ORIGINAL RESEARCH ARTICLE

Drug Safety 1999 Feb; 20 (2): 195-205
0114-5916/99/0002-0195/$05.50/0

Safety Profile of Lansoprazole

The US Clinical Trial Experience

James W. Freston,[1] *Pamela A. Rose*,[2] *Caren A. Heller*,[2] *Marian Haber*[3] and *Dennis Jennings*[2]

1 Department of Medicine, University of Connecticut Health Center, Farmington, Connecticut, USA
2 TAP Pharmaceuticals, Inc., Deerfield, Illinois, USA
3 Department of Pathology, Medical College of Pennsylvania and Hahneman University, Philadelphia, Pennsylvania, USA

Abstract

Objective: Lansoprazole has undergone extensive clinical evaluation for the treatment of acid-peptic diseases. The aim of this study was to define the safety profile of lansoprazole and compare it to that of other therapeutic agents evaluated in the same controlled trials.

Methods: The clinical safety profile of lansoprazole and comparative agents (placebo, ranitidine and omeprazole) was reviewed for 3281 patients who participated in short term (up to 8 weeks) and long term (up to 56 months) clinical trials conducted in the US. Adverse events, laboratory value changes and gastric biopsy changes that occurred during treatment were compared statistically for differences between treatments.

Results: The incidence of adverse events and number of patients discontinuing treatment because of adverse events was similar for lansoprazole and comparative agents. Other than elevated serum gastrin levels, a known effect of proton pump inhibitors, no trends in laboratory changes were observed. Median values for gastrin levels remained within the normal range; about 2% of patients had gastrin levels >400 pg/ml at any time, while <1% had 2 or more gastrin values >500 pg/ml. Values returned to baseline levels after therapy was discontinued. No significant changes in gastric endocrine cell growth from baseline to final visit were observed, nor was there evidence of dysplasia or neoplasia.

Conclusion: Lansoprazole is well tolerated for both short and long term treatment of acid-related disease. The tolerability of lansoprazole is comparable to that of ranitidine, omeprazole and placebo in the treatment of these diseases.

Lansoprazole, a proton pump inhibitor similar to omeprazole, has undergone extensive clinical evaluation for the treatment of acid-related diseases, including endoscopically documented gastroesophageal reflux disease (GERD), duodenal ulcer, gastric ulcer, eradication of *Helicobacter pylori* in combination with antibacterials, and Zollinger-Ellison syndrome. Efficacy results from clinical trials of lansoprazole in GERD, duodenal ulcer and Zollinger-Ellison syndrome[1-4] indicate that the agent is a highly effective treatment for these conditions. Lansoprazole was superior to H_2-receptor antagonists (usually ranitidine 300 mg/day) in relieving clinical symptoms as well as in healing both oesophageal erosions and peptic ulcers. Additionally, lansoprazole was comparable to om-

eprazole in healing oesophageal erosions, faster in controlling heartburn,[5-7] and significantly more effective than either placebo or ranitidine in preventing the recurrence of erosive GERD.[8-9]

Our purpose here is to define the safety profile of lansoprazole and to compare it with that of the other therapeutic agents evaluated in US clinical trials.

Materials and Methods

Patient Population

A total of 3281 patients participated in clinical trials comparing lansoprazole with placebo, ranitidine or omeprazole in the treatment of GERD, duodenal ulcer, gastric ulcer, Zollinger-Ellison syndrome or Barrett's epithelium. Of these patients 2233 received lansoprazole, and of these patients 1457 had GERD, 469 had duodenal ulcer, 207 had gastric ulcer, 66 had Zollinger-Ellison syndrome and 34 had Barrett's epithelium. All non–Zollinger-Ellison syndrome conditions required endoscopic documentation for study entry; studies in Zollinger-Ellison syndrome required documentation of increased acid secretion. Patients with GERD and duodenal ulcer were studied in both acute healing trials (4 to 12 weeks) and long term (1-year) trials. Most patients in the long term GERD and duodenal ulcer studies entered from short term studies. Those with gastric ulcer were enrolled only in acute healing trials (8 weeks). Patients with Zollinger-Ellison syndrome or Barrett's epithelium had participated in on-going, long term studies, and safety data from these populations reflect treatment for up to 56 months.

Table I summarises the demographic characteristics of lansoprazole-treated patients involved in the US clinical trial programme. In short term studies, 86% of patients were Caucasian and 66% were male. Their mean age was 48 years (range 18 to 84 years); 32% were tobacco users and 49% consumed alcohol. Demographic characteristics were similar in long term studies.

Lansoprazole Exposure by Dosage

In short term studies, 28% of patients received lansoprazole 15 mg/day, 52% received 30 mg/day,

Table I. Demographic characteristics of lansoprazole patients in US trials

	Short term trials (n = 1885)	Long term trials		
		GU/DU/GERD[a] (n = 502)	BE (n = 34)	ZES (n = 66)
Gender (%)				
Female	34.2	35.5	14.7	36.4
Male	65.8	64.5	85.3	63.6
Age (y)				
Mean	48	47.3	61	50.5
Range	18-84	19-83	38-81	22-88
Race (%)				
Caucasian	85.9	89.8	97.1	69.7
African-American	9.1	7	0	28.8
Other	5	3.2	2.9	1.5
Tobacco users (%)				
Yes	32.1	34.1	26.5	42.2
No	67.9	65.9	73.5	57.8
Alcohol users (%)				
Yes	48.8	46.6	29.4	35.6
No	51.2	53.4	70.6	64.4

a 254 of these patients received lansoprazole during a short term trial as well as in the long term trials.

BE = Barrett's epithelium; **DU** = duodenal ulcer; **GERD** = gastroesophageal reflux disease; **GU** = gastric ulcer; **ZES** = Zollinger-Ellison syndrome.

Table II. Final dosage of lansoprazole in long term studies

Lansoprazole dosage (mg/day)	No. of patients (%)			
	GU/DU/GERD[a] (n = 502)	BE (n = 34)	ZES (n = 66)	Total (n = 602)
≤ 15	107 (21%)		7 (11%)	114 (19%)
30-45	395 (79%)		18 (27%)	413 (69%)
60		34 (100%)	22 (33%)	56 (9%)
75-105			9 (14%)	9 (1%)
120-180			10 (15%)	10 (2%)

a 254 of these patients received lansoprazole during a short term trial as well as in the long term trials.

BE = Barrett's epithelium; **DU** = duodenal ulcer; **GERD** = gastroesophageal reflux disease; **GU** = gastric ulcer; **ZES** = Zollinger-Ellison syndrome.

and 20% received 60 mg/day. Ranitidine was given at a dosage of 300 mg/day and omeprazole at a dosage of 20 mg/day. In long term, placebo-controlled GERD and duodenal ulcer trials, most patients (79%) received between 30 to 45 mg/day of lansoprazole. In the Barrett's epithelium trial, all patients received lansoprazole 60 mg/day. Patients with Zollinger-Ellison syndrome were given 60 mg/day initially, with dosages adjusted up or down to meet a target basal acid output. Table II summarises the final dosages of lansoprazole in long term studies.

Adverse Event Reporting

An adverse event was defined as any adverse sign or symptom that occurred during treatment, whether or not it was considered to be drug-related. Investigators were asked to judge whether the event may have been caused by the drug based on the following definitions:

- probable (temporal relationship and no potential alternate aetiology apparent)
- possible (temporal relationship but a potential alternative aetiology existed)
- unrelated (evidence existed that the adverse event was definitely related to another aetiology).

Clinical Laboratory Tests

Clinical laboratory evaluations were conducted at a central clinical laboratory (SciCor Inc., Indianapolis, IN). Changes that might be clinically meaningful (table III) were defined in advance of each study according to criteria established by the US Food and Drug Administration to detect values requiring a more in-depth review; the same criteria were used for all studies. Laboratory values meeting these criteria for individual patient review were analysed separately. Serum samples for determination of gastrin levels were drawn after an 8-hour fast.

Gastric Biopsies

In a blinded study to assess the effect of lansoprazole and other test agents on endocrine cells, a subset of investigators obtained full-mucosal thickness gastric biopsies. Four biopsy specimens were obtained from the gastric mucosa of the body of the stomach along the greater curvature. All samples were evaluated under the direction of Drs Walter Rubin and Marian Haber at the Medical College of Pennsylvania in consultation with Dr Juan Lechago, Baylor College of Medicine. Slides were evaluated qualitatively for patterns of hyperplasia according to the classification of gastric endocrine cell distribution adapted from Solcia et al.[10]

Statistical Methods

Data from all patients who entered the treatment period and received at least 1 dose of study medication were included in all safety analyses for which they had baseline and treatment-period observations. P-values ≤ 0.05 were deemed statistically significant. Adverse events and laboratory changes were analysed in all studies. The frequency of possibly or probably treatment-related adverse events reported during the study are presented in this report.

Table III. Criteria for clinical laboratory levels of clinical concern[a]

Laboratory value	Clinical review level[b]
Haematology	
Haematocrit	≤ 0.371 (M); ≤ 0.321 (F)
Haemoglobin level	≤ 115 g/L (M); ≤ 95 g/L (F)
Platelet count	$\leq 75 \times 10^9$/L
WBC count	$\leq 2.8 \times 10^9$/L
Hepatic	
Alkaline phosphatase level	>3 × ULN
GGT level	>3 × ULN
AST level	>3 × ULN
ALT level	>3 × ULN
Total bilirubin level	≥ 68 μmol/L
Metabolic/nutritional	
Albumin level	≤ 25 g/L
Glucose level	≥ 14 mmol/L
Total protein level	≤ 50 g/L
Renal	
BUN level	≥ 11 mmol/L
Creatinine level	≥ 178 μmol/L
Calcium level	≥ 3 mmol/L
Phosphorus level	≤ 0.48 mmol/L
Uric acid level	≥ 625 μmol/L (M); ≥ 506 μmol/L (F)

a Values were predefined based on US Food and Drug Administration requirements, with the same criteria used in each trial.

b Value must also have been more abnormal or equal to the patient's baseline value.

ALT = alanine amino transferase; **AST** = aspartate amino transferase; **BUN** = blood urea nitrogen; **F** = female; **GGT** = γ-glutamyl transferase; **M** = male; **ULN** = upper limit of normal; **WBC** = white blood cell.

Data from long term studies of Zollinger-Ellison syndrome and Barrett's epithelium were analysed separately by indication. Since reporting patterns might have varied across studies, tests for treatment differences in proportions of patients experiencing adverse events were adjusted for study using the Mantel-Haenszel method for combining (2 × 2) tables. For each laboratory test variable, the proportions of patients exhibiting changes meeting predefined criteria of clinical concern (table III) were compared between treatment groups using Fisher's exact test.

The percentage changes from baseline to each evaluation point were calculated for all patients who had fasting serum gastrin values available. The Kruskal-Wallis test was used to test for baseline differences between treatment groups in gastrin levels. For the short term studies, pairwise comparisons of percentage changes from baseline between treatment groups were performed using the Wilcoxon 2-sample test. For long term controlled studies, in which baseline values were obtained after drug treatment, the Wilcoxon 2-sample test was performed on actual values rather than on changes from baseline. For long term noncomparative studies, changes from baseline were analysed using the Wilcoxon signed rank test.

Changes in Solcia classification of gastric biopsies from baseline to final visit were categorised as decreased, unchanged or increased. The Cochran-Mantel-Haenszel methodology for ordered response variables was used to compare treatment groups.

Results

Adverse Events

In the controlled trials, the incidence of adverse events was similar between lansoprazole and the comparator agents. Figure 1 shows the adverse event profile lansoprazole and placebo in the four placebo-controlled studies. There is a marked similarity between the profiles for lansoprazole and placebo. The incidence of none of the adverse events differed significantly between the 2 treatment groups.

Figure 2 shows the incidence of adverse events in lansoprazole, omeprazole and placebo-treated patients from a large, 3-arm study; no significant differences among the treatment groups were observed.

In the ranitidine-controlled trials, diarrhoea was reported significantly more often among lansoprazole-treated patients compared with ranitidine-treated patients (4.3 *vs* 1.5%, respectively, $p \leq 0.05$). A dose-response analysis of placebo-controlled trials using different dosages of lansoprazole indicated that the incidence of diarrhoea was dose dependent. The incidence was 1.4% in patients receiving lansoprazole 15 mg/day, 4.2% in patients

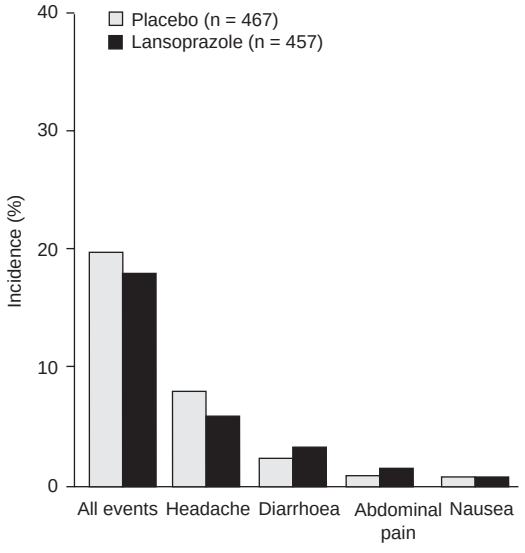

Fig. 1. Incidence (%) of the most frequent adverse events in short term, placebo-controlled studies. Lansoprazole had a similar adverse event safety profile to placebo.

receiving 30 mg/day, and 7.4% in patients receiving lansoprazole 60 mg/day. The incidence of diarrhoea in the placebo groups was 2.9%, and a statistically significant difference was evident between placebo and lansoprazole 60 mg/day. In the study comparing lansoprazole to omeprazole, the incidence of diarrhoea was comparable between the two groups; the incidence in the lansoprazole 30 mg/day group was 3.6%, and that compared with 3.9% in the omeprazole 20 mg/day recipients.

In long term studies, lansoprazole was as well tolerated as placebo and no significant between-group differences were evident in the incidence of any adverse event. Diarrhoea occurred in 2% of placebo-treated patients and 3.2% of lansoprazole-treated patients — this was the only event considered treatment-related and reported by at least 2% of patients in any treatment group.

In the open-label study of 34 patients with Barrett's epithelium treated with lansoprazole 60 mg/day, five patients (15%) reported a treatment-related adverse event and diarrhoea was the only event reported by more than one patient (n = 3). Among the 66 patients with Zollinger-Ellison syndrome, adverse events reported by more than one patient were diarrhoea (n = 4), nausea (n = 3) and headache (n = 3).

Premature Discontinuations

Withdrawals from all clinical trials due to adverse events occurred infrequently (table IV). At all dosage levels in both short and long term studies, the rate of premature discontinuations occurring in lansoprazole groups was similar to that in control groups. Upon review of drug-related causes for study withdrawal, there were no discernible trends.

Laboratory Value Changes

Tables V and VI summarise laboratory values that met criteria for clinical concern, requiring a review of individual patients' laboratory data. Statistically significant between-group differences were observed only in the number of patients with low haemoglobin levels or haematocrit values. In the short term, placebo-controlled trials, a significantly greater incidence of low haemoglobin levels

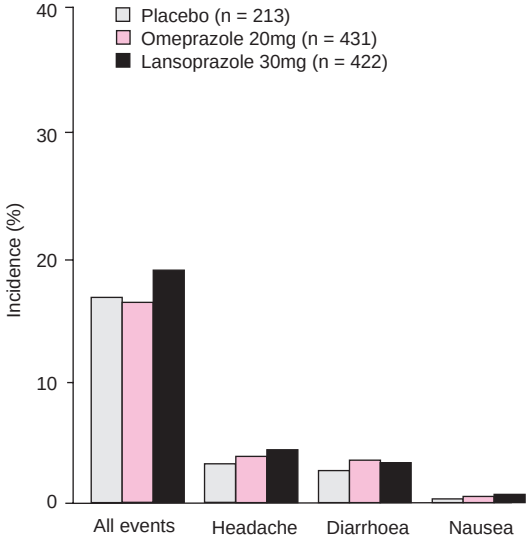

Fig. 2. Incidence (%) of the most frequent adverse events in a short term, controlled studies comparing omeprazole, lansoprazole and placebo. Lansoprazole had a similar adverse event profile to placebo and to omeprazole.

Table IV. Percentage of patients discontinuing clinical trials because of adverse events

	Comparative drug (n/N)	Lansoprazole (n/N)
Short term studies		
Placebo-controlled	1.7 (8/467)	2.3 (33/1457)
Ranitidine-controlled	3.8 (13/338)	4.3 (23/533)
Omeprazole-controlled	2.1 (9/431)	1.4 (9/640)
Long term studies		
Placebo-controlled	8 (16/201)	6 (19/315)

n/N = number of patients discontinuing clinical trials because of adverse events/total number of patients in the clinical trial(s).

occurred during placebo administration than during lansoprazole administration; in long term trials, a greater incidence of low haematocrit values was evident in lansoprazole-treated patients. There were no corresponding significant differences in other measures of low red blood cell count in these patient groups. Review of data from individual patients indicated that the majority of changes were sporadic during treatment, had returned to near baseline values by the final treatment visit or were associated with a concurrent condition. Changes in laboratory values among patients over 65 years of age were similar to those in the total population.

Serum Gastrin Levels

During short term trials, most fasting serum gastrin values remained within the normal range. Among the few patients exhibiting very high gastrin levels, values in lansoprazole recipients were significantly higher than those in ranitidine 300 mg/day recipients and were similar to those observed in omeprazole 20 mg/day recipients (fig. 3). Increases in gastrin levels were dose dependent,

Table V. Percentage of patients exhibiting laboratory values of clinical concern in short term controlled trials

Laboratory value	Placebo-controlled trials		Ranitidine-controlled trials	
	placebo (n/N)	lansoprazole (n/N)	ranitidine (n/N)	lansoprazole (n/N)
Haematology[a]				
Haematocrit	2.1 (9/432)	1.2 (16/1379)	0.9 (3/332)	2.1 (11/518)
Haemoglobin level	1.4 (6/433)[b]	0.4 (5/1382)	0.3 (1/332)	0.8 (4/518)
WBC count	0	0	0.3 (1/332)	0
Platelet count	0.2 (1/432)	0	0	0
Hepatic				
AST level	0.7 (3/438)	0.3 (4/1394)	0.3 (1/332)	0.8 (4/518)
ALT level	0.7 (3/438)	0.4 (5/1394)	0	0.4 (2/518)
GGT level	0.5 (2/438)	0.9 (12/1393)	0.9 (3/332)	1.4 (7/518)
Total bilirubin level	0.2 (1/437)	0	0	0
Metabolic/nutritional				
Albumin level	0	0.1 (1/1391)	0.3 (1/332)	0
Glucose level	0.2 (1/437)	0.4 (5/1391)	0	0.2 (1/518)
Total protein level	0	0.1 (1/1394)	0.3 (1/332)	0
Renal[a]				
BUN level	0	0.3 (4/1393)	0.9 (3/332)	0.2 (1/518)
Creatinine level	0.2 (1/438)	0.1 (1/1393)	0.6 (2/332)	0.2 (1/518)
Phosphorus level	0	0.1 (1/1386)	0	0
Uric acid level	0	0.7 (10/1394)	0.6 (2/332)	0.8 (4/518)

a No patients had alkaline phosphatase or calcium values of clinical concern.

b $p \leq 0.05$ *vs* lansoprazole group.

ALT = alanine amino transferase; **AST** = aspartate amino transferase; **BUN** = blood urea nitrogen; **GGT** = γ-glutamyl transferase; **n/N** = number of patients discontinuing clinical trials because of adverse events/total number of patients in the clinical trial(s); **WBC** = white blood cell.

Table VI. Percentage of patients exhibiting laboratory values of clinical concern in short and long term trials

Laboratory value	Short term studies (omeprazole-controlled)		Long term studies (placebo-controlled)	
	omeprazole (n/N)	lansoprazole (n/N)	placebo (n/N)	lansoprazole (n/N)
Haematology[a]				
Haematocrit	2 (8/395)	2.1 (12/585)	0	2.3 (7/310)[b]
Haemoglobin level	0.8 (3/397)	0.5 (3/588)	0	0.6 (2/310)
WBC count	0	0	0	0
Hepatic[a]				
AST level	0.2 (1/402)	0.5 (3/599)	1.1 (2/188)	0
ALT level	0.2 (1/402)	0.8 (5/599)	0.5 (1/188)	0
GGT level	1.5 (6/402)	1.8 (11/598)	0.5 (1/188)	1.3 (4/310)
Metabolic/nutritional				
Albumin level	0	0	0	0
Glucose level	0.8 (3/400)	1 (6/597)	0	1.3 (4/310)
Total protein level	0	0	0	0
Renal[a]				
BUN level	0.7 (3/402)	0	0	0
Creatinine level	0.5 (2/402)	0	0	0.6 (2/310)
Phosphorus level	0	0	0	0.3 (1/310)
Uric acid level	0.2 (1/402)	0.8 (5/599)	0	1 (3/310)

a No patients had platelet counts, alkaline phosphatase, bilirubin or calcium values of clinical concern.

b $p \leq 0.05$ *vs* placebo group.

ALT = alanine amino transferase; **AST** = aspartate amino transferase; **BUN** = blood urea nitrogen; **GGT** = γ-glutamyl transferase; **n/N** = number of patients discontinuing clinical trials because of adverse events/total number of patients in the clinical trial; **WBC** = white blood cell.

with the largest median percent increase occurring in the lansoprazole 60 mg/day recipients (fig. 4). Changes in the lansoprazole 30 mg/day and 60 mg/day recipients were significantly greater than those in the lansoprazole 15 mg/day recipients ($p = 0.016$ and 0.001, respectively). The median increase was 50% to 100% over baseline, which reached a plateau after 4 weeks of lansoprazole therapy. As shown in figure 4, values in all treatment groups returned to near-baseline levels by 1 month after treatment.

Similar results were seen in the long term controlled GERD and duodenal ulcer studies, in which patients received lansoprazole for up to 15 months. Serum gastrin values increased significantly from baseline values, reaching a plateau after 2 months of treatment. As in the short term studies, most gastrin values remained within the normal range (fig. 5). The highest fasting serum gastrin level seen in any patient during lansoprazole therapy was 1389 pg/ml. Approximately 2% of patients had a gastrin level exceeding 400 pg/ml at any time during treatment, while fewer than 1% of patients had values above 500 pg/ml on 2 or more occasions.

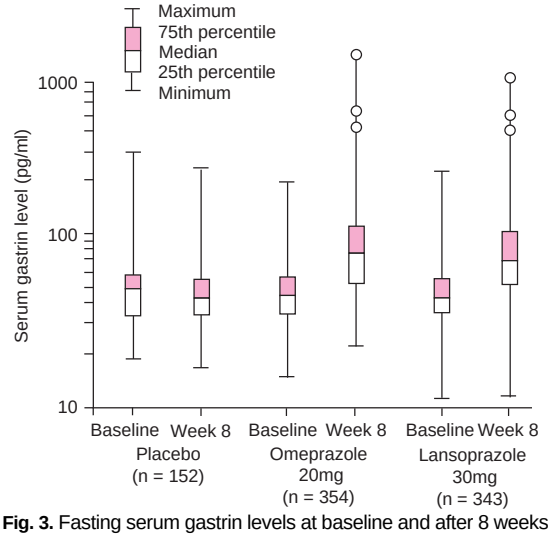

Fig. 3. Fasting serum gastrin levels at baseline and after 8 weeks of daily treatment with placebo, omeprazole 20mg, or lansoprazole 30mg. A similar increase in the gastrin levels was observed with both proton pump inhibitors. º = gastrin value >400 pg/ml.

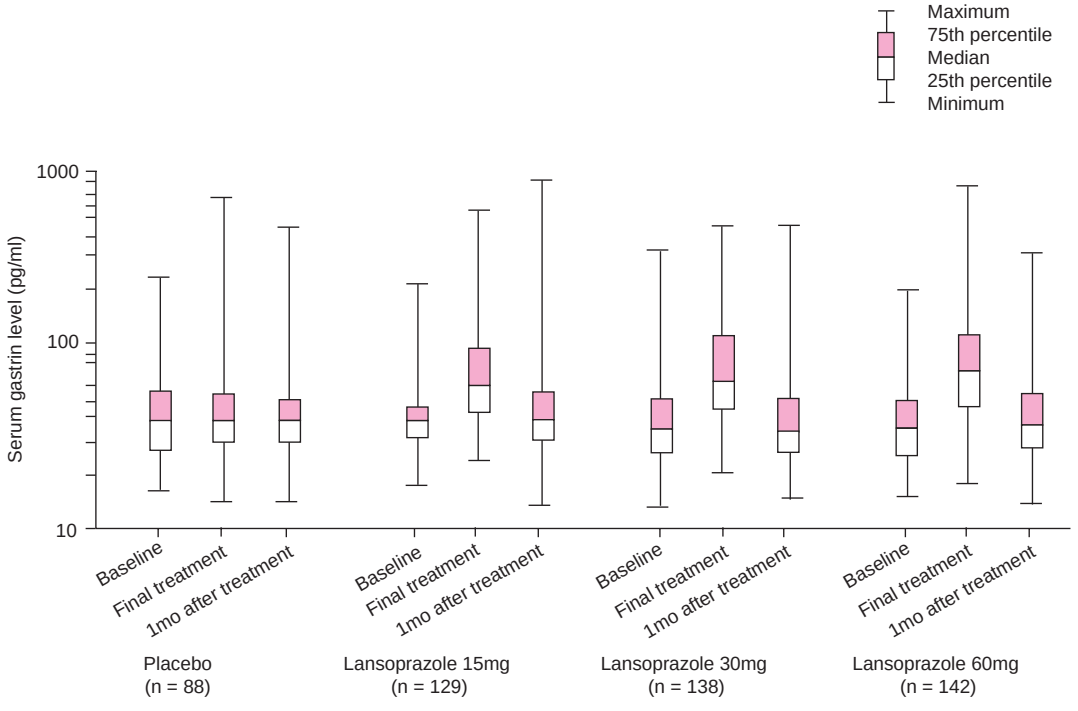

Fig. 4. Fasting serum gastrin levels at baseline, at final treatment visit and at 1 month (mo) after treatment in short term, placebo-controlled studies. There was a significant dose-related increase in median gastrin levels observed among the lansoprazole treatment groups. Nevertheless, the median gastrin levels stayed within the normal range in all treatment groups during therapy.

Gastric Biopsies

There were no significant changes in the Solcia classification of gastric endocrine cell distribution from baseline to final visit in either short or long term studies. Eight short term study patients (1.2%) receiving lansoprazole treatment exhibited higher than normal qualitative histopathological changes at the final visit and all 8 had simple (diffuse) hyperplasia. In long term studies, 3 patients receiving lansoprazole for GERD had normal first biopsies followed by simple hyperplasia on biopsies taken later at recurrence of GERD or at the final visit. One patient treated for Barrett's epithelium had a normal first biopsy and simple hyperplasia on biopsy after 3.5 years of lansoprazole treatment. Two patients with Zollinger-Ellison syndrome had normal biopsies at baseline, with either simple or micronodular hyperplasia on final biopsies after more than 2.6 years of lansoprazole therapy.

Biopsy results for changes in acute and chronic inflammation in controlled maintenance studies demonstrated that there were no adverse changes of clinical concern. Changes in the corpus were similar in placebo- and lansoprazole-treated patients for both acute and chronic inflammation, with increases in chronic inflammation grade observed in both groups. In the antral biopsies, a smaller percentage of patients in the lansoprazole group showed increased inflammation compared to the placebo group.

The prevalence of corpus gastric atrophy among *H. pylori*–positive patients treated with long term lansoprazole was 1% (1 out of 99 patients). When

antral biopsies were evaluated for the presence of gastric atrophy in 87 patients, only 1 had atrophy identified at the final visit (1.1% or 1 out of 87 patients) and this patient was *H. pylori*–positive. At baseline, before any lansoprazole treatment, 3 patients (6.3% or 3 out of 87 patients) presented with atrophy and all were *H. pylori*–positive. Only 1 patient had both corpus and antral gastric atrophy identified during a long term study.

The point prevalence of intestinal metaplasia during lansoprazole treatment was similar to the point prevalence observed at baseline. One lansoprazole-treated and 1 placebo-treated patient had possible evidence of incomplete (colonic) intestinal metaplasia during treatment; both patients were *H. pylori*–positive. These results suggest that lansoprazole treatment is not associated with the development of intestinal metaplasia.

Overall, there was no evidence of dysplasia or neoplasia among lansoprazole-treated patients, and changes from baseline were similar to those seen with the comparative drugs (table VII). Analyses of these studies indicate that long term treatment with lansoprazole produced no clinically meaningful adverse effects on gastric mucosa morphology.

Discussion

Results of these safety analyses demonstrate that lansoprazole is well tolerated. Like omeprazole,[11-12] the adverse effect profile of lansoprazole is generally comparable to that observed with placebo. In a direct comparison study, rates of adverse events (including diarrhoea) and laboratory changes (including gastrin levels) were similar for lansoprazole and omeprazole. Short term studies comparing lansoprazole and ranitidine indicated a higher incidence of diarrhoea with lansoprazole compared with ranitidine. However, placebo-controlled, dose-response trials indicated a lower incidence of diarrhoea in patients taking lansoprazole 15 and 30 mg/day compared with placebo and a significantly higher incidence of diarrhoea in patients taking lansoprazole 60 mg/day compared with placebo. These differences may reflect an increased tolerance to H_2-antagonist ther-

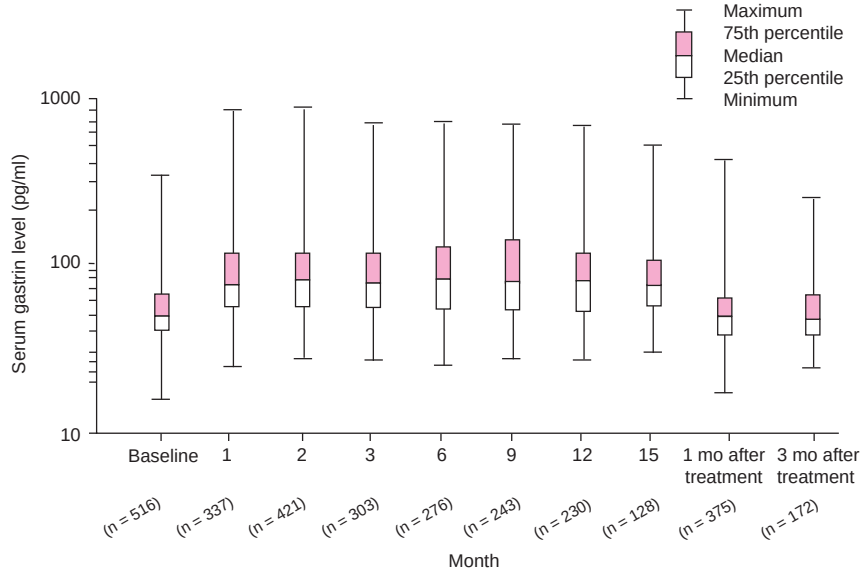

Fig. 5. Fasting serum gastrin levels at baseline, during maintenance treatment, and 1 and 3 months (mo) after treatment. The median gastrin level, which stayed within the normal range during the treatment period, reached a maximal level by month 2, remained fairly constant throughout treatment, and returned towards baseline by 1 mo after treatment.

Table VII. Gastric biopsy comparisons in controlled trials

First biopsy	Last biopsy	Short term studies				Long term studies	
		no. of placebo recipients (%)	no. of ranitidine recipients (%)	no. of omeprazole recipients (%)	no. of lansoprazole recipients (%)	no. of placebo recipients (%)	no. of lansoprazole recipients (%)
Normal	Normal	160 (98.8)	169 (96)	257 (100)	731 (98.3)	107 (99.1)	204 (97.1)
Normal	Hyperplastic	0	2 (1.1)	0	7 (0.9)	0	3 (1.4)
Hyperplastic	Normal	1 (0.6)	2 (1.1)	0	5 (0.7)	1 (0.9)	2 (1)
Hyperplastic	Hyperplastic	1 (0.6)	3 (1.7)	0	1 (0.1)	0	1 (0.5)

apy in the patients receiving ranitidine, since most of these patients had received a 12-week course of ranitidine treatment before entering the studies reported here. Consequently, the incidence of diarrhoea experienced by these patients during ranitidine therapy was probably lower than that generally experienced with that drug. This observation is supported by a large study of adverse reactions to ranitidine in which diarrhoea was the most frequently reported event: 3.3% among 18 126 patients receiving short term therapy and 2.9% among 3553 patients receiving maintenance treatment.[13]

A primary concern about the use of proton pump inhibitors is the indirect effect on serum gastrin levels and the possibility that long term treatment might be associated with gastric endocrine cell effects and carcinoid tumour formation. The frequency and magnitude of hypergastrinaemia was similar during lansoprazole and omeprazole treatment. The 2% incidence of gastrin values above 400 pg/ml at any time during lansoprazole treatment in non–Zollinger-Ellison syndrome patients is well within the range of 11% reported for omeprazole at dosages of 20 to 60 mg/day given long term for GERD.[14]

In the rat model, long term treatment with proton pump inhibitors resulted in prolonged, markedly elevated levels of gastrin[15-16] and a dose- and gender-dependent incidence of enterochromaffin-like (ECL) cell gastric carcinoid tumours.[16-17] Two major differences between rats and humans in the development of ECL cell tumours have been identified: the magnitude of exposure to elevated gastrin levels, and a genetic predisposition in rats toward ECL cell hyperplasia.[18] Based on human and experimental animal experience, these investigators concluded that severe, long-standing hypergastrinaemia acting on genetically normal, gastritis-free gastric mucosa in humans does not produce carcinoids, nor even preclinical lesions. However, when coupled with other tumourigenic factors, including the genetic trait of MEN-1 syndrome, or severe, long-standing chronic atrophic gastritis of pernicious anaemia, gastrin may work as a tumour promoter by acting on genetically-transformed cells. The conclusion that acid-suppression with proton pump inhibitors will not lead to carcinoid tumour development in humans is further supported by long term experience with omeprazole[14,19-20] and the experience with lansoprazole reported here. Treatment with lansoprazole for up to 4 years, and with omeprazole for up to 7 years, has not been associated with any gastric endocrine or non-endocrine cell neoplastic or dysplastic changes.

Conclusion

In conclusion, this analysis indicates that lansoprazole is well tolerated for both short and long term treatment of acid-related disease. Moreover, no clinically significant interaction between lansoprazole and other drugs metabolised by the cytochrome P450 system have been observed.[21,22] The recommended dosages of lansoprazole 15 and 30 mg/day for non–Zollinger-Ellison syndrome conditions show an adverse effect profile comparable to that of placebo, and its overall safety profile is consistent with that of omeprazole and ranitidine. Safety and tolerability are similar in both short and long term clinical experiences, in-

cluding, in comparison with omeprazole, the changes seen in fasting gastrin levels, as well as the magnitude of such changes.

Acknowledgements

This research was supported by a grant from TAP Pharmaceuticals, Inc., Deerfield, IL, the licensee for lansoprazole in the US.

References

1. Robinson M, Sahba B, Avner D. A comparison of lansoprazole and ranitidine in the treatment of erosive oesophagitis. Aliment Pharmacol Ther 1995; 9: 25-31
2. Feldman M, Harford W, Fisher R. Treatment of reflux esophagitis resistant to H_2-receptor antagonists with lansoprazole, a new H+/K+-ATPase inhibitor: a controlled, double-blind study. Am J Gastroenterol 1993; 88: 1212-7
3. Lanza F, Goff J, Scrowcroft C. Double-blind comparison of lansoprazole, ranitidine, and placebo in the treatment of acute duodenal ulcer. Am J Gastroenterol 1994; 89: 1191-200
4. Metz D, Pisegna J, Ringham G. Prospective study of efficacy and safety of lansoprazole in Zollinger-Ellison syndrome. Dig Dis Sci 1993; 38: 245-56
5. Castell DO, Richter JE, Robinson M, et al. Efficacy and safety of lansoprazole in the treatment of erosive reflux esophagitis. Am J Gastroenterol 1996; 91: 1749-57
6. Hatlebakk JG, Berstad A, Carling L, et al. Lansoprazole *vs* omeprazole in short-term treatment of reflux oesophagitis – results of a Scandinavian multi-centre trial. Scand J Gastroenterol 1993; 28: 224-8
7. Mee AS, Rowley JS. Rapid symptom relief in reflex oesophagitis: a comparison of lansoprazole and omeprazole. Aliment Pharmacol Ther 1996; 10: 757-63
8. Robinson M, Lanza F, Avner D, et al. Effective maintenance treatment of reflux esophagitis with low-dose lansoprazole. Ann Intern Med 1996; 124: 859-67
9. Sontag S, Kogut D, Fleischmann R, et al. Lansoprazole prevents recurrence of erosive reflux esophagitis previously resistant to H2-RA therapy. Am J Gastroenterol 1996; 91: 1758-65
10. Solcia E, Bordi C, Creutzfeldt W, et al. Histopathological classification of nonantral gastric endocrine growths in man. Digestion 1988; 41: 185-200
11. Solvell L. The clinical safety of omeprazole. Scand J Gastroenterol 1989; 24 Suppl. 166: 106-10
12. Joelson S, Joelson IB, Lundborg P, et al. Safety experience from long-term treatment with omeprazole. Digestion 1992; 51 Suppl. 1: 93-101
13. Das AF, Freston JW, Jacobs J, et al. An evaluation of safety in 37,252 patients treated with cimetidine or ranitidine. Int Med Specialists 1990; 11: 3-14
14. Klinkenberg-Knol EC, Festen HPM, Jansen JBM, et al. Efficacy and safety of long-term treatment with omeprazole for refractory reflux esophagitis. Ann Intern Med 1994; 121: 161-7
15. Carlsson E, Larsson H, Mattsson H, et al. Pharmacology and toxicology of omeprazole-with special reference to the effects on the gastric mucosa. Scand J Gastroenterol; 1986; 21 Suppl. 118: 31-8
16. Ekman L, Hansson E, Havu N, et al. Toxicological studies on omeprazole. Scand J Gastroenterol 1985; 20 Suppl. 108: 53-69
17. Havu N. Enterochromaffin-like cell carcinoids of gastric mucosa in rats after life-long inhibition of gastric secretion. Digestion 1986; 35 Suppl. 1: 42-55
18. Freston JW, Borch K, Brand SJ, et al. Effects of hypochlorhydria and hypergastrinemia on structure and function of gastrointestinal cells: a review and analysis. Dig Dis Sci 1995; 40 Suppl.: 50S-62S
19. Solcia E, Fiocca R, Havu N, et al. Gastric endocrine cells and gastritis in patients receiving long-term omeprazole treatment. Digestion 1992; 51 Suppl. 1: 82-92
20. Lamberts R, Creutzfeldt W, Struber HG, et al. Long-term omeprazole therapy in peptic ulcer disease: gastrin, endocrine cell growth, and gastritis. Gastroenterol 1993; 104: 1356-70
21. Rodrigues AD, Freston JW. Do PPI effects on the cytochrome P_{450} system have implications to significant drug interactions? In: Guile R, Tytgat G, Dameester T, et al., editors. The esophageal mucosa. Amsterdam: Elsevier, 1994: 460-4
22. Freston JW. Long-term acid control and proton pump inhibitors: interactions and safety issues in perspective. Am J Gastroenterol 1996; 92 (4): 51S-7S

Correspondence and reprints: Professor *James W. Freston*, Department of Medicine, University of Connecticut Health Center, Farmington, CT 06032, USA.
E-mail: freston@nso.uchc.edu