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|---|---|---|---|
| Drug product: | NEXIUM® | **SYNOPSIS** | |
| Drug substance(s): | esomeprazole magnesium | | |
| Document No.: | GI.000-014-535 | | |
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| Study code: | D961AC00001 | | |
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# A Multicenter, Randomized, Double-Blind, Placebo-Controlled Efficacy Study Comparing 4 Weeks of Treatment with Esomeprazole 20 mg qd and 40 mg qd to Placebo qd in Patients with Heartburn and Sleep Disturbances Associated with Gastroesophageal Reflux Disease (GERD)

## Study center(s)

This study was conducted in the USA (74 centers).

## Publications

None to date.

| **Study dates** | | **Phase of development** |
|---|---|---|
| **First patient enrolled** | 16 April 2003 | Therapeutic use (IV) |
| **Last patient completed** | 15 August 2003 | |

## Objectives

The primary objective of this study was to demonstrate a difference in the relief of nighttime heartburn between esomeprazole 20 mg qd (E20) and placebo and between esomeprazole 40 mg qd (E40) and placebo after 4 weeks of treatment in patients with gastroesophageal reflux disease (GERD) as measured by a daily diary card.

The secondary objectives of this study were the following:

1. To assess the impact of treatment with E20 versus placebo and E40 versus placebo on sleep disturbances associated with GERD as measured by:

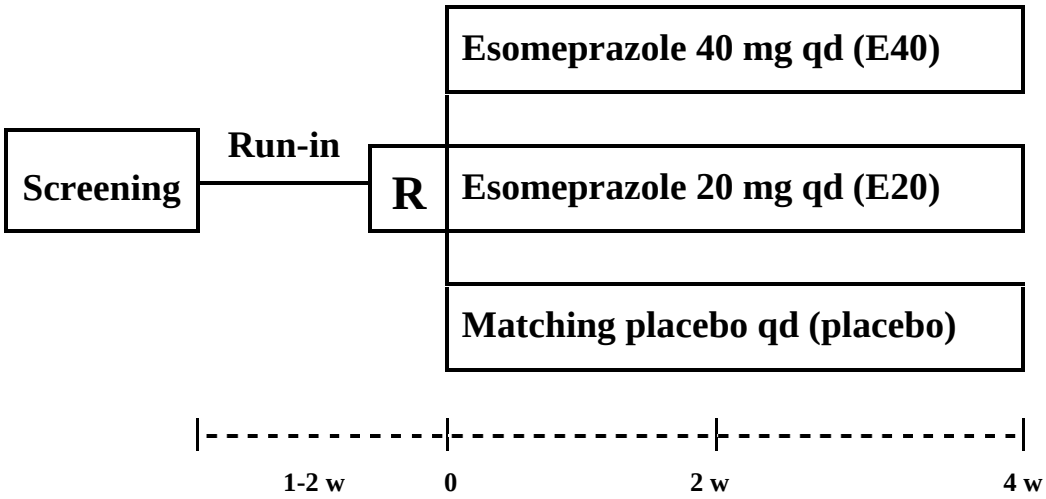
- Change in global Pittsburgh Sleep Quality Index (PSQI) score
- Complete resolution of GERD-related sleep disturbances
- Relief of GERD-related sleep disturbances
- Percent of days without GERD-related sleep disturbances
- Time to first relief and first resolution

2. To assess the impact of treatment with E20 versus placebo and E40 versus placebo on heartburn as measured by:
   - Complete resolution of daytime heartburn
   - Complete resolution of nighttime heartburn
   - Relief of daytime heartburn
   - Improvement of frequency and severity of daytime, nighttime, and 24-hour heartburn
   - Complete resolution of 24-hour heartburn
   - Relief of 24-hour heartburn
3. To quantify any difference during 4 weeks of treatment between E20 and E40 in patients with GERD as measured by:
   - Relief of nighttime heartburn
   - Relief of GERD-related sleep disturbances
4. To assess the impact of sleep disturbances associated with GERD on work productivity and regular daily activities using the Work Productivity and Activity Impairment Questionnaire: Sleep Disturbance-GERD (WPAI-SLEEP-GERD) at Baseline and after 4 weeks of treatment in patients with GERD.
5. To assess the safety and tolerability of E20 and E40 through 4 weeks of treatment.

**Study design**

This was a multicenter, randomized, double-blind, placebo-controlled study.

**Study Flow Chart**




Screening=informed consent and screening
Run-in=1-2 weeks, no study treatment except rescue medication (GELUSIL®, Parke Davis), daily diary
R=randomization; w=week(s)

**Target patient population and sample size**

This study was conducted in male and female patients, 18 to 85 years of age, and included 675 patients with GERD. At screening, the investigator established any past history of erosive esophagitis (EE) or of episodes of heartburn or acid regurgitation for 3 months or longer. No endoscopy was done for inclusion in this study so it was expected that the study population would include symptomatic gastroesophageal reflux disease patients (sGERD) with and without erosions. The patient's nighttime symptoms were to average at least 2 or 3 episodes in a 7-day period in order to be a candidate for the Run-in phase. Furthermore, the patient should have had at least a 1-month history of sleep disturbances associated with GERD.

Once the investigator determined that the patient had a history of heartburn or acid regurgitation for 3 months or longer (or any history of EE), nighttime heartburn averaging at least 2 or 3 times per week, and associated sleep disturbances, the patient was entered into the Run-in phase of the study. During the Run-in, the patient filled out a diary card documenting both heartburn symptoms and sleep disturbances associated with GERD. To be eligible for randomization, the patient must have had both sleep disturbances associated with GERD on at least 3 of the last 7 nights of the Run-in period and nighttime heartburn graded as moderate or severe on at least 3 of the last 7 nights of the same Run-in period. Sleep disturbances associated with GERD could have included, but were not limited to, trouble falling asleep, unwanted awakenings, or overall poor sleep quality.

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

| Drug | Dosage | Mode of Administration | Batch Number |
| --- | --- | --- | --- |
| esomeprazole magnesium | 20 mg once daily | oral | H1189-04-01-06 |
| esomeprazole magnesium | 40 mg once daily | oral | H1222-04-01-09 |
| matching placebo | once daily | oral | H0459-06-03-09 |

**Duration of treatment**

Four weeks of once daily (morning) dosing.

**Criteria for evaluation (main variables)**

**Efficacy**

The following efficacy endpoints were based on the patient's daily diary responses, the PSQI, and/or the WPAI-SLEEP-GERD.

Primary variable: Relief of nighttime heartburn on patient's last 7 days in the study. Relief was defined as a daily diary card response of "none" on at least 6 of 7 days, allowing for 1 "mild" response.

Secondary variables: The secondary outcome variables are presented in the following list.

1. Endpoints for sleep disturbances associated with GERD:

   - Change in global PSQI scores from Baseline to Week 4.

   - Complete resolution of sleep disturbances associated with GERD after 1, 2, and 4 weeks of treatment. Complete resolution of GERD-related sleep disturbances was defined as "No" on 7 consecutive days.

   - Relief of sleep disturbances associated with GERD after 1, 2, and 4 weeks of treatment, and on the patient's last 7 days in the study. Relief of sleep disturbances associated with GERD was defined as a daily diary response of "Yes" on not more than 2 of 7 consecutive days.

   - Percentage of patients with symptom improvement based on weekly symptom score from Baseline (mean weekly score of 2-week Baseline period) compared to last week of study drug treatment. Improvement was defined as any decrease in weekly symptom score from Baseline.

   - Percentage of days without GERD-related sleep disturbances during the 4-week treatment period.

- Days to first relief of sleep disturbances associated with GERD during the 4-week treatment period.

- Days to first resolution of sleep disturbances associated with GERD during the 4-week treatment period.

- Days to first complete resolution of sleep disturbances associated with GERD during the 4-week treatment period.

2. Endpoints for heartburn:

   - Complete resolution of daytime, nighttime, and 24-hour heartburn after 1, 2, and 4 weeks of treatment.

   - Relief of daytime and 24-hour heartburn after 1, 2, and 4 weeks of treatment. Relief was defined as a daily diary response of "none" on at least 6 of 7 days, allowing for 1 "mild" response.

3. Endpoints for WPAI-SLEEP-GERD:

   - Percent work time missed because of sleep disturbances due to GERD symptoms.

   - Percent impairment while working because of sleep disturbances due to GERD symptoms.

   - Percent overall work impairment because of sleep disturbances due to GERD symptoms.

   - Percent activity impairment because of sleep disturbances due to GERD symptoms.

**Safety**

Another secondary objective of this study was to assess the safety and tolerability of E20 and E40 through 4 weeks of treatment. Safety and tolerability assessments included physical examination, review of adverse events, clinical laboratory evaluations, and vital sign measurements.

**Statistical methods**

The primary efficacy analysis was performed on a modified Intention-to-treat (ITT) population as defined in the Protocol and the Statistical Analysis Plan. Patients were considered to be evaluable and were included in the modified ITT efficacy analysis as long as they met all of the following conditions:

1. Patient took at least 1 dose of study medication and had post-treatment data.

2. Patient had a reported history of heartburn and reported nighttime heartburn graded as moderate or severe on at least 3 out of any consecutive 7 days of the run-in period.

3. Prior to randomization, the patient had sleep disturbances associated with GERD as documented in the run-in diary on at least 3 of the last 7 days of the run-in period.

The per protocol (PP) population included all patients from the ITT population who met a prospectively defined set of evaluability criteria according to a blinded review completed by AstraZeneca prior to unblinding the study data. The safety population included all patients who took at least 1 dose of study drug and for whom post-randomization data existed.

The primary endpoint (percentage of patients in the ITT population who exhibited relief of nighttime heartburn, as measured by the diary on the patient's last 7 days in the study) was analyzed using a chi-square statistic to assess differences in the relief rates for each esomeprazole treatment group as compared to placebo.

Prior to the study, it was estimated that a sample size of 200 patients per treatment arm would provide at least 95% power to detect a 20% difference in relief rates. This power calculation assumed a 76% relief rate for each esomeprazole treatment group and 56% for the placebo treatment group using a 2-sided hypothesis test with an alpha level of 0.025 for the 2 comparisons (each esomeprazole treatment group to placebo). These relief rates were based on heartburn results from 2 prior esomeprazole studies (AstraZeneca LP Report No. 225 1999, AstraZeneca LP Report No. 226 1999).

Adverse events, laboratory test values, and vital sign values are presented descriptively. No inferential statistical methods were used for the safety data.

**Patient population**

In total, 874 patients were screened and 675 patients were randomized to study treatment. A large number of screen failures were anticipated due to the inclusion/exclusion criteria; therefore, it was planned to screen over 800 patients in order to enroll approximately 600 evaluable patients. Three patient populations were analyzed: ITT, PP, and the safety population. The randomized population was used for the summarization of adverse events. Characteristics of the overall study population are summarized in Table S1.

**Table S1 Patient population and disposition**

| | | E20 | | E40 | | Placebo | | Total | |
|---|---|---|---|---|---|---|---|---|---|
| **Disposition** | | **n** | **(%)** | **n** | **(%)** | **n** | **(%)** | **n** | **(%)** |
| Randomized | | 226 | (100.0) | 220 | (100.0) | 229 | (100.0) | 675 | (100.0) |
| Completed protocol | | 218 | (96.5) | 212 | (96.4) | 212 | (92.6) | 642 | (95.1) |
| Withdrawals | | 8 | (3.5) | 8 | (3.6) | 17 | (7.4) | 33 | (4.9) |
| Evaluable for Safety | | 225 | (99.6) | 218 | (99.1) | 229 | (100.0) | 672 | (99.5) |
| Evaluable for ITT | | 220 | (97.3) | 209 | (95.0) | 221 | (96.5) | 650 | (96.3) |
| Evaluable for PP | | 205 | (90.7) | 196 | (89.0) | 208 | (90.8) | 602 | (89.2)) |
| **Demographic characteristics (ITT population)** | | | | | | | | | |
| | n | 220 | | 209 | | 221 | | 650 | |
| Gender, n | Male | 88 | (40.0) | 84 | (40.2) | 90 | (40.7) | 262 | (40.3) |
| (%) | Female | 132 | (60.0) | 125 | (59.8) | 131 | (59.3) | 388 | (59.7) |
| Age, years | Mean (SD) | 46.8 | (14.0) | 46.3 | (14.6) | 46.5 | (13.6) | 46.6 | (14.0) |
| | Median | 47.0 | | 46.0 | | 45.0 | | 46.0 | |
| | Range | 19.0 to 81.0 | | 19.0 to 80.0 | | 19.0 to 80.0 | | 19.0 to 81.0 | |
| Race, n (%) | Caucasian | 190 | (86.4) | 173 | (82.8) | 186 | (84.2) | 549 | (84.5) |
| | Black | 16 | (7.3) | 18 | (8.6) | 17 | (7.7) | 51 | (7.8) |
| | Oriental | 1 | (0.5) | 3 | (1.4) | 2 | (0.9) | 6 | (0.9) |
| | Other | 13 | (5.9) | 15 | (7.2) | 16 | (7.2) | 44 | (6.8) |

a Number of patients who took at least 1 dose of study treatment and had at least 1 data point after dosing.
E20 is esomeprazole 20 mg; E40 is esomeprazole 40 mg; P is placebo; ITT is Intention-to-treat population; n is number; PP is Per protocol population.

## Efficacy results

The primary variable in this study was the percentage of patients with relief of nighttime heartburn during the last 7 days in the study. Relief was defined as a daily diary card response of "none" on at least 6 of 7 days, allowing for 1 "mild" response. Relief was analyzed in the Intention-to-treat (ITT) and per protocol (PP) populations.

For both the ITT and PP populations, the proportion of patients with relief of nighttime heartburn was statistically higher ($p < 0.0001$) in both esomeprazole treatment groups versus the placebo treatment group (Table S2).

**Table S2 Number and percentage of patients with relief of heartburn in the ITT and PP populations**

| | E20 | | E40 | | Placebo | | Differences (p-value) | |
|---|---|---|---|---|---|---|---|---|
| **Population** | **n/N** | **(%)** | **n/N** | **(%)** | **n/N** | **(%)** | **E20 vs P** | **E40 vs P** |
| ITT | 93/220 | (42.3) | 92/209 | (44.0) | 17/221 | (7.7) | <0.0001 | <0.0001 |
| PP | 89/205 | (43.4) | 86/196 | (43.9) | 15/208 | (7.2) | <0.0001 | <0.0001 |

E20 is esomeprazole 20 mg; E40 is esomeprazole 40 mg; P is placebo; ITT is Intention-to-treat population; PP is Per protocol population.

Secondary variables assessed the impact of esomeprazole treatment on sleep disturbances associated with GERD and on heartburn. In addition, a statistical comparison was performed to determine if a treatment difference existed between E20 and E40.

Both E20 and E40 were effective in reducing sleep disturbances associated with GERD. A statistically significant treatment effect in favor of E20 and E40 versus placebo was shown for complete resolution ($p<0.0001$) and relief ($p<0.0001$) of GERD-related sleep disturbances in both the ITT and PP populations. In addition, the mean percentage of days without GERD-related sleep disturbances was statistically greater for both E20 ($p<0.0001$) and E40 ($p<0.0001$) versus placebo in both the ITT and PP populations. Based on analysis of PSQI scores, both E20 ($p<0.0001$) and E40 ($p<0.0001$) were statistically more effective than placebo in improving sleep quality.

Both E20 and E40 were effective in reducing heartburn. A statistically significant treatment effect in favor of E20 and E40 versus placebo was shown for complete resolution ($p<0.0001$, E20 and E40) and relief ($p<0.0001$, E20 and E40) of daytime, nighttime, and 24-hour heartburn after 1, 2, and 4 weeks of treatment in both the ITT and PP populations.

No statistically significant treatment differences were observed between E20 and E40 in the relief of nighttime heartburn during the last 7 days of the study or in improvement of sleep quality as measured by PSQI. Daily rescue medication usage was statistically lower for both the E20 ($p<0.0001$) and E40 treatment groups ($p<0.0001$) compared with the placebo treatment group.

Health Economics variables assessed the affect of esomeprazole treatment on work productivity reduced by sleep disturbances associated with GERD. Work productivity, as measured by WPAI scores, was improved by both E20 and E40. Both E20 ($p<0.0001$) and E40 ($p<0.0001$) were statistically more effective than placebo in reducing the equivalent number of work hours lost, the degree that sleep disturbance affected productivity, and the degree that sleep disturbance affected regular (nonwork) activity. The numbers of hours absent from work were lower for both E20 and E40 treatments than for placebo treatment, but the differences were not statistically significant.

**Safety results**

Both doses of esomeprazole (E20 and E40) were well tolerated. In the E40 treatment group, a higher percentage of patients (33.6%) experienced an adverse event (AE) than in the E20 (26.1%) and placebo (25.3%) treatment groups. Four patients had a total of 6 serious adverse events (SAEs), which were all deemed unrelated to study drug by the Principal Investigator. There were no deaths and no other significant adverse events (OAEs) (Table S3).

The majority of the most common AEs reported were in the gastrointestinal system (Table S4). In general, the AEs were similar with respect to frequency except for diarrhoea NOS, which was higher in the E20 group (4.9%), and headache, which was higher in the E40 group (5.0%).

## Table S3 Number (%) of patients who had an adverse event in any category (all randomized patients)

| | Number (%) of patients who had an adverse event in each category[a] | | | | | |
|---|---|---|---|---|---|---|
| | E20 (N=226) | | E40 (N=220) | | Placebo (N=229) | |
| **Category of adverse event** | **n** | **(%)** | **n** | **(%)** | **n** | **(%)** |
| Any adverse events | 59 | (26.1) | 74 | (33.6) | 58 | (25.3) |
| Serious adverse events | 1 | (0.4) | 2 | (0.9) | 1 | (0.4) |
| Leading to death | 0 | | 0 | | 0 | |
| Not leading to death | 1 | (0.4) | 2 | (0.9) | 1 | (0.4) |
| Discontinuations of study treatment due to adverse events | 3 | (1.3) | 1 | (0.5) | 1[b] | (0.4) |
| Treatment-related adverse events | 15 | (6.6) | 15 | (6.8) | 7 | (3.1) |
| Other significant adverse events | 0 | | 0 | | 0 | |
| | **Total number of adverse events** | | | | | |
| Any adverse events[c] | 106 | | 132 | | 91 | |
| Serious adverse events[c] | 3 | | 2 | | 1 | |
| Other significant adverse events[c] | 0 | | 0 | | 0 | |

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 Patient E0079014 (placebo) developed an AE (*H. pylori*) requiring an exclusionary medication. The reason for study discontinuation was recorded by Investigator as exclusionary medication. The AE report of *H. pylori* recorded study discontinuation as one of the outcomes. This information was picked up in the programming of Table S3 as a discontinuation due to AE. Text discussions in this CSR consider the patient as discontinued due to exclusionary medication (vs. discontinued due to an AE) based on the Investigator-recorded information.

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.

E20 is esomeprazole 20 mg; E40 is esomeprazole 40 mg

## Table S4 Number (%) of patients with the most commonly reported[a] adverse events by preferred term sorted in decreasing order of frequency as summarized over all treatment groups (all randomized patients)

| Adverse event (preferred term) | E20 (N=226) | | E40 (N=220) | | Placebo (N=229) | |
|---|---|---|---|---|---|---|
| | **n** | **(%)** | **n** | **(%)** | **n** | **(%)** |
| Diarrhoea NOS | 11 | (4.9) | 5 | (2.3) | 7 | (3.1) |
| Headache | 4 | (1.8) | 11 | (5.0) | 5 | (2.2) |
| Nausea | 3 | (1.3) | 6 | (2.7) | 4 | (1.7) |
| Flatulence | 4 | (1.8) | 5 | (2.3) | 1 | (0.4) |
| Abdominal pain NOS | 4 | (1.8) | 4 | (1.8) | 3 | (1.3) |

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

E20 is esomeprazole 20 mg; E40 is esomeprazole 40 mg; NOS is not otherwise specified

Date of the report 19 February 2004