AstraZeneca

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 placebo for the prevention of gastric ulcers associated with daily NSAID use in patients at risk

Study centre(s)

This was a multicentre study with 56 centres in 11 countries

- Argentina: 2 centres
- Brazil: 1 centre
- Bulgaria: 7 centres
- Hong Kong (China), 1 centre
- Hungary: 10 centres
- Mexico: 6 centres
- Poland: 5 centres
- Singapore: 2 centres
- South Africa: 4 centres
- Sweden: 7 centres
- USA: 11 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	23 March, 2001	Therapeutic confirmatory (III)
Last patient completed	28 December, 2002	

Objectives

Primary objective:

To assess the efficacy of esomeprazole 40 mg once daily (qd) versus placebo and esomeprazole 20 mg qd versus placebo for up to 6 months of treatment for the prevention of gastric and/or duodenal ulcers in patients receiving daily nonsteroidal anti-inflammatory drugs (NSAIDs) therapy and being at risk for developing ulcers. Efficacy was defined as the absence of gastric and/or duodenal ulcers.

Secondary objectives:

Investigator-assessed symptoms, defined as resolution and relief of NSAID-associated upper gastrointestinal (GI) symptoms for up to 6 months of treatment with esomeprazole 40 mg qd versus placebo and esomeprazole 20 mg qd versus placebo in patients receiving daily NSAID therapy.

Safety and tolerability of esomeprazole 40 mg qd versus placebo and esomeprazole 20 mg qd versus placebo when administered for up to 6 months to patients receiving daily NSAID therapy.

Study design

The study was a randomised, double-blind, parallel-group, 6-months, comparative efficacy and safety study of esomeprazole and placebo in patients receiving daily NSAID therapy who were at risk of developing NSAID-associated gastric and/or duodenal ulcers. The study population comprised *Helicobacter pylori (H. pylori)*-negative patients who had been taking a stable daily dose of one or more NSAIDs for at least 4 weeks, had no current gastric and/or duodenal ulcer and were at risk of developing NSAID-associated ulcers (risk was defined as patients having a documented gastric and/or duodenal ulcer within the past 5 years and/or age ≥ 60 years). Patients who developed ulcer(s) during the study period were withdrawn from the study.

Target patient population and sample size

Male or female patients aged 18 years and above, with no active/current gastric and/or duodenal ulcers, who were *H. pylori* negative, and were receiving daily NSAID therapy (including cyclooxygenase-2 [COX-2]–selective NSAIDs), and were at risk of developing

NSAID-associated gastric and/or duodenal ulcers (documented gastric and/or duodenal ulcer within the past 5 years and/or age ≥60 years).

A sample size of 504 patients (168 randomised patients per group) was needed to provide 90% power to detect a 12.0% difference in ulcer occurrence rates (5% for the esomeprazole groups and 17% for the placebo group) at the significant level of 0.025.

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

Esomeprazole 40 mg, orally once daily (E40), batch numbers: H 1222-04-01-09, H 1222-04-01-10

Esomeprazole 20 mg, orally once daily (E20), batch numbers: H 1189-04-01-06, H 1189-04-01-07

Placebo, orally once daily, batch number: H 0459-06-03-09

Duration of treatment

The duration of treatment was 6 months.

Criteria for evaluation (main variables)

Efficacy

- Primary variable: The proportion of patients who developed a gastric and/or duodenal ulcer identified by the investigator during endoscopy at any time during the study (up to 6 months of treatment).

- Secondary variables: The proportion of patients with rating of “none” (resolution), or “none” or “mild” (relief), for the past 7 days at Months 1, 3 and 6 of treatment for each NSAID-associated GI symptom.

Safety

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

Statistical methods

For the primary efficacy analysis (estimated percentage of patients who remained ulcer-free through Month 6), the Kaplan-Meier method was used to estimate the time-to-event curves for maintenance of ulcer free status. The log-rank test was used to assess differences between treatment groups.

The absence of GI symptoms, as well as the presence of no worse than mild symptoms (symptom relief), was analysed for each symptom separately, using a Cochran-Mantel-Haenszel statistic, stratified on the absence/presence of the respective symptom at baseline, for the Month 1 visit. Summaries of the GI symptoms were also provided for Months 3 and 6, but without inferential statistics.

Patient population

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

Table S 1 Patient population and disposition, ITT population

		E40		E20		Placebo	
Disposition							
N randomised		198		195		192	
N (%) of patients who	completed	168	(84.8)	163	(83.6)	131	(68.2)
	discontinued	30	(15.2)	32	(16.4)	61	(31.8)
N analysed for safety [a]		196		192		185	
N analysed for efficacy (ITT)		196		192		185	
N analysed for efficacy (PP)		160		135		139	
Demographic characteristics (ITT)							
Sex (n and % of patients)	Male	49	(25.0)	39	(20.3)	42	(22.7)
	Female	147	(75.0)	153	(79.7)	143	(77.3)
Age (years)	Mean (SD)	63.6	(10.7)	63.9	(10.7)	64.0	(11.8)
	Range	24 to 84		21 to 89		19 to 88	
Race (n and % of patients)	Caucasian	151	(77.0)	153	(79.7)	140	(75.7)
	Black	9	(4.6)	7	(3.6)	8	(4.3)
	Oriental	16	(8.2)	14	(7.3)	16	(8.6)
	Other	20	(10.2)	18	(9.4)	21	(11.4)
Baseline characteristics, n (%)							
Type of chronic condition							
Rheumatoid arthritis		52	(26.5)	53	(27.6)	46	(24.9)
Osteoarthritis		108	(55.1)	102	(53.1)	111	(60.0)
Other chronic condition		36	(18.4)	37	(19.3)	28	(15.1)
H. pylori status (histology)							
Negative		172	(87.8)	155	(80.7)	159	(85.9)
Positive		22	(11.2)	35	(18.2)	25	(13.5)
Unknown		2	(1.0)	2	(1.0)	1	(0.5)
NSAID type							
COX-2-selective NSAID		29	(14.8)	24	(12.5)	35	(18.9)
Non-selective NSAID		167	(85.2)	168	(87.5)	150	(81.1)

[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

The most common reasons for withdrawal from the study were:

- Consent withdrawn, 10 in E 40, 12 in E20 and 18 in placebo
- Adverse event (AE), 7 in E 40, 5 in E20 and 17 in placebo
- Lack of therapeutic response, 6 in E40, 3 in E20 and 13 in placebo

The number of patients withdrawn due to AE may differ from Table S3 as only the main reason for withdrawal is listed above, and a patient may have had more than one reason for being withdrawn from the study.

Efficacy results

This efficacy evaluation demonstrated that E40 and E20 in comparison with placebo, significantly reduced the proportions of patients with ulcers (both gastric and/or duodenal ulcers) in a population of NSAID users who were at high risk of developing ulcers. The effect of both doses of esomeprazole was evident from within 1 month of treatment and continuing throughout the 6-month study period. This effect was observed both in the intention-to-treat (ITT) and the per-protocol (PP) analyses. Table S 2.

Table S 2 Summary of efficacy results

Study period	Statistic	E40	E20	Placebo
Cumulative proportion of patients without a GU or DU at Month 6 (Primary)				
Total (ITT)	Observed Response Rate (%)	188/196 (95.9%)	183/192 (95.3%)	165/185 (89.2%)
	95% CI	92.1, 98.2	91.3, 97.8	83.8, 93.3
	Life Table Rate	95.6	94.8	87.7
	95% CI	92.6, 98.592	91.5, 98.12	82.6, 92.76
	Log rank test p-value (vs Placebo)	0.0074*	0.0180*	
Total (PP)	Observed Response Rate (%)	157/160 (98.1%)	126/135 (93.3%)	122/139 (87.8%)
	95% CI	94.6, 99.6	87.7, 96.9	81.1, 92.7
	Life Table Rate	98.0	92.8	87.0
	95% CI	95.7, 100.00	88.3, 97.34	81.2, 92.75
	Log rank test p-value (vs Placebo)	0.0003*	0.1012	
Observed rate (Secondary), ITT population		**E40**	**E20**	**Placebo**
Month 1	Maintained Free	188/196(95.9%)	181/192(94.3%)	162/185(87.6%)
	Occurred	2/196(1.0%)	2/192(1.0%)	10/185(5.4%)
	Disc., Ulcer Free	6/196(3.1%)	9/192(4.7%)	13/185(7.0%)
	CMH test, p-value (vs Placebo)	0.0144*	0.0161*	
Month 3	Maintained Free	174/196(88.8%)	172/192(89.6%)	139/185(75.1%)
	Occurred	6/196(3.1%)	5/192(2.6%)	17/185(9.2%)
	Disc., Ulcer Free	16/196(8.2%)	15/192(7.8%)	29/185(15.7%)
	CMH test, p-value (vs Placebo)	0.0123*	0.0069*	
Month 6	Maintained Free	164/196(83.7%)	159/192(82.8%)	129/185(69.7%)
	Occurred	8/196(4.1%)	9/192(4.7%)	20/185(10.8%)
	Disc., Ulcer Free	24/196(12.2%)	24/192(12.5%)	36/185(19.5%)
	CMH test, p-value (vs Placebo)	0.0133*	0.0302*	
Resolution of investigator-assessed upper GI symptoms (Secondary), ITT population				
Month 1		**E40**	**E20**	**Placebo**
Upper abdominal bloating	Baseline	106/196 (54.1%)	100/192 (52.1%)	105/185 (56.8%)
	Month 1	126/190 (66.3%)	119/183 (65.0%)	112/172 (65.1%)
	CMH test, p-value (vs Placebo)	0.6887	0.6132	
Heartburn	Baseline	98/196 (50.0%)	93/192 (48.4%)	99/185 (53.5%)
	Month 1	135/190 (71.1%)	131/183 (71.6%)	95/172 (55.2%)
	CMH test, p-value (vs Placebo)	0.0004*	0.0001*	
Acid regurgitation	Baseline	123/196 (62.8%)	99/192 (51.6%)	100/185 (54.1%)
	Month 1	146/190 (76.8%)	143/183 (78.1%)	113/172 (65.7%)
	CMH test, p-value (vs Placebo)	0.0953	0.0017*	
Nausea	Baseline	160/196 (81.6%)	140/192 (72.9%)	131/185 (70.8%)
	Month 1	162/190 (85.3%)	153/183 (83.6%)	135/172 (78.5%)

Study period	Statistic	E40	E20	Placebo
	CMH test, p-value (vs Placebo)	0.4563	0.2208	
Sleep disturbance	Baseline	155/196 (79.1%)	140/192 (72.9%)	135/185 (73.0%)
	Month 1	160/190 (84.2%)	155/183 (84.7%)	133/172 (77.3%)
	CMH test, p-value (vs Placebo)	0.3083	0.0308	

* Statistically significant value

Safety results

The frequency of AEs was similar in all treatment groups, 49.5% in the E40 group, 43.8% in the E20 group and 49.7% in the placebo group.

The most commonly reported AEs were from the organ class GI system disorders, ie, nausea/nausea aggravated, diarrhoea, dyspepsia/dyspepsia aggravated, flatulence and abdominal pain. The findings did not indicate a dose relationship.

Two patients died during the study. In the E40 group, 1 patient with known cardiovascular disease was reported to have died due to sudden death. In the placebo group, 1 patient died due to myocardial infarction. Neither of these events was assessed by the investigator as related to the study drug.

Sixty-seven Serious Adverse Events (SAEs) were reported for 52 patients, 15 patients in the E40 group, 16 in the E20 group and 21 in the placebo group.

The most commonly reported SAEs were from the system organ class GI disorders, and were reported for 0.5 % of the patients in the E40 group, 1% in the E20 group and 5.4% in the placebo group.

The number of patients who stopped taking the study drug due to an AE was higher in the placebo (13%) group compared to E40 (5.6%) and E20 (5.7%). One reason for this difference was that discontinuations due to GI symptoms were more common in the placebo group.

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

AE-subgroup analyses with regard to gender, age, race, type of NSAID medication, indication for NSAID use and risk factors were performed. There were minor differences found in some of the groups. However, the overall information does not indicate any particular trends in the subgroups.

There were no clinically relevant trends in any of the 3 treatment groups regarding laboratory variables, physical examination or vital signs. Isolated changes both within and outside the laboratory reference ranges were found for most of the safety laboratory variables.

Table S 3 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=196)	E20 (n=192)	Placebo (n=185)
Any adverse events	97 (49.5)	84 (43.8)	92 (49.7)
Serious adverse events	15 (7.7)	16 (8.3)	21 (11.4)
Serious adverse events leading to death	1 (0.5)	0	1 (0.5)
Serious adverse events not leading to death	14 (7.1)	16 (8.3)	20 (10.8)
Discontinuations of study treatment due to adverse events	11 (5.6)	11 (5.7)	24 (13.0)
Other significant adverse event	0	0	0
Attributable adverse events[c]	14 (7.1)	12 (6.3)	10 (5.4)
	Total number of adverse events		
Any adverse events[b]	222	186	226
Serious adverse events[b]	20	19	28
Discontinuations adverse events[b]	15	16	28
Other significant adverse event[b]	0	0	0
Attributable adverse events[c]	24	20	15

[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.

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

Table S 4 Number of patients with the most commonly reported adverse events in decreasing order of frequency sorted by the total for both esomeprazole groups combined (safety population)

Preferred term	E40 (n=196)		E20 (n=192)		Placebo (n=185)	
	n	(%)	n	(%)	n	(%)
Nausea/nausea (aggravated)	12	(6.1)	9	(4.7)	8	(4.3)
Diarrhoea	12	(6.1)	8	(4.2)	7	(3.8)
Dyspepsia/dyspepsia aggravated	12	(6.1)	8	(4.2)	15	(8.1)
Flatulence	8	(4.1)	10	(5.2)	7	(3.8)
Abdominal pain	8	(4.1)	6	(3.1)	9	(4.9)
Gastritis	6	(3.1)	7	(3.6)	10	(5.4)
Gastroesophageal reflux	6	(3.1)	4	(2.1)	9	(4.9)
Gastric ulcer	2	(1.0)	2	(1.0)	9	(4.9)
Oesophagitis	3	(1.5)	0		11	(5.9)

AEs experienced by at least 4% of the patients and 4 patients in any treatment group are included in this table.