ASTRA
ASTRA HÄSSLE
Astra Hässle AB
S–431 83 Mölndal
Sweden

CLINICAL STUDY SYNOPSIS

TRADE NAME(S): Losec® NAMES OF ACTIVE INGREDIENT(S) IN: Omeprazole	REFERENCE IN THE DOSSIER Volume: Ref. number: Page:	(FOR NATIONAL AUTHORITY USE ONLY) STUDY CODE: I–900 REPORT NO: I–900

Title of the study: Duodenal ulcer healing and relief of symptoms during treatment with omeprazole 20 or 40 mg o.m. for 2–8 weeks and prevention of duodenal ulcer relapse during maintenance treatment with omeprazole 10 mg o.m., omeprazole 20 mg o.m. or ranitidine 150 mg h.s. for twelve months. An international multicentre study.

Publication: (reference): European Journal of Gastroenterology & Hepatology 1992, 4:995–1000

Study period: November 1989 – December 1991.

Clinical phase: Phase III

Objectives: Healing phase. Healing rates and symptom relief after 2 weeks. Cumulative healing rates after 4 and 8 weeks. Cumulative healing rates after 12 and 16 weeks after open treatment with omeprazole 40 mg o.m.
Maintenance phase. Compare the time to ulcer relapse during a twelve month period. The type and frequency of adverse events and influence on laboratory variables were also to be compared during both study phases.

Study design: Double–blind randomised controlled parallel group design study.

Number of patients: 1004 patients (693 M/311 F, 18–80 years, 496 in omeprazole 20 mg o.m., 508 in omeprazole 40 mg o.m. group) in the healing phase; 928 patients (637 M/291 F, 308 in omeprazole 10 mg o.m., 308 in omeprazole 20 mg o.m., 312 in ranitidine 150 mg h.s. group) in the maintenance phase.

November 20, 1992

Diagnosis and criteria for inclusion:

Outpatients with at least one active duodenal ulcer with a greater axis of at least 5 mm, verified by endoscopy within 4 days of study entry. All patients with healed ulcers and who were free from ulcer symptoms (only mild symptoms were accepted) were allowed to participate in the maintenance phase.

Investigational product:

All formulations were hard gelatine capsules containing enteric-coated omeprazole granules or sucrose granules for oral administration. Double-dummy technique. Batch numbers: Omeprazole capsules 10 mg H 499-14-2-1, --14-2-2, --14-2-3. Omeprazole placebo 10 mg H 459-5-1, --6-1-1, --6-1-2. Omeprazole capsules 20 mg H 431-13-2-1, --13-2-2. Omeprazole placebo 20 mg H 459-5-1, -- 6-1-1, --6-1-2. Omeprazole capsules 40 mg H 743-2-1-1, --2-1-2, Omeprazole placebo 40 mg H 761-2-1-1.

Reference therapy(ies):

Ranitidine tablets and matching placebos for oral administration. Double-dummy technique. Batch numbers: Ranitidine tablets 150 mg H 538-1-22, --5-1-2, --5-1-3, --5-1-5. Ranitidine placebo 150 mg H 539-3-2, --4-1-1, --4-1-2, --4-1-3.

Duration of treatment:

2-8 weeks healing phase; open treatment in unhealed patients for a further 4-8 weeks and a maximum of 12 months maintenance phase.

Assessment methods:

Endoscopy including biopsies at pre-entry, 2, 4, 8, 12 and 16 weeks (in unhealed patients), 3, 6, 12 months or on symptomatic relapse. Ulcer symptoms at all visits. Laboratory screen including serum gastrin at all visits except for 3 and 9 months. Adverse events at all visits except pre-entry. Physical examination before and after each study phase.

Statistical methods:

Healing data: Healing rates were compared using the Mantel-Haenszel test with stratification by pre-entry ulcer size (Per Protocol, PP, and All Patient Treated, APT, approaches were used). A logit analysis of prognostic factors was performed with healing as response variable.
Ulcer symptoms: In the healing phase a Wilcoxon test with stratification according to pre-entry symptoms was used in the overall assessment of symptoms and epigastric pain (PP approach).
Remission data: Time in remission data were used to estimate survival curves, according to the actuarial lifetable method, (PP and APT approach). Analysis of the possible influence of prognostic factors on the time in remission was performed using a Cox regression analysis (PP and APT approach).
Biopsy data: Change in classification of endocrine cells and pathological, anatomical diagnosis from baseline to last day of treatment were analysed descriptively by cross-tabulations.
Laboratory data: Gastrin was analysed with parametric confidence intervals within treatments and with unpaired t-tests between treatments (true mean change from pre-entry to last day). For all other variables conversion factors have been applied to normalise varying sorts of units. Within-group comparisons

of the number of patients with increased and decreased values respectively, were based on sign test and between-group comparisons were based on the Chi-square test.
Adverse events: Descriptive statistics.

Summary of results:

Healing rates obtained in the omeprazole 20 mg group at 2 and 4 (n=493) and 8 (n=492) weeks were 64%, 89% and 92% while those in the 40 mg group (n=505) were 70%, 94% and 96%, respectively. Statistically significant difference between the two groups at 4 (p=0.005) and 8 (p=0.002) but not at 2 weeks. The only prognostic factors found to have a statistically significant influence on ulcer healing was ulcer size and dose of omeprazole (survival analysis). Almost all patients were symptom free after 2 weeks' treatment. Continued treatment for up to 16 weeks' healed all ulcers. Of 954 healed patients 928 entered the maintenance phase. The estimated remission rates up to 12 months were 71% for the omeprazole 10 mg group, 87% for the omeprazole 20 mg group and 63% for the ranitidine 150 mg group. Omeprazole 20 mg differed significantly from both omeprazole 10 mg (p=0.0001) and ranitidine 150 mg (p=0.0001) but there was no significant difference between omeprazole 10 mg and ranitidine 150 mg. Patients requiring longer treatment courses to heal, smokers, long ulcer history and young patients seemed to have a lower chance of staying in remission.

The overall number of patients reporting adverse events did not differ between treatment groups within each phase. Omeprazole induced a dose related increase in median fasting serum gastrin levels (most within the normal reference range). No dysplastic or neoplastic lesions were observed in any biopsy specimen. A slight increase in the severity of gastritis paralleled by an increase in the number of patients with focal hyperplasia of endocrine cells was more prevalent in the omeprazole-treated patients. Independent of study drug, the frequency of focal hyperplasia was observed to be related to elevated gastrin levels.