| | | | |
|---|---|---|---|
| Drug product | NEXIUM® | **SYNOPSIS** | |
| Drug substance(s) | Esomeprazole | | |
| Document No. | GI.000-011-103 | | |
| Edition No. | Final | | |
| Study code | SH-NEN-0014 | | |
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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 center(s)

This study was conducted in the US (110 investigator sites enrolled patients).

## Publications

None at the time of writing this report.

| **Study dates** | | **Phase of development** |
|---|---|---|
| **First patient enrolled** | 1 February 2001 | Therapeutic exploratory (II)/ Therapeutic confirmatory (III) |
| **Last patient completed** | 5 March 2003 | |

## Objectives

To assess the efficacy of esomeprazole 40 mg once daily (qd) (E40) versus placebo and esomeprazole 20 mg qd (E20) 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 drug (NSAID) therapy who are at risk for developing ulcers. Efficacy was defined as the absence of gastric and/or duodenal ulcers.

The secondary objectives were to assess the following:

1. investigator-assessed symptoms, defined as resolution and relief of NSAID-associated gastrointestinal (GI) symptoms, for up to 6 months of treatment with E40

versus placebo and E20 versus placebo, in patients receiving daily NSAID therapy, and

2. safety and tolerability of E40 versus placebo and E20 versus placebo when administered for up to 6 months to patients receiving daily NSAID therapy.

**Study design**

The study was a randomized, double-blind, parallel-group, 6-month, 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 or duodenal ulcer, and were at risk of developing NSAID-associated ulcers (documented gastric or duodenal ulcer within the past 5 years and/or age ≥60 years). Randomization was stratified by NSAID type: those patients taking COX-2 selective NSAIDs and those taking nonselective NSAIDs. Enrollment into the COX-2 selective NSAID group was limited to approximately 40% of the total study population. Patients had 4 visits, at Baseline, Month 1, Month 3, and Month 6, at which esophagogastroduodenoscopy (EGD) was performed and safety evaluations were conducted. If an ulcer was determined to be present prior to Month 6 of treatment, the patient was discontinued due to lack of therapeutic response.

**Target patient population and sample size**

Male and female patients aged 18 years and above, with no current gastric or duodenal ulcers verified by EGD at baseline, who were *H. pylori* negative, who were receiving daily NSAID therapy (including COX-2 selective NSAIDs), and were at risk of developing NSAID-associated gastric and/or duodenal ulcers (documented gastric or duodenal ulcer within the past 5 years and/or age ≥60 years).

A sample size of 786 patients (262 randomized patients per group) was needed to provide 90% power to detect a 9.0% difference in ulcer occurrence rates, 5% for the esomeprazole groups and 14% for the placebo 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 |
| esomeprazole | 20 mg qd | oral | H-1189-04-01-06 |
| placebo | | oral | H-0459-06-03-09 |
| rescue medication | GELUSIL® Acid binding capacity <16 mmol HCl | oral | 04360B, 04260B, 04160B, 04060B, 03960B, 03860B, 03760B, 03560B, 03360B |

**Duration of treatment**

The duration of treatment was 6 months.

## Criteria for evaluation (main variables)

### Efficacy

- Primary variable: Gastric and/or duodenal ulcer status through 6 months of treatment (determined as ulcer-free status maintained or ulcer occurred). The proportion of patients who developed a gastric and/or duodenal ulcer identified by the investigator on the basis of EGD at any time during the study (up to 6 months of treatment) was determined.

- Secondary variables: The proportion of patients with rating of "None" (resolution) or "None" or "Mild" (relief) for the past 7 days at Month 1, Month 3, and Month 6 of treatment for each investigator-assessed NSAID-associated GI symptom.

### Safety

Safety assessments included adverse events (AEs), clinical laboratory data (hematology 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. From the primary analysis only, multiple comparisons of each esomeprazole dose versus placebo were adjusted using Hochberg's method. When the p-values from each test were ≤0.05, both comparisons were declared statistically significant. If one p-value was >0.05, the other would need to be ≤0.025 to be declared statistically significant. The absence of GI symptoms (resolution), as well as the presence of no worse than mild symptoms (relief), was analyzed 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 disposition and demographic and baseline characteristics of the study population are described in Table S1. The most common reasons for discontinuation of the study were:

- Adverse event (AE), 33 (11.7%) in the E40 group, 15 (5.3%) in the E20 group, 33 (11.7%) in the placebo group.

- Lack of therapeutic response, 7 (2.5%) in the E40 group, 8 (2.8%) in the E20 group, and 44 (15.7%) in the placebo group.

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

**Table S1 Patient population and disposition**

| | | E40 | | E20 | | Placebo | |
|---|---|---|---|---|---|---|---|
| **Disposition** | | | | | | | |
| N randomized | | 282 | | 281 | | 281 | |
| N (%) of patients who | completed | 216 | (76.6) | 217 | (77.2) | 172 | (61.2) |
| | discontinued | 66 | (23.4) | 64 | (22.8) | 109 | (38.8) |
| N (%) analysed for safety [a] | | 276 | (97.9) | 272 | (96.8) | 269 | (95.7) |
| N (%) analysed for efficacy (ITT) | | 271 | (96.1) | 267 | (95.0) | 267 | (95.0) |
| N (%) analysed for efficacy (PP) | | 240 | (85.1) | 228 | (81.1) | 223 | (79.4) |
| **Demographic characteristics (ITT)** | | **E40 (n=271)** | | **E20 (n=267)** | | **Placebo (n=267)** | |
| Sex (n and % of patients) | Male | 87 | (32.1) | 94 | (35.2) | 85 | (31.8) |
| | Female | 184 | (67.9) | 173 | (64.8) | 182 | (68.2) |
| Age (years) | Mean (SD) | 66.0 | (8.82) | 66.0 | (8.97) | 65.6 | (9.27) |
| | Range | 29-88 | | 25-88 | | 21-88 | |
| Race (n and % of patients) | Caucasian | 233 | (86.0) | 230 | (86.1) | 229 | (85.8) |
| | Black | 17 | (6.3) | 18 | (6.7) | 19 | (7.1) |
| | Oriental | 4 | (1.5) | 2 | (0.7) | 0 | (0.0) |
| | Other | 17 | (6.3) | 17 | (6.4) | 19 | (7.1) |
| **Baseline characteristics, n (%) (ITT)** | | | | | | | |
| Type of chronic condition | | | | | | | |
| Rheumatoid arthritis | | 33 | (12.2) | 37 | (13.9) | 44 | (16.5) |
| Osteoarthritis | | 197 | (72.7) | 193 | (72.3) | 182 | (68.2) |
| Other chronic condition | | 41 | (15.1) | 37 | (13.9) | 41 | (15.4) |
| *H. pylori* status (histology) | | | | | | | |
| Negative | | 243 | (89.7) | 245 | (91.8) | 237 | (88.8) |
| Positive | | 23 | (8.5) | 20 | (7.5) | 28 | (10.5) |
| Unable to assess/missing | | 5 | (1.8) | 2 | (0.7) | 2 | (0.7) |
| NSAID type | | | | | | | |
| COX-2 selective NSAID | | 112 | (41.3) | 101 | (37.8) | 99 | (37.1) |
| Nonselective NSAID | | 159 | (58.7) | 166 | (62.2) | 168 | (62.9) |

[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

## Efficacy results

The efficacy evaluation demonstrated that E40 and E20, in comparison with placebo, significantly reduced the proportion of patients who developed ulcers (both gastric and 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 continued throughout the 6-month study period. In addition, a significantly greater proportion of patients experienced resolution of heartburn, acid regurgitation, or upper GI symptoms when treated with E40 and E20 as compared with placebo (Table S2). The results in the per-protocol (PP) analysis were similar to those in the intention-to-treat (ITT) analysis.

## Table S2 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 (%) | 260/271 (95.9%) | 255/267 (95.5%) | 221/267 (82.8%) |
| | 95% CI | 93.6, 98.3 | 93.0, 98.0 | 78.2, 87.3 |
| | Life Table Rate | 95.3 | 94.7 | 79.6 |
| | 95% CI | 92.5, 98.0 | 91.8, 97.6 | 74.3, 84.9 |
| | Log rank test p-value (vs Placebo) | < 0.0001 | < 0.0001 | |
| Total (PP) | Observed Response Rate (%) | 229/240 (95.4%) | 217/228 (95.2%) | 184/223 (82.5%) |
| | 95% CI | 92.8, 98.1 | 92.4, 98.0 | 77.5, 87.5 |
| | Life Table Rate | 94.7 | 94.5 | 80.2 |
| | 95% CI | 91.7, 97.8 | 91.4, 97.7 | 74.6, 85.8 |
| | Log rank test p-value (vs Placebo) | < 0.0001 | < 0.0001 | |

| **Observed rate (ITT population) (Secondary)** | | **E40 (n=271)** | **E20 (n=267)** | **Placebo (n=267)** |
|---|---|---|---|---|
| Month 1 | Maintained free | 253 (93.4%) | 246 (92.1%) | 221 (82.8%) |
| | Occurred | 3 (1.1%) | 4 (1.5%) | 25 (9.4%) |
| | Disc., ulcer-free | 15 (5.5%) | 17 (6.4%) | 21 (7.9%) |
| | CMH test, p-value (vs Placebo) | < 0.0001 | 0.0001 | |
| Month 3 | Maintained free | 235 (86.7%) | 235 (88.0%) | 191 (71.5%) |
| | Occurred | 6 (2.2%) | 5 (1.9%) | 34 (12.7%) |
| | Disc., ulcer-free | 30 (11.1%) | 27 (10.1%) | 42 (15.7%) |
| | CMH test, p-value (vs Placebo) | < 0.0001 | < 0.0001 | |
| Month 6 | Maintained free | 212 (78.2%) | 208 (77.9%) | 159 (59.6%) |
| | Occurred | 11 (4.1%) | 12 (4.5%) | 46 (17.2%) |
| | Disc., Ulcer-free | 48 (17.7%) | 47 (17.6%) | 62 (23.2%) |
| | CMH test, p-value (vs Placebo) | < 0.0001 | < 0.0001 | |

| **Resolution of investigator-assessed upper GI symptoms at Month 1 (ITT population) (Secondary), n (%)** | | | | |
|---|---|---|---|---|
| **GI symptom at baseline** | | **E40 Resolved** | **E20 Resolved** | **Placebo Resolved** |
| Upper abdominal bloating | Absent[a] | 124 (86.1%) | 140 (87.0%) | 137 (87.8%) |
| | Present[b] | 60 (52.2%) | 46 (50.0%) | 46 (49.5%) |
| | Total | 184 (71.0%) | 186 (73.5%) | 183 (73.5%) |
| | CMH p-value (vs Placebo) | NS | NS | |
| Heartburn | Absent | 110 (84.6%) | 116 (88.5%) | 96 (75.0%) |
| | Present | 79 (61.2%) | 78 (63.9%) | 39 (32.2%) |
| | Total | 189 (73.0%) | 194 (76.7%) | 135 (54.2%) |
| | CMH p-value (vs Placebo) | < 0.0001 | < 0.0001 | |
| Acid regurgitation | Absent | 148 (91.4%) | 154 (93.3%) | 129 (81.6%) |
| | Present | 65 (67.0%) | 56 (63.6%) | 47 (51.6%) |
| | Total | 213 (82.2%) | 210 (83.0%) | 176 (70.7%) |
| | CMH p-value (vs Placebo) | 0.0010 | 0.0009 | |
| Nausea | Absent | 194 (96.0%) | 186 (93.9%) | 180 (91.4%) |
| | Present | 40 (70.2%) | 35 (63.6%) | 34 (65.4%) |
| | Total | 234 (90.3%) | 221 (87.4%) | 214 (85.9%) |
| | CMH p-value (vs Placebo) | NS | NS | |
| Sleep disturbance | Absent | 177 (95.7%) | 177 (96.2%) | 164 (90.1%) |
| | Present | 49 (66.2%) | 51 (73.9%) | 41 (61.2%) |
| | Total | 226 (87.3%) | 228 (90.1%) | 205 (82.3%) |
| | CMH p-value (vs Placebo) | NS | 0.0067 | |
| Upper GI symptom | Absent | 117 (90.0%) | 113 (85.6%) | 95 (73.6%) |
| | Present | 77 (60.6%) | 75 (62.0%) | 40 (33.6%) |
| | Total | 194 (75.5%) | 188 (74.3%) | 135 (54.4%) |
| | CMH p-value (vs Placebo) | < 0.0001 | < 0.0001 | |

[a] Absent is a severity rating of "None" for a specific symptom.

[b] Present is a severity rating "Mild, Moderate, or Severe" for a specific symptom.

NS = Not significant

**Safety results**

The frequency of AEs was similar among the treatment groups, 85.1% in the E40 group, 84.2% in the E20 group, and 89.2% in the placebo group (Table S3). The most commonly reported AEs were from the organ class GI system disorders, ie, gastritis/gastritis aggravated, dyspepsia/dyspepsia aggravated, flatulence, gastroesophageal reflux, gastrointestinal symptoms NOS and nausea (Table S4). The findings did not indicate a dose relationship.

One patient in the E40 group died during the study due to lung cancer. This event was assessed as not related to the study product by the investigator.

Forty-seven (47) serious AEs (SAEs) including the one death were reported for 38 patients, 24 (in 6.5% of patients) in the E40 group, 13 (in 4.0% of patients) in the E20 group, and 10 (in 3.3% of patients) in the placebo group. There was a slightly higher percentage of SAEs reported for the E40 group than for the E20 or placebo groups. The most commonly reported (≥1% in any group) SAEs were from the system organ class GI disorders and body as a whole (general disorders). All SAEs assessed were judged 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 placebo group (16.7%) compared to the E40 (12.7%) or E20 (8.1%) groups, and the frequency was slightly higher in the E40 group than in the E20 group. The primary reason for these differences was that discontinuations due to GI symptoms were more common in the placebo group (12.6%) than in the E40 (6.9%) and E20 (4.8%) groups. Three patients, 2 in the placebo group and 1 in the E40 group, discontinued the study because of GI hemorrhagic events, none of which was judged as related to the study drug.

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

Subgroup AE analyses with regard to age, gender, race, type of NSAID medication, or indication for NSAID use did not indicate any particular 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 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=276) | | E20 (n=272) | | Placebo (n=269) | |
| Any adverse events | 235 | (85.1) | 229 | (84.2) | 240 | (89.2) |
| Serious adverse events | 18 | (6.5) | 11 | (4.0) | 9 | (3.3) |
| Serious adverse events leading to death | 1 | (0.4) | 0 | | 0 | |
| Serious adverse events not leading to death | 17 | (6.2) | 11 | (4.0) | 9 | (3.3) |
| Discontinuations of study treatment due to adverse events | 35 | (12.7) | 22 | (8.1) | 45 | (16.7) |
| Other significant adverse event | 0 | | 0 | | 0 | |
| Attributable adverse events[b] | 53 | (19.2) | 39 | (14.3) | 58 | (21.6) |
| | Total number of adverse events | | | | | |
| Any adverse events[c] | 828 | | 785 | | 961 | |
| Serious adverse events[c] | 24 | | 13 | | 10 | |
| Discontinuations adverse events[c] | 66 | | 29 | | 88 | |
| Other significant adverse event[c] | 0 | | 0 | | 0 | |
| Attributable adverse events | 111 | | 71 | | 134 | |

[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 adverse events in decreasing order of frequency sorted by the total for both esomeprazole groups combined (safety population)

| Preferred term | E40 (n=276) | | E20 (n=272) | | Placebo (n=269) | |
|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) |
| Gastritis/gastritis aggravated | 87 | (31.5) | 91 | (33.5) | 104 | (38.7) |
| Dyspepsia/dyspepsia aggravated | 62 | (22.5) | 66 | (24.3) | 100 | (37.2) |
| Flatulence | 62 | (22.5) | 64 | (23.5) | 60 | (22.3) |
| Gastroesophageal reflux | 49 | (17.8) | 52 | (19.1) | 83 | (30.9) |
| Gastrointestinal symptoms NOS | 42 | (15.2) | 47 | (17.3) | 65 | (24.2) |
| Nausea/nausea (aggravated) | 40 | (14.5) | 42 | (15.4) | 54 | (20.1) |
| Insomnia | 37 | (13.4) | 44 | (16.2) | 40 | (14.9) |
| Mucosal discolouration GI | 26 | (9.4) | 21 | (7.7) | 29 | (10.8) |
| Abdominal pain | 23 | (8.3) | 14 | (5.1) | 16 | (5.9) |
| Duodenitis | 19 | (6.9) | 11 | (4.0) | 38 | (14.1) |
| Headache | 16 | (5.8) | 10 | (3.7) | 3 | (1.1) |
| Diarrhea | 12 | (4.3) | 12 | (4.4) | 10 | (3.7) |
| Hypertension/hypertension aggravated | 15 | (5.4) | 9 | (3.3) | 9 | (3.3) |
| Respiratory infection | 6 | (2.2) | 18 | (6.6) | 14 | (5.2) |
| Esophagitis | 5 | (1.8) | 13 | (4.8) | 54 | (20.1) |
| Constipation | 12 | (4.3) | 5 | (1.8) | 7 | (2.6) |

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