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 Healing of NSAID-associated Gastric Ulcers When Daily NSAID Use is Discontinued

Study centers

This study was conducted in the USA (28 investigator sites were initiated, 8 investigator sites enrolled patients).

Publications

None at the time of writing this report.

Study dates		**Phase of development**
First patient enrolled	15 March 2001	Therapeutic exploratory (II)/ Therapeutic confirmatory (III)
Last patient completed	4 October 2001	
Date sites informed to terminate study	21 September 2001	

Objectives

The primary objective was to assess the efficacy of esomeprazole 40 mg qd (E40) versus placebo qd (placebo) and esomeprazole 20 mg qd (E20) versus placebo qd through 4 weeks of treatment for the healing of gastric ulcers in patients whose daily NSAID therapy had been discontinued. Healing was defined as the absence of gastric ulcers.

The secondary objectives were to (1) assess patient and investigator-assessed symptoms, defined as control of NSAID-associated GI symptoms for up to 4 weeks of treatment with E40 versus placebo and E20 versus placebo in patients whose daily NSAID therapy had been discontinued, and (2) assess safety and tolerability of E40 versus placebo and E20 versus placebo when administered for up to 4 weeks to patients whose daily NSAID therapy had been discontinued.

The Sponsor terminated the study early due to administrative reasons, ie. enrollment difficulties as a result of reluctance of investigators and/or patients to comply with various study procedures. Because only 10% of the planned number of patients were randomized to study treatment, a synopsis and a CTD report summary together with supporting safety appendices are provided in this report.

Study design

This was a Phase II/III, multicenter, randomized, double-blind, parallel-group, 4-week efficacy and safety study comparing esomeprazole to placebo in patients who were on a stable oral dose of one or more nonsteroidal anti-inflammatory drugs (NSAIDs). Patients were enrolled into one of three groups, E40, E20, or placebo, for up to 4 weeks of therapy. Patients were required to discontinue NSAID usage during the study period. GELUSIL tablets were dispensed as rescue medication; patients were permitted a maximum of six tablets per day. Patients were to be documented *Helicobacter pylori* negative by either a rapid serology test (FLEXSURE®) or by a *Campylobacter*-like organism test (CLOtest®, a rapid urease test) at baseline. Patients were to participate in the study up to 4 weeks, at which time they were to be discharged from the study. Study visits for efficacy and safety evaluations were to be completed at Week 2 and Week 4. Safety evaluations completed at each visit included adverse events and vital signs. Clinical laboratory evaluations and a physical examination were to be completed at the baseline and Week 4 visits only. Esophagogastroduodenoscopy (EGD) was to be done at baseline, Week 2, and Week 4. Efficacy evaluations at each visit included endoscopic evaluation for the presence of ulcers and erosions, and investigator assessment of NSAID-associated GI symptoms. Additionally, patients reported their NSAID-associated upper GI symptoms (pain, discomfort, burning in the upper abdomen) daily using an interactive voice response system (IVRS).

Target patient population and sample size

Patients had to have one or more EGD-verified gastric ulcer(s) ≥5 mm, but no ulcer more than 15 mm in diameter at the baseline EGD. Patients had to have been on a stable dose of one or more NSAIDs for at least 4 weeks prior to the baseline EGD. Stable was defined as having taken their prescribed NSAID on at least 5 of 7 days each week. Patients also had to be free of *Helicobacter pylori* infection at baseline (based on either CLOtest® or FLEXSURE® results), and have no history of a variety of other factors that might be causes of their gastric ulcer(s).

A sample size of 198 patients (66 randomized patients per group) was needed to provide 90% power to detect a 30% difference in ulcer healing rates, 70% for the esomeprazole groups and

40% for the placebo group at a significance level of 0.025. The expected ulcer healing rates were based on the experience with omeprazole for gastric ulcer healing.

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

Esomeprazole 40 mg, esomeprazole 20 mg, or placebo was administered orally once a day for 4 weeks. GELUSIL antacid tablets were dispensed as rescue medication; patients were permitted a maximum of six tablets per day. The batch numbers were as follows:

- esomeprazole capsules 40 mg, Lot H-1222-04-01-09
- esomeprazole capsules 20 mg, Lot H-1189-04-01-06
- esomeprazole capsules PLACEBO, Lot H-0459-06-03-09
- GELUSIL antacid tablets, Lot 03860B

Duration of treatment

The planned duration of treatment was four weeks.

Criteria for evaluation (main variables)

Efficacy

No efficacy summaries were made because of the early termination of the study. Entries into the IVRS by the patient were for the 24-hour period prior to the study medication dose. Patients registered the intensity of their worst upper GI symptom episode on a 7-graded scale from "None" to "Very Severe" and answered one "Yes/No" question regarding their nocturnal symptoms and one "Yes/No" question regarding NSAID use. Patients whose gastric ulcers were healed at Week 4 were considered to have completed the study as treatment successes.

Safety

No safety summaries were made because of the early termination of the study; however, all safety data were listed and are described in this synopsis.

All randomized patients who received at least one dose of study drug and had any available post-baseline information were to be included in the safety population for analysis. Information regarding adverse events was collected at each visit. Clinical laboratory evaluations were completed on fasting patients at baseline and at the final visit. Clinical laboratory tests included serum chemistry and hematology. Vital signs and body weight were recorded at each visit, and height was recorded at baseline only.

Statistical methods

Because this study was terminated early, no formal statistical analyses were performed. Some descriptive statistics for demographic and adverse event data are presented in this document.

Patient population

Of the 210 patients planned for enrollment, 21 patients were randomized to study treatment and 17 patients completed the study. Four patients discontinued from the study early; one patient (placebo) discontinued due to an adverse event and 3 patients (2 in E40 and 1 placebo groups) discontinued from the study early because the study was terminated. There were 15 females and 6 males; most (76%) were Caucasian with a mean age 54.1 years, ranging from 25 to 77 years, see Table S1.

Table S1 Patient population and disposition

		E40	E20	Placebo	Total
Population					
N randomized (N planned)		8 (70)	7 (70)	6 (70)	21 (210)
Demographic characteristics					
Sex (n of patients)	Male	3	2	1	6
	Female	5	5	5	15
Age (years)	Mean (SD)	47.4 (17.8)	58.9 (17.2)	57.5 (8.9)	54.1 (15.8)
	Range	25 to 72	33 to 77	40 to 64	25 to 77
Race (n of patients)	Caucasian	7	5	4	16
	Black	0	0	0	0
	Other	1	2	2	5
Disposition					
N of patients who	completed	6	7	4	17
	discontinued	2	0	2	4
N analyzed for safety		7	7	6	20[a]

[a]Patient 019 Site 722 (E40) was randomized, received no study medication and was not included in the safety population. No adverse events were reported for this patient.

Efficacy results

No efficacy summaries were made because the study terminated early and data were available for only 21 patients (10% of the planned patients).

Safety results

No safety summaries were made because of the early termination of the study; however, all safety data were listed. A total of 21 patients were enrolled in the study, of which 20 patients were evaluated for safety, and 12 patients reported at least one adverse event, see Table S2. Thirty-eight adverse events were reported by 12 patients and 4 patients had an AE that was severe in intensity; see Table S2. There were no deaths or serious adverse events reported in the study. One patient (Patient 014, Site 722) discontinued study treatment due to adverse events. He discontinued on Study Day 5 due to moderate nausea, dizziness, headache, and

sweating increased. The study investigator judged the events to be causally related to study treatment.

Table S2 Number of patients who had at least 1 adverse event in any category, and total numbers of adverse events (safety population)

Category of adverse event	E40 (n=7)	E20 (n=7)	Placebo (n=6)
No. (%) of patients with: [a]			
any AE	4	4	4
SAEs leading to death	0	0	0
SAEs not leading to death	0	0	0
drug stopped due to AE	0	0	1
temporarily stopped due to AE	0	0	0
AE with severe intensity	3	1	0
attributable AE [c]	0	0	1
Total no. of AEs recorded [b]	7	18	13

[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.

Date of the report

17 December 2002