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|---|---|---|---|
| Drug Substance(s) | Esomeprazole | **SYNOPSIS** | (For national authority use only) |
| Study Code | D9612C00100 | | |
| Date | 15 December 2005 | | |

# An Open, Single-centre, Randomised, Six-way crossover, Dose-response Study of Esomeprazole 20, 40 and 80 mg and Lansoprazole 15, 30 and 60 mg Regarding 24-hour Intragastric pH Following Repeated Oral Dose Administration in Healthy Male and Female Subjects

## Study centre

Single centre study

| **Study dates** | | **Phase of development** |
|---|---|---|
| **First subject enrolled** | 25 June 2002 | Clinical pharmacology (I) |
| **Last subject completed** | 25 October 2002 | |

## Objectives

The primary objective was to investigate the dose-response relationship of esomeprazole and lansoprazole following repeated once-daily administration of 20, 40 and 80 mg esomeprazole and 15, 30 and 60 mg lansoprazole in healthy male and female subjects by assessment of the percentage of time with intragastric pH>4 over the 24-hour period on study day 5.

Secondary objectives of the study were

- to investigate the dose-response relationship of esomeprazole and lansoprazole following repeated once-daily administration of 20, 40 and 80 mg esomeprazole and 15, 30 and 60 mg lansoprazole in healthy male and female subjects by assessment of 24-hour median pH on study day 5

- to compare esomeprazole 40 mg and 80 mg versus lansoprazole 60 mg by assessment of the percentage of time with intragastric pH>4 over the 24-hour period on study day 5

- to evaluate the safety of esomeprazole by assessment of adverse events and laboratory variables.

**Study design**

The study was conducted as a single-centre (Switzerland), open, randomised, six-way cross-over study in which 40 healthy subjects received 20, 40 and 80 mg esomeprazole or 15, 30 and 60 mg lansoprazole once in the morning for 5 days. Intragastric pH recording was done at baseline and on Day 5 in each period, using a glass micro electrode attached to a Mark III Gastrograph data logger.

**Target subject population and sample size**

Healthy male and female subjects aged between 20 and 50 years with a minimum of 25 % of either gender. The study included 40 healthy male and female subjects in order to have at least 30 subjects completing the study. In order to facilitate the evaluation of the pharmacodynamic effect only subjects who had pH>4 less than 30% of the time at baseline were included in the study.

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

Investigational product: Esomeprazole 20 mg, 40 mg and 80 mg om in oral capsule form.
Batch No.: H 1189-04-01-06 (esomeprazole 20 mg capsule) and H 1222-04-01-09 (esomeprazole 40 mg capsule).

Comparator: Lansoprazole 15 mg, 30 mg and 60 mg om in oral capsule form.
Batch No.: H-1460-03-01-01 (lansoprazole 15 mg capsule) and H 0995-07-01-01 (lansoprazole 30 mg capsule)

**Duration of treatment**

Six treatment periods of 5 days each. The treatment periods were separated by washout periods of at least 13 days.

**Variables**

**- Pharmacodynamic**

- The percentage of time during 24 hours with intragastric pH>4
- The median 24-hour pH.

**- Safety**

- Adverse event (AE)

- Laboratory screening
- Blood pressure (BP)
- Pulse

**Statistical methods**

The Per Protocol (PP) population was used in all the statistical analyses of the pharmaco-dynamic variables. Detailed criteria and identification of the Per Protocol population was determined before clean file status was declared.

The safety population was defined as subjects who received at least one dose of any study drug and for whom post-dose data were available. Missing values were not replaced in the analysis.

Pharmacodynamic statistical evaluation

The percentage of time with intragastric pH>4 during the 24-hour period was analysed using a mixed model ANOVA, with treatment, sequence and period as fixed effects and subjects within sequence as a random effect. Consecutive doses were compared for each drug and only subjects with assessments on the two treatments being compared were included in the analysis. The mean for each treatment and the mean treatment difference was estimated with 95% confidence and the p-values for the comparisons were calculated.

The median 24-hour pH was analysed in the same way.

Comparisons of the esomeprazole 40 mg and 80 mg versus (vs) lansoprazole 60 mg were evaluated using the ANOVA model and presented as mean differences, including 95% CIs and p-values. The 2 comparisons were evaluated separately, including only subjects with assessments on the two treatments being compared. Comparison of esomeprazole 40 mg vs lansoprazole 30 mg and esomeprazole 20 mg vs lansoprazole 30 mg and 15 mg were also made ad hoc in the same way as described for esomeprazole 40 mg and 80 mg vs lansoprazole 60 mg.

Individual listings and descriptive statistics for all pharmacodynamic variables, including baseline measurements, are presented.

Safety statistical evaluation

AE data and laboratory variables are presented descriptively. Individual data for laboratory variables, pulse, BP, ECG and physical examination are listed for each subject.

**Subject population**

Healthy male and female subjects. Of the 40 randomised subjects, 39 were Caucasians and one of other ethnic origin (mixed asian-caucasian). All randomised subjects received at least one dose of the investigational product or comparator and were thus included in the safety analysis.

| | **Total** |
|---|---|
| No. enrolled | 49 |
| No. randomised | 40 |
| No. treated | 40 |
| Males/Females | 19/21 |
| Mean age (range) | 30.9 years (21-55) |
| No. included in at least one of the pharmacodynamic analyses | 37 |
| No. analysed for safety | 40 |
| No. completed | 37 |
| Males/Females | 18/19 |

**Summary of pharmacodynamic results**

The effect of esomeprazole after po administration once daily (od) for 5 days provided significantly higher percentage of time with intragastric pH>4 as the dose was increased from 20 mg to 40 mg, with a mean increase of 15.53 percentage points (95% CI: 11.66, 19.40). No further statistically significant difference in percentage of time with intragastric pH>4 was seen when increasing the esomeprazole dose from 40 mg to 80 mg with a mean difference of 4.57 percentage points (95% CI: -0.49, 9.63), favouring esomeprazole 80 mg.

For lansoprazole, a significantly higher percentage of time with intragastric pH>4 was seen when the dose was increased from 15 mg to 30 mg and from 30mg to 60 mg. The estimated mean difference in percentage of time with intragastric pH>4, was 9.32 percentage points (95% CI: 3.99, 14.64) between lansoprazole 15 mg and 30 mg, and 6.16 percentage points (95% CI: 2.20, 10.13) between lansoprazole 30 mg and 60 mg.

An equal pattern as for time with intragastric pH>4 was also shown for the mean 24-hour median intragastric pH between escalated doses of esomeprazole and lansoprazole on Day 5.

The comparison among three different doses of esomeprazole and lansoprazole showed that repeated dosing of esomeprazole 20 mg provided significantly more effective acid control measured as time with intragastric pH>4 than lansoprazole 15 mg, and an effect equal to that of lansoprazole 30 mg in healthy subjects. Furthermore, esomeprazole 40 mg provided significantly more effective acid control than both lansoprazole 30 mg and 60 mg. Consequently, esomeprazole 80mg also showed significantly better effect than lansoprazole 60 mg.

**Summary of safety results**

The most commonly reported AEs were headache and abdominal pain and these occurred in a similar frequency on both study drugs. There were no AEs classified as Other Significant

AEs (OAEs). The differences in the frequency of reported AEs when comparing the treatment groups were assessed to have no clinical relevance.

No serious adverse events (SAEs) or discontinuations due to adverse events (DAEs) were reported during study days (treatment). During the wash-out period two AEs (pharyngitis and mouth disorder) leading to discontinuation from the study were reported after lansoprazole 15 mg and esomeprazole 20 mg, respectively. Also during the wash-out period one subject committed suicide, reported as SAE. In addition it came to AstraZeneca's knowledge that another subject committed suicide after the study. Both these subjects had a history of episodes of depression not revealed at the pre-entry visit.