AstraZeneca

I-901-B

SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Losec™

ACTIVE INGREDIENT: Omeprazole

Trial Title (number): Open treatment with omeprazole 40 mg once daily during 2-8 weeks and a twelve-month follow-up of the relapse rate of duodenal ulcer during maintenance treatment with omeprazole 20 mg once daily. A double blind multicentre placebo controlled study.

Development Phase: Phase III
First Subject Recruited:
Last Subject Completed:
Approval Date: 25 November 1992

OBJECTIVES

To evaluate the duodenal ulcer healing rates and symptom relief after 2 weeks treatment with omeprazole 40 mg once daily and the cumulative healing rates after 4 and 8 weeks treatment. To compare the time in remission and the relapse pattern during a twelve- month maintenance treatment with either omeprazole 20 mg or placebo.

METHODS

Study design

Open healing phase; double-blind randomized maintenance placebo controlled comparison. Primary endpoint was relapse (an ulcer with or without symptoms).

Target subject population and sample size

Outpatients with a history of at least 3 episodes of DU in the past 24 months and with current active DU verified by endoscopy within 4 days of study entry. 129 patients (40 F/89 M, 17-79 years) in healing phase; 123 patients (60 in omeprazole 20 mg, 63 in placebo group) in maintenance phase.

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

All formulations were hard gelatin capsules containing enteric-coated omeprazole granules or sucrose granules. Double-dummy techniques.

- Omeprazole 40 mg H-743-2-1-1
- Omeprazole 20 mg H-431-13-2-1
- Omeprazole 20 mg placebo H-459-6-1-1

Duration of treatment

2-8 weeks healing phase; a maximum of 12 months maintenance phase.

Criteria for evaluation
Efficacy (including HRQOL assessments; hereafter referred to as Patient Reported Outcomes [PRO]):

- Endoscopy was performed pre-study, after 2, 4 and 8 weeks (in unhealed patients) in the healing phase and at 3, 6 and 12 months or on symptomatic relapse in the maintenance phase. Gastric biopsies for histochemical examination were taken at the time of each biopsy.
- Laboratory screening and blood samples for serum gastrin concentration was performed at each visit (except at 3 and 9 months) as was standardized questioning on ulcer symptoms and adverse events (not pre-study). A physical examination was performed before and after each study phase.

Safety

Statistical methods

All patients Treated approach has been used in all analyses except for time in remission where also a Per Protocol Analysis was used.
Remission data: Time in remission data were used to estimate survival curves, according to the actuarial life-table method, which were compared by the Mantel-Haenszel (log rank) test.
Biopsy data: 2- way tables of change in classification of endocrine cells and pathological, anatomical diagnosis from baseline to last study visit.
Laboratory data including gastrin analysis: Analyses of change from pre-study to end of maintenance; 95% confidence limits for the mean change. Cross tabulation of baseline versus last visit values in relation to normal range.
Adverse events: Descriptive statistics.

RESULTS

Subject population

129 patients (40 F/89 M, 17-79 years) in healing phase; 123 patients (60 in omeprazole 20 mg once daily, 63 in placebo group) in maintenance phase.

123 patients entered maintenance. 60 patients were randomized to omeprazole treatment and 63 to placebo.

Efficacy and PRO results

Healing rates (n=128) following open omeprazole 40 mg treatment were 81%, 95%, and 97% at 2,4, and 8 weeks, respectively. Of the 124 patients who completed the healing phase all patients were healed within eight weeks and symptoms were rapidly relieved.

There was a significant difference between the two treatment groups regarding the risk of having a relapse, 6% versus 91% in the omeprazole and placebo group respectively (APT anlysis; 4% versus 91% PP).

Safety results

There were no remarkable endoscopic or biopsy findings, instances of significant laboratory findings were few and both the healing and maintenance therapies were well tolerated. Increased serum gastrin levels remained stable during omeprazole treatment. Gastrointestinal symptoms constituted the most serious adverse events considered causally related to omeprazole treatment.

Safety results from the long-term maintenance phase are given in Table 1.

Table 1 **Long-term omeprazole study data (data from maintenance phase only)**

Trial	Treatment	Omep dose (mg)	Planned duration (months	N	Average days of treatment	Total exposure (pt-yrs)	% dropouts	# CV SAEs	# deaths all cause	# deaths CV	# MIs	# MI fatal	# deaths or MIs	# Non heam. stroke
I-901B	Omeprazole	20	12	60	319.0	52.4	13.3	1	1	0	0	0	1	0
	Placebo		12	63	121.0	20.9	6.3	0	1	0	0	0	1	0

(mg milligram; N number of patient; CV Cardiovascular; SAE Serious adverse event; MI Myocardial infarction.)

As with any comprehensive clinical trial programme, individual studies may include both approved and non-approved treatment regimens, including doses higher than those approved for clinical use. Before prescribing Losec™ (omeprazole), Healthcare Professionals should view their specific country information.