Drug product	NEXIUM®	**SYNOPSIS**	
Drug substance(s)	Esomeprazole		
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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 70 study centers in Bulgaria, Indonesia, Romania, the Ukraine, and the United States.

Publications: None at the time of writing this report.

Study dates		**Phase of development**
First patient enrolled	21 February 2001	Therapeutic exploratory (II)/ Therapeutic confirmatory (III)
Last patient completed	03 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, and

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 raniditine 150 bid (R150) when given to patients who had been receiving a stable daily dose of one or more NSAIDs (including aspirin ≥80 mg/day) for at least 4 weeks and who had an NSAID-associated gastric ulcers (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 diary 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 one or more GU(s) (≥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 two 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, 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 (25.9%).

Table S1 Patient populations and baseline demographic characteristics

Disposition		**E40**	**E20**	**R150**
N randomized		141	150	149
N (%) of patients who	completed	128 (90.8)	132 (88.0)	130 (87.2)
	discontinued	13 (9.2)	18 (12.0)	19 (12.8)
N (%) analysed for safety [a]		140 (99.3)	145 (96.7)	147 (98.7)
N (%) analysed for efficacy (ITT)		133 (94.3)	138 (92.0)	139 (93.3)
N (%) analysed for efficacy (PP)		95 (67.4)	100 (66.7	93 (62.4)
Demographic characteristics (ITT)		**E40 (N=133)**	**E20 (N=138)**	**R150 (N=139)**
Age (years)	Mean (SD)	56.2 (13.1)	58.8 (12.8)	57.3 (13.9)
	Min-Max	21 to 86	26 to 85	22 to 88
Sex (n and % of patients)	Male	48 (36.1)	43 (31.2)	50 (36.0)
	Female	85 (63.9)	95 (68.8)	89 (64.0)
Race (n and % of patients)	Caucasian	100 (75.2)	109 (79.0)	105 (75.5)
	Black	6 (4.5)	5 (3.6)	8 (5.8)
	Oriental	19 (14.3)	17 (12.3)	17 (12.2)
	Other	8 (6.0)	7 (5.1)	9 (6.5)
Baseline characteristics, n (%) (ITT)		**E40 (N=133)**	**E20 (N=138)**	**R150 (N=139)**
Baseline EGD findings, n (%)	GU present,	133 (100.0)	138 (100.0)	139 (100.0)
	Mean max GU size, mm (SD)	8.2 (3.3)	8.0 (3.4)	8.5 (3.6)[b]
	<5 mm	2 (1.5)	1 (0.7)	1 (0.7)
	5-9 mm	92 (69.2)	95 (68.8)	89 (64.0)[b]
	≥10 mm	38 (28.6)	42 (30.4)	49 (35.3)[b]
	DU present	10 (7.5)	16 (11.6)	8 (5.8)
	Mean max DU size, mm (SD)	7.8 (2.39)	7.1 (3.05)	9.0 (2.20)
Chronic condition, n (%)	Rheumatoid arthritis	22 (16.5)	20 (14.5)	27 (19.4)
	Osteoarthritis	68 (51.1)	77 (55.8)	64 (46.0)
	Other chronic condition	43 (32.3)	41 (29.7)	48 (34.5)
H. pylori status (histology) n, (%)	Negative	98 (73.7)	105 (76.1)	99 (71.2)
	Positive	34 (25.6)	33 (23.9)	40 (28.8)
	Unable to assess/missing	1 (0.8)	0	0
NSAID type, n (%)	COX-2 selective NSAID	14 (10.5)	12 (8.7)	21 (15.1)
	Nonselective NSAID	119 (89.5)	126 (91.3)	117 (84.2)
	No value	0	0	1 (0.7)

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

[b] After database lock, 2 patients in the R150 group were identified as having incorrect ulcer sizes reported at the baseline visit: Patient 637/012 had an incorrect ulcer size of 70 mm recorded (the correct size was 7 mm); Patient 035/005 had an ulcer size of 1017 mm recorded (the correct size was 10 mm). Table S1 presents the corrected value for mean maximum ulcer size and corrected values for ulcers stratified by size (The original incorrect values are present in the dataset because these errors were found after the database was locked).

ITT Intention to treat. PP Per-protocol.

Efficacy results

The efficacy evaluation based on the ITT population demonstrated that patients in the E40 and E20 treatment groups had significantly higher observed GU healing rates at Week 4 and numerically higher rates at Week 8 compared with R150 group (Table S2). The Week 4 and Week 8 results in the PP population were similar to those in the ITT population.

A trend toward higher GU healing rates in the esomeprazole treatment groups compared with the R150 group was observed across all subgroups evaluated for the ITT population (eg, gender, age, *H. pylori* status, and baseline NSAID type), except for observed GU healing rates

by baseline GU size at Week 8. In patients with ulcers in the ≥10 mm size, at Week 4 a numerically higher proportion of patients in the E40 and E20 groups had GU healing compared to R150 patients; however, at Week 8, the E40 and R150 treatment groups had similar healing rates but rates were slightly lower in the E20 group. Patient numbers were very small in some subgroups and results must be interpreted with caution.

In addition, for the ITT population, there was a significant difference between the Kaplan-Meier estimated gastric ulcer healing time-to-event curves for both E40 and E20 groups compared with R150 group (see Table S2), showing that E40 and E20, compared with R150, healed patients earlier. This finding supports the significantly higher observed GU healing rates observed at Week 4 for both E40 and E20 patients compared with R150. Based on these time-to-event curves, the estimated GU healing rate through final visit was higher in the E40 and E20 groups than for the R150 group

For the following secondary variables (time to first symptom control, time to sustained symptom resolution, percentages of upper GI symptom-free days and symptom-free nights, and time to sustained nighttime symptom control), no significant differences were observed between E40 and E20 versus the R150 group. At Week 8, resolution and relief of investigator-assessed GI symptoms were generally similar among the treatment groups.

Table S2 Summary of observed and estimated GU healing rates

Week	Variable	E40	E20	R150
Observed GU Status (primary variable)		**N=133**	**N=138**	**N=139**
Week 4 (ITT)	Healed	94/133 (70.7%)	100/138 (72.5%)	77/139 (55.4%)
	Chi-Square p-value (vs R150)	0.009[a]	0.003[a]	
Week 8 (ITT)	Healed	114/133 (85.7%)	117/138 (84.8%)	106/139 (76.3%)
	Chi-Square p-value (vs R150)	0.047	0.073	
		N=95	**N=100**	**N=93**
Week 4 (PP)	Healed	70/95 (73.7%)	74/100 (74.0%)	54/93 (58.1%)
	Chi-Square p-value (vs R150)	0.024[a]	0.019[a]	
Week 8 (PP)	Healed	81/95 (85.3%)	84/100 (84.0%)	70/93 (75.3%)
	Chi-Square p-value (vs R150)	0.085	0.131	
Estimated Kaplan-Meier (KM) GU healing status (secondary variable)		**N=133**	**N=138**	**N=139**
Week 4 (ITT)	Estimated KM GU healing rate	71.6%	75.2%	58.4%
	95% C.I. for Estimated KM GU healing rate	(63.9%, 79.4%)	(67.8%, 82.5%)	(49.9%, 66.8%)
Week 8 (ITT)	Estimated KM GU healing rate	92.1%	94.6%	89.2%
	95% C.I. for Estimated KM GU healing rate	(87.4%, 96.8%)	(90.7%, 98.5%)	(83.7%, 94.7%)
	Log-Rank p-value (vs R150)	0.047[b]	0.002[b]	

[a] Significant vs R150 (Hochberg adjusted).

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

Safety results

The proportion of patients with AEs was similar among the treatment groups (Table S3). The most commonly reported AEs were from the organ class GI system disorder except insomia (Table S4). There was 1 death (reported as sudden death) in the E20 group, which the

investigator assessed as not related to study drug. No individual SAE occurred in more than 1 patient and investigators assessed all SAEs as unrelated to study drug. For each category of AE, the percentage of patients with AEs was similar among the treatment groups (Table S3).

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. There were isolated changes from baseline that were outside the laboratory standard reference ranges.

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=140)	E20 (N=145)	R150 (N=147)
Any adverse events	79 (56.4)	84 (57.9)	85 (57.8)
Serious adverse event	4 (2.9)	6 (4.1)	4 (2.7)
Serious adverse events not leading to death	4 (2.9)	5 (3.4)	4 (2.7)
Serious adverse event leading to death	0	1 (0.1)	0
Discontinuations of study drug due to adverse events	3 (2.1)	5 (3.4)	6 (4.1)
Attributable adverse events[b]	12 (8.6)	13 (9.0)	10 (6.8)
	Total number of adverse events[c]		
Any adverse events	202	214	231
Serious adverse events	6	6	4
Discontinuations adverse events	5	9	8
Attributable adverse events[b]	21	20	24

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 drug 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=140)		E20 (N=145)		R150 (N=147)	
	n	(%)	n	(%)	n	(%)
Gastritis	22	(15.7)	25	(17.2)	25	(17.0)
Flatulence	18	(12.9)	27	(18.6)	20	(13.6)
Dyspepsia/dyspepsia aggravated	14	(10.0)	19	(13.1)	18	(12.2)
Insomnia	17	(12.1)	13	(9.0)	17	(11.6)
Nausea/nausea (aggravated)	17	(12.1)	11	(7.6)	17	(11.6)
Gastroesophageal reflux	12	(8.6)	14	(9.7)	9	(6.1)
Gastric ulcer/gastric ulcer aggravated	8	(5.7)	8	(5.5)	13	(8.8)
Abdominal pain	5	(3.6)	7	(4.8)	8	(5.4)
Duodenitis	3	(2.1)	7	(4.8)	12	(8.2)
Diarrhea	6	(4.3)	3	(2.1)	7	(4.8)

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

Date of the report

30 October 2003