days or nights was similar for both treatment groups (mean heartburn-free days: esomeprazole=51.6 ±35.7, lansoprazole=57.8±35.9; mean heartburn-free nights: esomeprazole=75.3±26.6, lansoprazole=73.3±31.8).

Table S4 Mean percentage of heartburn-free days (24 hours) and nights (intent-to-treat population)

Parameter		Esomeprazole 40 mg qd n=138	Lansoprazole 30 mg bid n=144
Heartburn-free days	Mean (SD)	51.6 (35.7)	57.8 (35.9)
Heartburn-free nights	Mean (SD)	75.3 (26.6)	73.3 (31.8)

Table S5 Analysis of percentage of heartburn-free days (ANCOVA) (intent-to-treat population)

		End of treatment			
Treatment	**n**	**LS Mean**	**SEM**		
Esomeprazole 40 mg qd	138	54.43	3.06		
Lansoprazole 30 mg bid	144	57.50	2.89		
		Difference between treatments			
				90 % CI	
		LS Mean	**SEM**	**L CI**	**U CI**
E40-L30	NA	-3.07	3.60	-9.02	2.87

E40=Esomeprazole 40 mg qd, L30=Lansoprazole 30 mg bid, CI=Confidence interval, L CI=Lower limit of the 90% confidence interval, U CI=Upper limit of the 90% confidence interval

NA=Not applicable

No statistically significant differences were observed between treatment groups for any of the secondary variables. Patient weekly average scores (from Day 8 to the end of study treatment) for heartburn, acid regurgitation, and epigastric pain were nearly identical for the 2 treatment groups. At the final week of the study, the percentage of patients with symptom improvement for heartburn was the same for both treatment groups, and was similar for acid regurgitation and epigastric pain. Treatment with both esomeprazole and lansoprazole resulted in clinically significant improvements from the 2-week baseline period in heartburn, acid regurgitation, and epigastric pain based on the scores reported for the last 2 weeks of the study (Weeks 7 and 8). Mean GELUSIL use in the 2 treatment groups was also similar.

Safety results

In this study, 326 patients received at least 1 dose of study drug; 2 patients were randomized but did not receive any study medication. A majority of patients received study drug for 56 days or longer. No deaths occurred during this study. Three patients experienced 4 serious adverse events; 1 of these patients withdrew from the study as a result of a serious adverse event. None of the SAEs was attributed to study drug treatment. Twenty-three patients experienced 39 nonserious adverse events that resulted in withdrawal from the study. Similar numbers of patients in the 2 treatment groups experienced AEs that resulted in study withdrawal. Both esomeprazole and lansoprazole were well-tolerated, although more treatment-related AEs were reported in the esomeprazole treatment group. The most common AEs in the study were gastrointestinal system disorders. For most laboratory variables, isolated changes both within and outside the reference range were found. There were no clear trends in any direction for any of the abnormal laboratory findings. There were no hematology, vital sign, or physical finding abnormalities considered to be clinically significant by the investigators. One patient experienced a clinically significant laboratory abnormality, which was recorded by the investigator as an adverse event.

Table S6 Number (%) of patients who had an adverse event in any category (safety population)

	Number (%) of patients who had an adverse event in each category[a]					
	Esomeprazole 40 mg qd (n=159)		Lansoprazole 30 mg bid (n=167)		Total (n=326)	
Category of adverse event	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Any adverse events	72	(45.3)	65	(38.9)	137	(42.0)
Serious adverse events	0	(0.0)	3	(1.8)	3	(0.9)
Serious adverse events leading to death	0	(0.0)	0	(0.0)	0	(0.0)
Serious adverse events not leading to death	0	(0.0)	3	(1.8)	3	(0.9)
Discontinuations of study treatment due to adverse events	13	(8.2)	10	(6.0)	23	(7.1)
Treatment-related adverse events	18	(11.3)	10	(6.0)	28	(8.6)
Other significant adverse event	0	(0.0)	0	(0.0)	0	(0.0)
	Total number of adverse events					
Any adverse events	134		136		270	
Serious adverse events	0		4		4	
Treatment-related adverse events	32		11		43	
Discontinuations of study treatment due to adverse events	24		15		39	
Other significant adverse events	0		0		0	

[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.

Table S7 **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)**

	Esomeprazole 40 mg qd (n=159)		Lansoprazole 30 mg bid (n=167)		Total n=326	
Preferred term	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Abdominal pain	11	(6.9)	5	(3.0)	16	(4.9)
Diarrhea	4	(2.5)	12	(7.2)	16	(4.9)
Nausea	9	(5.7)	7	(4.2)	16	(4.9)
Respiratory infection	6	(3.8)	8	(4.8)	14	(4.3)
Headache	5	(3.1)	5	(3.0)	10	(3.1)
Flatulence	5	(3.1)	3	(1.8)	8	(2.5)
Epigastric pain	2	(1.3)	5	(3.0)	7	(2.1)
Pain	4	(2.5)	3	(1.8)	7	(2.1)
Bronchitis	2	(1.3)	4	(2.4)	6	(1.8)
Vomiting	2	(1.3)	4	(2.4)	6	(1.8)
Gastroenteritis	5	(3.1)	0	(0.0)	5	(1.5)
Sinusitis	0	(0.0)	5	(3.0)	5	(1.5)

[a] AEs experienced by at least 2% of the patients in any treatment group are included in this table.

Date of the report

18 September 2003