Drug product	Nexium	**SYNOPSIS**	
Drug substance(s)	Esomeprazole		
Document No.			
Edition No.			
Study code	SH-NEN-0003		
Date	13 January 2003		

Efficacy of esomeprazole 40 mg once daily versus placebo and esomeprazole 20 mg once daily versus placebo in treatment for relief of upper gastrointestinal symptoms associated with continuous use of NSAIDs including COX-2 selective NSAIDs

Study centre(s)

This was a multi-centre study with 116 centres participating in 11 countries.

- Australia: 6 centres
- Canada: 18 centres
- Czech Republic: 4 centres
- Italy: 6 centres
- Norway: 12 centres
- Poland: 5 centres
- Slovak Republic: 3 centres
- South Africa: 4 centres
- Sweden: 14 centres
- United Kingdom: 20 centres
- USA: 24 centres

Publications

No publications based on this report have been made prior to the date of the report.

Study dates		**Phase of development**
First patient enrolled	11 Dec 2000	Therapeutic Confirmatory (III)
Last patient completed	05 Sep 2002	

Objectives

Primary objective:

To assess the efficacy of esomeprazole 40 mg orally once daily (qd) (E40) versus placebo orally qd and esomeprazole 20 mg orally qd (E20) versus placebo orally qd through 4 weeks of treatment of upper GI symptoms associated with nonsteroidal anti-inflammatory drug (NSAID) use in patients receiving daily NSAID therapy. The primary variable is the mean change in the upper GI symptoms score from the last 7 days in the run-in period to the patients' last 7 days in the study rated by the patients on a 7-graded severity scale in daily diary cards.

Secondary objective:

To assess the safety and tolerability of esomeprazole 40 mg orally qd versus placebo orally qd and 20 mg orally qd versus placebo orally qd when administered for up to 4 weeks to patients receiving daily NSAID therapy and to assess the impact of treatment of upper GI symptoms on relevant aspects of Patient-Reported Outcomes (PRO).

Note: The term HRQL was used in the protocol instead of PRO. The current preffered term is PRO.

Additional objectives:

To describe the burden of illness among the randomised patients the standard version of Short Form-36 (SF-36) was filled in at visit 2 as a part of the PRO evaluation.

<u>This applies to the Swedish study centres only.</u>

To assess lost productivity because of upper GI symptoms a productivity questionnaire, Work Productivity and Activity Impairment questionnaire(WPAI), was administered to patients at the Swedish study centres.

Study design

This study was a randomised, double-blind, parallel-group and placebo controlled study comparing the efficacy of esomeprazole 40 mg orally qd vs placebo and esomeprazole 20 mg

orally qd vs placebo when given to patients on continuous use of NSAIDs, including COX-2 selective NSAIDs, for a treatment period of 4 weeks for relief of upper GI symptoms.

Visit 2 corresponds to baseline, visit 3 to the 2 week visit and visit 4 to the 4 week visit. The period between visit 1 and visit 2 was the run-in period and the patients were randomised into one of the treatment arms at visit 2.

Target patient population and sample size

Helicobacter pylori negative male and female patients, aged 18 years and above, with a chronic condition (e.g., osteoarthritis or rheumatoid arthritis) requiring continuous treatment with NSAIDs (including COX-2 selective NSAIDs, multiple NSAIDs, and high-dose aspirin [>325 mg/day]) for upper GI symptoms.

The sample size was based on the test power requirements for the follow-up prevention of symptom relapse study (SH-NEN-0004) and the expected continuation rate (50% for patients in each esomeprazole group and 25% of the patients in the placebo group). To have 300 patients available for randomisation into study SH-NEN-0004 (100 per group) it was estimated that 720 patients (240 per group) were needed for the current study.

This would provide 90% power to detect a difference in the mean change in symptom severity score of 0.4 between the esomeprazole and placebo groups.

During the study it was observed that the overall continuation rate for SH-NEN-0004 was higher than expected. Thus the study team decided to lower the sample size but still to provide a reasonable test power.

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

Capsule Esomeprazole 40 mg, orally qd, batch numbers: H 1222-04-01-09, H 1222-04-01-10

Capsule Esomeprazole 20 mg, orally qd, batch numbers: H 1189-04-01-06, H 1189-04-01-07

Capsule Placebo, orally qd, batch number: H 0459-06-03-09

Duration of treatment

4 weeks

Criteria for evaluation (main variables)

Efficacy

- Primary variable: mean change in the upper GI symptoms (pain, discomfort or burning in the upper abdomen), rated on a 7-graded severity scale, from the last 7

days of the run-in period to the patients' last 7 days in the study. The last 7 days in the study are counted from last dose date.

- Secondary variables:
  -Mean change in the upper GI symptom score from the last 7 days in the run-in period to the last 7 days prior to the 2-week visit and from the last 7 days in the run-in period to the last 7 days prior to the 4-week visit.
  -The proportion of days with an upper GI symptom score of 'None' at 2 and 4 weeks of treatment.
  -Mean upper GI symptom score by day over the duration of the study.
  -Cumulative proportion of patients who achieve relief of upper GI symptoms by Week 2 and Week 4.
  -Proportions of patients with upper GI symptoms during night, by study day over the duration of the study.
  -The proportion of patients with resolution of investigator-recorded symptoms of heartburn, acid regurgitation, nausea and upper abdominal bloating at the 2-week, and 4-week visits.
  -The proportion of patients with relief of investigator-recorded symptoms of heartburn, acid regurgitation, nausea and upper abdominal bloating at the 2-week, and 4-week visits.
  -The mean change in the three dimensions Reflux, Abdominal pain and Indigestion of the Gastrointestinal Symptom Rating Scale (GSRS) and the mean change in the three dimensions Emotional distress, Sleep disturbance and Food/Drink problems of the Quality Of life in Reflux And Dyspepsia (QOLRAD) instrument from randomisation to the last visit.
  -Patient's global evaluation of relief of upper GI symptom (Overall Treatment Evaluation, OTE) at the 2-week, and 4-week visits.
  -Short Form-36 (SF-36) score at baseline.

Safety

Safety assessments included adverse events (AEs), clinical laboratory data (haematology and clinical chemistry), vital signs and physical examination.

Statistical methods

The primary efficacy variable (the mean change in the upper GI symptom score from run-in period to end of study) was analysed using an analysis of covariance model, with treatment as main effect and the average upper GI symptom score from the run-in period as a baseline covariate. For each comparison (esomeprazole 40 mg versus placebo and esomeprazole 20 mg versus placebo) the least squares mean difference, the 95% confidence intervals and the p-values are presented. The least squares mean difference from baseline is also presented for each treatment along with the corresponding 95% confidence interval.

For the secondary variables based on mean change in symptom score and mean change in PRO dimensions, an analysis of covariance similar to the primary analysis was used.

Patient population

The demographic characteristics of the study population are described in Table S1.

Table S1 Patient population and disposition, ITT population

		E40		E20		Placebo	
Disposition							
N randomised		180		187		189	
N (%) of patients who	completed	160	(88.9)	170	(90.9)	170	(89.9)
	discontinued	20	(11.1)	17	(9.1)	19	(10.1)
N analysed for safety [a]		177		187		189	
N analysed for efficacy (ITT)		178		187		189	
N analysed for efficacy (PP)		130		141		147	
Demographic characteristics (ITT)							
Sex, n (%)	Male	43	(24.2)	47	(25.1)	45	(23.8)
	Female	135	(75.8)	140	(74.9)	144	(76.2)
Age (years)	Mean (SD)	53.0	(13.0)	53.4	(12.7)	55.0	(12.9)
	Range	19 to 85		21 to 87		26 to 83	
Race, n (%)	Caucasian	161	(90.4)	173	(92.5)	173	(91.5)
	Black	4	(2.2)	0	(0.0)	3	(1.6)
	Oriental	1	(0.6)	3	(1.6)	0	(0.0)
	Other	12	(6.7)	11	(5.9)	13	(6.9)
Baseline characteristics, n (%)							
Type of chronic condition							
Rheumatoid arthritis		37	(20.8)	41	(21.9)	47	(24.9)
Osteoarthritis		76	(42.7)	73	(39.0)	76	(40.2)
Other chronic condition		65	(36.5)	73	(39.0)	66	(34.9)
H. pylori status (histology)							
Negative		154	(86.5)	169	(90.4)	166	(87.8)
Positive		22	(12.4)	12	(6.4)	20	(10.6)
Unknown		2	(1.1)	6	(3.2)	3	(1.6)
NSAID type							

	E40		E20		Placebo	
COX-2 selective NSAID	73	(41.0)	61	(32.6)	74	(39.2)
Nonselective NSAID	105	(59.0)	126	(67.4)	115	(60.8)

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

ITT Intention to treat; N Number; PP Per-protocol

Demographic characteristics, type of condition requiring NSAID treatment and type of NSAID used were similar in the three groups.

The most common reasons for discontinuation of study were:

- Lack of therapeutic response: 3 in E40, 6 in E20 and 12 in placebo.
- Eligibility criteria not fulfilled: 3 in E40, 3 in E20 and 4 in placebo.
- Adverse events: 5 in E40, 3 in E20 and 1 in placebo.

The number of patients discontinued due to AE may differ form table S3 as only main reason for discontinuation is listed above, and a patient may have had more than 1 reason to be with drawn from the study.

Efficacy results

As evaluated from patient diary cards, co-administration of either E40 or E20 with any NSAID (including COX-2 selective NSAIDs) resulted in statistically significant improvements in upper GI symptoms associated with NSAID use compared with placebo. The magnitude was of clinical relevance. This effect was evident for both doses of esomeprazole (40 mg and 20 mg) from the results obtained from the mean change in symptom score from the last 7 days of run-in period to the last 7 days of study treatment (primary variable), the proportion of patients with relief, the proportion of symptom-free days following 4 weeks of treatment, and from the time to relief of symptoms.

In addition, patients treated with esomeprazole 40 mg and 20 mg, as compared to placebo, experienced less symptoms of esophageal reflux (investigator assessed symptoms) and was less bothered by reflux (GSRS). Moreover, these patients had less problems to drink and eat due to the upper GI symptoms (QOLRAD). Overall, patients treated with E40 or E20 reported an improvement in NSAID-associated upper GI symptoms and that the improvement was important (OTE). The efficacy evaluation (Table S2) demonstrated a consistent effect of E40 and E20 across the different outcome measures that was beneficial to patients who experienced NSAID associated upper GI symptoms.

No dose-related effects were observed for the efficacy variables evaluated in the study, and the study was not designed to demonstrate any potential differences in efficacy between the two doses of esomeprazole

Table S2 Summary of efficacy results

Study variable	E40 vs placebo		E20 vs placebo		Statistic
	Est. mean diff.	p-value	Est. mean diff.	p-value	
Primary Variable: Mean change in upper GI symptom from run-in (last 7 days) to					ANCOVA
Study period (last 7 days) ITT	-0.49	0.0002	-0.61	<0.0001	
Study period (last 7 days) PP	-0.59	<0.0001	-0.61	<0.0001	
Week 2 (last 7 days prior) ITT	-0.52	<0.0001	-0.64	<0.0001	
Week 4 (last 7 days prior) ITT	-0.46	0.0004	-0.57	<0.0001	
COX-2 selective NSAID					
Study period (last 7 days) ITT	-0.70	0.0013	-0.72	0.0015	
Nonselective NSAID					
Study period (last 7 days) ITT	-0.36	0.0351	-0.55	0.0005	

	E40	p-value vs placebo	E20	p-value vs placebo	Placebo	
Proportion of symptom-free days (%)						t-test
At 4 weeks	27.1%	<0.0001	29.0%	<0.0001	13.9%	
Time to relief of upper GI symptom, median days						Log-rank
	11	0.0002	10	<0.0001	21	
Proportion of patients (%) with resolved investigator-assess GI symptoms						Cochran- Mantel- Haenszel
At 4 weeks						
-Heartburn	63.0%	<0.0001	61.6%	<0.0001	33.9%	
-Acid regurgitation	75.8%	<0.0001	66.1%	0.0060	52.5%	
- Upper abdominal bloating	52.7%	NS	52.5%	NS	41.8%	
-Nausea	77.0%	NS	71.8%	NS	73.4%	

	E40 vs placebo		E20 vs placebo		
	Est. mean diff.	p-value	Est. mean diff.	p-value	
GSRS					ANCOVA
-Reflux	-0.61	<0.0001	-0.55	<0.0001	
-Abdominal pain	-0.04	NS	-0.25	NS	
-Indigestion	-0.04	NS	-0.12	NS	
QOLRAD					ANCOVA
-Emotional Distress	0.19	NS	0.38	0.0030	
-Sleep disturbance	0.25	NS	0.38	0.0070	
-Food/drink problems	0.33	NS	0.52	<0.0001	

NS= Not statistically significant different versus placebo

Safety results

The frequency of adverse events was similar in all treatment groups.

The most commonly reported AEs were from the organ class gastrointestinal system disorders, e.g. flatulence, nausea, diarrhoea, dyspepsia and gastroesophageal reflux symptoms, and the findings did not indicate a dose relationship.

There were 2 non fatal SAEs reported (E20 and placebo), both assessed as not related to study drug by the investigator. There were no fatal SAEs reported.

Discontinuation of study drug due to AE was reported for 9 patients in the E40 group, 5 patients in the E20 group and 3 patients in the placebo group.

No event was classified as an other significant adverse event (OAE).

Subgroup analyses with regard to age, gender, race, type of NSAID medication and indication for NSAID treatment were done. There were no particular trends found in the subgroups.

Isolated changes both within and outside the laboratory reference ranges were found for most of the safety laboratory variables. There were no clinically significant trends found in any of the treatment groups.

There were no clinically relevant changes in the three treament groups regarding physical examination or vital signs.

Table S3 Adverse event frequency by category and total number of adverse events, safety population

	E40	**E20**	**Placebo**
	n=177	**N=187**	**n=189**
No. (%) of patients with: [a]			
any AE	62 (35.0)	75 (40.1)	67 (35.4)
SAEs leading to death	0	0	0
SAEs not leading to death	0	1 (0.5)	1 (0.5)
drug stopped due to AE	9 (5.1)	5 (2.7)	3 (1.6)
temporarily stopped due to AE	3 (1.7)	2 (1.1)	2 (1.1)
attributable AE[b]	14 (7.9)	16 (8.6)	10 (5.3)
other significant AE	0	0	0
Total no. of AEs recorded [c]	*128*	*134*	*137*

[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 causal relationship to study treatment as judged by the investigator.
[c] Events are counted by included term.

Table S4 Most commonly reported adverse events (preferred term), sorted by the total for both esomeprazole groups combined, safety population. Number of patients n (%) with AE.

	E40	E20	Placebo
No. of patients:	**n=177**	**n=187**	**n=189**
Flatulence	11 (6.2)	11 (5.9)	9 (4.8)
Nausea/nausea (aggravated)	7 (4.0)	13 (7.0)	10 (5.3)
Diarrhoea	10 (5.6)	8 (4.3)	5 (2.6)
Dyspepsia	7 (4.0)	10 (5.3)	9 (4.8)
Gastroesophageal reflux	7 (4.0)	9 (4.8)	8 (4.2)
Headache	6 (3.4)	7 (3.7)	10 (5.3)
Constipation	7 (4.0)	5 (2.7)	2 (1.1)
Respiratory infection	6 (3.4)	6 (3.2)	6 (3.2)
Dizziness/vertigo	4 (2.3)	2 (1.1)	1 (0.5)
Abdominal pain	4 (2.3)	1 (0.5)	6 (3.2)
Arthralgia	5 (2.8)	0	2 (1.1)
Sinusitis	1 (0.6)	1 (0.5)	4 (2.1)

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

Date of the report

13 January 2003