Drug product	NEXIUM®	**SYNOPSIS**	
Drug substance(s)	Esomeprazole		
Document No.	GI.000.000.617		
Edition No.	Final		
Study code	SH-NEN-0005		
Date	29 October 2003		

A Comparative Efficacy and Safety Study of NEXIUM® (esomeprazole magnesium) Delayed-Release Capsules (40 mg qd and 20 mg qd) Versus Ranitidine (150 mg bid) for the Healing of NSAID-associated Gastric Ulcers When Daily NSAID Use is Continued

Study centers: This study was conducted at 67 investigational sites in Bulgaria, Romania, Ukraine, and the United States.

Publications: None at the time of writing this report.

Study dates		**Phase of development**
First patient enrolled	23 February 2001	Therapeutic exploratory (II)/ Therapeutic confirmatory (III)
Last patient completed	01 April 2003	

Objectives: To assess the efficacy of esomeprazole 40 mg qd versus ranitidine 150 mg bid and esomeprazole 20 mg qd versus ranitidine 150 mg bid through 8 weeks of treatment for the healing of gastric ulcers in patients receiving daily NSAID therapy. Healing was defined as the absence of gastric ulcers.

The secondary objectives were to assess the following:

1. Patient and investigator-assessed symptoms, defined as control of NSAID-associated GI symptoms for up to 8 weeks of treatment with esomeprazole 40 mg qd versus ranitidine 150 mg bid and esomeprazole 20 mg qd versus ranitidine 150 mg bid in patients receiving daily NSAID therapy.
2. Safety and tolerability of esomeprazole 40 mg qd versus ranitidine 150 mg bid and esomeprazole 20 mg qd versus ranitidine 150 mg bid when administered for up to 8 weeks to patients receiving daily NSAID therapy.

Study design: This was a Phase II/III multicenter, randomized, double-blind, parallel-group, 8-week comparative efficacy and safety study of esomeprazole (40 mg qd [E40] or 20 mg qd [E20]) and ranitidine 150 mg bid [R150] when given to patients who had been receiving a stable daily dose of 1 or more NSAIDs (including aspirin ≥80 mg/day) for at least 4 weeks

and who had an NSAID-associated gastric ulcer (GU) verified by esophagogastroduodenoscopy (EGD) at baseline. Patients had 3 visits, at Baseline, Week 4 and Week 8, at which EGD was performed, investigator-assessed upper GI symptoms were collected, and safety evaluations were conducted. Additionally, upper GI symptoms were assessed by the patient using either daily dairy cards or the IVRS system at US sites. Patients whose GU(s) were healed at Week 4 were to continue in the study until Week 8.

Target patient population and sample size: Men or women 18 years of age or above, who were *Helicobacter pylori* (*H. pylori*) negative by CLOtest® or FlexSure®, with a chronic condition expected to require daily NSAID treatment, and who were found to have 1 or more GUs (≥5 mm in diameter but no ulcer >25 mm at its greatest diameter) at a baseline EGD.

A sample size of 390 patients (130 randomized patients per group) was needed to provide 90% power to detect a 20% difference in ulcer healing rates (80% for the esomeprazole groups and 60% for the ranitidine group), at a significance level of 0.025.

Study drug and comparator(s): dosage, mode of administration and batch numbers

Drug	Dosage	Mode of Administration	Batch Number
esomeprazole	40 mg qd	oral	H-1222-04-01-09, H-1222-04-01-10
esomeprazole	20 mg qd	oral	H-1189-04-01-06, H-1189-04-01-07
esomeprazole placebo	0 mg qd	oral	H-0459-06-03-09
ranitidine	150 mg bid	oral	H-0538-05-01-26, H-0538-05-01-28
ranitidine placebo	0 mg bid	oral	H-0539-05-01-01

Duration of treatment: 8 weeks.

Criteria for evaluation (main variables)

Efficacy:

Primary variable (assessed for each patient): Observed GU healing status through Week 8.

Secondary variables (assessed for each patient):

1. GU healing status through Week 4.
2. Duodenal ulcer (DU) healing status through Week 4 and through Week 8 (for patients with concurrent DU at baseline).
3. Time until symptom control of upper GI symptoms
4. Time until sustained symptom resolution of the patients' upper GI symptoms
5. Percentage of upper GI symptom-free days
6. Time until sustained nighttime symptom resolution of upper GI symptoms
7. Percentage of upper GI symptom-free nights
8. Symptom resolution of investigator-assessed NSAID-associated GI symptoms determined at Week 4 and Week 8 for heartburn, acid regurgitation, nausea, upper abdominal bloating, and sleep disturbance.

9. Symptom relief of investigator-assessed NSAID-associated GI symptoms determined at Week 4 and Week 8 for heartburn, acid regurgitation, nausea, upper abdominal bloating, and sleep disturbance.

Safety: Safety assessments included the following: adverse events (AEs), clinical laboratory evaluations, vital signs, and physical examination.

Statistical methods: All efficacy analyses were based on the Intention-to-Treat (ITT) patient population. The primary efficacy endpoint (observed GU healing rate through Week 8) was analyzed using a chi-square test, using the Hochberg method to adjust for multiplicity of 2 pairwise treatment group comparisons. A Per-Protocol (PP) population was also analyzed for the primary efficacy endpoint.

The estimated GU healing rate, time to symptom control, time to sustained symptom resolution, and time to sustained nighttime symptom resolution were all analyzed using a log-rank test to assess differences between the treatment groups' Kaplan-Meier time-to-event curves.

The percentage of upper GI symptom-free days and percentage of upper GI symptom-free nights were analyzed separately using ANOVA with treatment group included in the model.

The percentage of patients who exhibited resolution of investigator-assessed symptoms and the percentage with relief of investigator-assessed symptoms were analyzed for each of the 5 NSAID-associated GI symptoms at Week 4 and Week 8 using a Cochran-Mantel-Haenszel test stratified on the baseline severity of each symptom.

The safety data (adverse events, laboratory data, and vital signs data) are presented descriptively.

Patient population: The disposition and demographic and baseline characteristics of the study population are shown in Table S1. The primary reason for exclusion from the PP population was *H. pylori* positivity by histology (19.7%).

Table S1 Patient population and disposition

Disposition	**E40**	**E20**	**R150**
N randomized	132	140	134
N (%) of patients who completed	125 (94.7%)	127 (90.7%)	123 (91.8%)
discontinued	7 (5.3%)	13 (9.3%)	11 (8.2%)
N (%) analyzed for safety [a]	131 (99.2%)	140 (100%)	133 (99.3%)
N (%) analyzed for efficacy (ITT)	129 (97.7%)	138 (98.6%)	132 (98.5%)
N (%) analyzed for efficacy (PP)	98 (74.2%)	104 (74.3%)	99 (73.9%)
Demographic characteristics (ITT)	**E40 (N=129)**	**E20 (N=138)**	**R150 (N=132)**
Age (years)			
Mean (SD)	59.5 (12.27)	58.4 (13.28)	57.1 (12.90)
Min-Max	29-86	18-83	19-83
Sex (n and % of patients)			
Male	36 (27.9%)	40 (29.0%)	38 (28.8%)
Female	93 (72.1%)	98 (71.0%)	94 (71.2%)
Race (n and % of patients)			
Caucasian	114 (88.4%)	119 (86.2%)	113 (85.6%)
Black	9 (7.0%)	5 (3.6%)	7 (5.3%)
Oriental	0 (0.0%)	3 (2.2%)	0 (0.0%)
Other	6 (4.7%)	11 (8.0%)	12 (9.1%)
Baseline characteristics, n (%) (ITT)	**E40 (N=129)**	**E20 (N=138)**	**R150 (N=132)**
Baseline EGD findings			
GU present	129 (100.0%)	138 (100.0%)	132 (100.0%)
Mean maximum GU size, mm (SD)	7.9 (3.97)	7.8 (3.96)	7.5 (3.40)
<5 mm	1 (0.8%)	3 (2.2%)	2 (1.5%)
5-9 mm	94 (72.9%)	97 (70.3%)	97 (73.5%)
≥10 mm	34 (26.4%)	38 (27.5%)	33 (25.0%)
DU present	6 (4.7%)	7 (5.1%)	8 (6.1%)
Mean maximum DU size, mm (SD)	6.8 (3.49)	7.4 (5.86)	6.5 (1.93)
Chronic condition			
Rheumatoid arthritis	11 (8.5%)	12 (8.7%)	20 (15.2%)
Osteoarthritis	76 (58.9%)	83 (60.1%)	74 (56.1%)
Other chronic condition	42 (32.6%)	43 (31.2%)	38 (28.8%)
H. pylori status (by histology)			
Negative	104 (80.6%)	110 (79.7%)	106 (80.3%)
Positive	24 (18.6%)	27 (19.6%)	26 (19.7%)
Unable to assess/missing	1 (0.8%)	1 (0.7%)	0 (0.0%)
NSAID type			
COX-2 Selective NSAID	23 (17.8%)	22 (15.9%)	29 (22.0%)
Nonselective NSAID	106 (82.2%)	116 (84.1%)	102 (77.3%)
No value	0 (0.0%)	0 (0.0%)	1 (0.8%)

[a] Number of patients who had taken at least one dose of study drug and had any available post-dose information.

Efficacy results

The efficacy evaluation based on the ITT population demonstrated that E40 and E20 treatment, compared to R150 treatment, resulted in significantly higher observed GU healing rates at both Week 4 and Week 8 in patients who continued to use daily NSAIDs. The Week 8 results in the PP population were similar to those in the ITT population. The trend toward higher observed GU healing rates in the esomeprazole treatment groups compared to the R150 group was observed across all subgroups evaluated for the ITT population.

In addition, for the ITT population, there was a significant difference between the Kaplan-Meier estimated gastric ulcer healing time-to-event curves for E20 vs R150, but there was no significant difference between the time-to-event curves for E40 vs. R150. Based on these time-to-event curves, the estimated GU healing rate through the final visit was higher in the E40 and E20 groups than for the R150 group.

Esomeprazole treatment also resulted in some significantly beneficial effects on patient- and investigator-assessed NSAID-associated upper GI symptoms following 8 weeks of treatment.

Table S2 Summary of observed and estimated GU healing rates

Week	Variable	E40	E20	R150
Observed gastric ulcer healing status (Primary)				
		N=129	**N=138**	**N=132**
Week 4 (ITT)	Healed	101/129 (78.3%)	109/138 (79.0%)	88/132 (66.7%)
	Chi-Square p-value (vs R150)	0.036[a]	0.023[a]	
Week 8 (ITT)	Healed	118/129 (91.5%)	122/138 (88.4%)	98/132 (74.2%)
	Chi-Square p-value (vs R150)	<0.001[a]	0.003[a]	
		N=98	**N=104**	**N=99**
Week 4 (PP)	Healed	75/98 (76.5%)	82/104 (78.8%)	65/99 (65.7%)
	Chi-Square p-value (vs R150)	0.092	0.036	
Week 8 (PP)	Healed	88/98 (89.8%)	92/104 (88.5%)	75/99 (75.8%)
	Chi-Square p-value (vs R150)	0.009[a]	0.018[a]	
Estimated Kaplan-Meier (KM) GU healing status (Secondary)		**N=129**	**N=138**	**N=132**
Week 4 (ITT)	Estimated KM GU Healing Rate	79.5%	80.9%	70.5%
	95% C.I. for Estimated KM GU Healing Rate	(72.5%, 86.5%)	(74.2%, 87.6%)	(62.5%, 78.6%)
Final visit (ITT)	Estimated KM GU Healing Rate	94.5%	94.4%	86.5%
	95% C.I. for Estimated KM GU Healing Rate	(90.5%, 98.5%)	(90.4%, 98.4%)	(80.4%, 92.6%)
	Log-Rank p-value (vs R150)	0.174	0.049[b]	

[a] Significant vs R150 (Hochberg adjusted).
[b] Significant vs R150 (for comparison of time-to-event curves).

Safety results

The proportion of patients experiencing AEs was similar between the esomeprazole treatment groups and slightly higher in the R150 group (Table S3). Except for insomnia and respiratory infection, all of the most commonly reported AEs were from the organ class GI system disorders (Table S4). Subgroup AE analyses with regard to age, gender, race, type of NSAID medication, or indication for NSAID did not indicate any trends in any subgroups.

There were no deaths reported in the study. Eight (8) SAEs were reported for 6 patients: 2 SAEs in the E40 group, 1 in the E20 group, and 5 in the R150 group. The most commonly reported SAEs (≥1% in any group) were from the system organ class GI system disorders. All SAEs were assessed by the investigator to be unrelated to study treatment. The percentage of patients who discontinued study medication due to an AE was higher in the R150 group (6.8%) compared to the E40 (0.8%) or E20 (1.4%) groups. The main reason for the higher

frequency of discontinuations due to AEs in the R150 group was the higher frequency of discontinuations due to GI-related AEs in this treatment group.

Subgroup AE analyses with regard to age, gender, race, type of NSAID medication, or indication for NSAID did not indicate any safety trends in any subgroups. There were no clinically relevant trends in any of the 3 treatment groups regarding laboratory variables, physical examination, or vital signs. Isolated changes from baseline to final visit both within and outside the laboratory reference ranges were found for most of the safety variables.

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 events	N (%) of patients who had an adverse event in each category[a]		
	E40 (N=131)	E20 (N=140)	R150 (N=133)
Any adverse events	80 (61.1)	79 (56.4)	100 (75.2)
Serious adverse events	1 (0.8)	1 (0.7)	4 (3.0)
Serious adverse events leading to death	0	0	0
Serious adverse events not leading to death	1 (0.8)	1 (0.7)	4 (3.0)
Discontinuations of study treatment due to adverse events	1 (0.8)	2 (1.4)	9 (6.8)
Attributable adverse events[b]	10 (7.6)	11 (7.9)	13 (9.8)
	Total number of adverse events[c]		
Any adverse events	166	183	292
Serious adverse events	2	1	5
Discontinuations adverse events	2	2	21
Attributable adverse events[b]	17	16	35

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 Attributable AEs are those for which there was a relationship to study treatment as judged by the investigator.

c 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.

Table S4 Number (%) of patients with the most commonly reported[a] adverse events, sorted by decreasing order of frequency as summarized by the total for both esomeprazole groups combined (safety population)

Preferred term	E40 (N=131) n (%)	E20 (N=140) n (%)	R150 (N=133) n (%)
Gastritis	25 (19.1)	27 (19.3)	27 (20.3)
Dyspepsia/dyspepsia aggravated	20 (15.3)	16 (11.4)	31 (23.3)
Flatulence	17 (13.0)	17 (12.1)	25 (18.8)
Gastroesophageal reflux	15 (11.5)	14 (10.0)	25 (18.8)
Nausea/nausea (aggravated)	10 (7.6)	13 (9.3)	20 (15.0)
Insomnia	8 (6.1)	11 (7.9)	16 (12.0)
Gastric ulcer/gastric ulcer aggravated	3 (2.3)	8 (5.7)	17 (12.8)
Diarrhea	1 (0.8)	9 (6.4)	2 (1.5)
Respiratory infection	6 (4.6)	2 (1.4)	3 (2.3)
Esophagitis	1 (0.8)	4 (2.9)	8 (6.0)
Vomiting	1 (0.8)	3 (2.1)	6 (4.5)
Duodenitis	0	3 (2.1)	8 (6.0)

[a] This table uses a cut-off of 4% and 4 patients in any treatment group.