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Clinical Study Synopsis

TRADE NAME(S): \ Losec NAME OF ACTIVE INGREDIENT(S) INN: \ Omeprazole	REFERENCE IN THE DOSSIER Volume: \ Ref. number: \ Page: \	(FOR NATIONAL AUTHORITY USE ONLY) \ STUDY CODE: I–621

Title of the study: Omeprazole in the maintenance treatment of erosive peptic oesophagitis: a double–blind, controlled study

Investigators, study centres: Multicentre study in Australia including 5 centres

Study period: August 1987 to October 1989

Clinical phase: III

Objectives: Phase a: to investigate the effect of treatment with 20 mg omeprazole over a period of four or eight weeks on objective indices of disease severity in patients with erosive peptic oesophagitis.
Phase b: to determine the recurrence rate of erosive peptic oesophagitis following healing over a twelve month treatment period with two omeprazole dosage regimens or ranitidine.

Study design: Phase a, acute treatment – open
Phase b, maintenance treatment – double–blind, randomised, controlled

Number of patients: Phase a – 204 entered (139 males, 65 females)
Phase b – 159 entered (106 males, 53 females)

Diagnosis, inclusion criteria: Erosive peptic oesophagitis of Grade 2 or greater endoscopically verified not more than seven days prior to the commencement of treatment.

Investigational drugs: Omeprazole 20 mg enteric–coated granules in gelatin capsules.
Batch nos: H431–9–5, H431–9–6, H431–9–8, H431–9–9
Omeprazole placebo enteric–coated granules in gelatin capsules.
Batch no: H459–5–1

Reference drugs: Ranitidine 150mg tablets, batch no: H538–1–15
Ranitidine placebo tablets, batch no: H539–3–1

Duration of treatment: Phase a – 4 or 8 weeks
Phase b – 12 months

Assessment methods: Phase a – Oesophagitis symptoms, physical examination, laboratory screen at pre–entry, Day 57. Adverse events at day 29 and 57. Endoscopy at Day 29 and healed (resolution of erosion/ulceration) patients entered Phase b. Unhealed underwent endoscopy at Day 57. Healed patients entered Phase b, unhealed left study.

Phase b – Symptoms, adverse events, compliance and gastrin level assessed at 1, 2, 3, 6, 9, and 12 months. Physical examination at 3, 6, 9 and 12 months. Laboratory screen at 6 and 12 months.

Endoscopy in patients with symptomatic recurrence and/or at 6 and 12 months.

Statistical methods:

Intention–to–treat analysis was performed. The proportion healed after 4 and 8 weeks in Phase a was calculated.

The survival curves in Phase b were estimated according to the actuarial lifetable method. The endpoint used in the analysis was withdrawal from treatment due to symptomatic or asymptomatic recurrence of oesophagitis.

If normally distributed, laboratory data were analysed in terms of mean change from pre–entry to last visit and 95% confidence intervals calculated. Differences in mean changes between treatment groups were analysed by one–way analysis of variance. Highly skewed variables were analysed using the sign test and pattern of changes tested using the chi–square test.

Summary of result:

All patients were included in the efficacy analyses.
124/204 (60.8%) patients were healed at Day 29 and 165/204 (80.9%) were healed at Day 57. Six healed patients did not enter Phase b and 53 patients were randomised to omeprazole 20 mg om, 55 to omeprazole weekend therapy 20 mg/20 mg/20 mg and 51 to ranitidine 150 mg bd.

Cumulative proportion of patients in remission at completion of Phase b was 89% for omeprazole 20 mg om, 32% for omeprazole 20/20/20 and 25% for ranitidine 150 mg bd. ($p<0.001$ for omeprazole 20 mg om vs omeprazole 20/20/20 and ranitidine).

One patient in the omeprazole 20 mg om group in Phase b did not receive any study drug and was excluded from the safety analysis.

The median gastrin level significantly increased during Phase a from 37 pg/mL to 47 pg/mL. The median 12 month level (55 pg/mL) in the omeprazole 20 mg om group was significantly different from the pre–entry value.
No clinically significant changes in other laboratory variables occurred.

The most commonly reported adverse events were related to reflux oesophagitis and occurred with a greater frequency in the omeprazole 20/20/20 and ranitidine groups. Serious adverse events were reported by 4 patients in Phase a and eleven patients in Phase b. None were attributable to treatment.

No pathological changes in the argyrophilic cell population of the gastric mucosa were seen during the study.