

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-406/S009

Trade Name: Prevacid Delayed Release Capsules

Generic Name: lansoprazole

Sponsor: Tap Holdings Inc.

Approval Date: February 25, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-406/S009

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-406/S009

APPROVAL LETTER

NDA 20-406/S-009

TAP Holdings Inc.
Attention: Judy Decker Wargel
2355 Waukegan Road
Deerfield, IL 60015

FEB 25 1997

Dear Ms. Wargel:

Please refer to your supplemental new drug application dated April 15, 1996, received April 16, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prevacid (lansoprazole) Delayed-Release Capsules.

The supplemental application provides for revisions to the PRECAUTIONS, Drug Interactions section of the package insert.

We have completed the review of this supplemental application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling in the submission dated April 15, 1996. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling submitted on April 15, 1996.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved supplemental NDA 20-406/S-009. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

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In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications,
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Should a letter communicating important information about this drug product (i.e., a "Dear Doctor" letter) be issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20852-9787

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Maria R. Walsh, M.S., Project Manager, at (301) 443-0487.

Sincerely yours,

Stephen B. Fredd, M.D.
Director
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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cc:

Original NDA 20-406/S-009

HFD-180/Div. files

HFD-180/PM/M. Walsh

HFD-180/Medical Officer/J.Senior

DISTRICT OFFICE

HF-2/Medwatch (with labeling)

HFD-92/DDM-DIAB (with labeling)

HFD-40/DDMAC (with labeling)

HFD-613/OGD (with labeling)

HFD-735/DPE (with labeling) - for all NDAs and supplements for adverse reaction changes.

HFI-20/Press Office (with labeling)

final: M. Walsh 2/24/97

87 2/24/97

APPROVAL (AP)

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-406/S009

LABELING

Labeling Orig 3LR/509
NDA No. 20-4116 Rc'd. 6/4/97
Reviewed by: M. Walsh/6/16/97

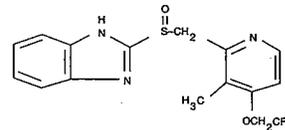
(1)

(Nos. 1541, 3046)
03-4793-R7-Rev. May, 1997

PREVACID®
(pre'-va-sid)
(lansoprazole)
Delayed-Release Capsules

DESCRIPTION

The active ingredient in PREVACID (lansoprazole) Delayed-Release Capsules is a substituted benzimidazole, 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl] methyl]sulfinyl] benzimidazole, a compound that inhibits gastric acid secretion. Its empirical formula is $C_{16}H_{14}F_3N_3O_2S$ with a molecular weight of 369.37. The structural formula is:



Lansoprazole is a white to brownish-white odorless, crystalline powder which melts with decomposition at approximately 166°C. Lansoprazole is freely soluble in dimethylformamide; soluble in methanol; sparingly soluble in ethanol; slightly soluble in ethyl acetate, dichloromethane and acetonitrile; very slightly soluble in ether; and practically insoluble in hexane and water.

Lansoprazole is stable when exposed to light for up to two months. The compound degrades in aqueous solution, the rate of degradation increasing with decreasing pH. At 25°C the $t_{1/2}$ is approximately 0.5 hour at pH 5.0 and approximately 18 hours at pH 7.0.

PREVACID is supplied in delayed-release capsules for oral administration. The delayed-release capsules contain the active ingredient, lansoprazole, in the form of enteric-coated granules and are available in two dosage strengths: 15 mg and 30 mg of lansoprazole per capsule. Each delayed-release capsule contains enteric-coated granules consisting of lansoprazole, hydroxypropyl cellulose, low substituted hydroxypropyl cellulose, colloidal silicon dioxide, magnesium carbonate, methacrylic acid copolymer, starch, talc, sugar sphere, sucrose, polyethylene glycol, polysorbate 80, and titanium dioxide. Components of the gelatin capsule include gelatin, titanium dioxide, D&C Red No. 28, FD&C Blue No. 1, FD&C Green No. 3*, and FD&C Red No. 40.

* PREVACID 15 mg capsules only.

CLINICAL PHARMACOLOGY
Pharmacokinetics and Metabolism

PREVACID Delayed-Release Capsules contain an enteric-coated granule formulation of lansoprazole. Absorption of lansoprazole begins only after the granules leave the stomach. Absorption is rapid, with mean peak plasma levels of lansoprazole occurring after approximately 1.7 hours. Peak plasma concentrations of lansoprazole (C_{max}) and the area under the plasma concentration curve (AUC) of lansoprazole are approximately proportional in doses from 15 mg to 60 mg after single-oral administration. Lansoprazole does not accumulate and its pharmacokinetics are unaltered by multiple dosing.

Absorption

The absorption of lansoprazole is rapid, with mean C_{max} occurring approximately 1.7 hours after oral dosing, and relatively complete with absolute bioavailability over 80%. In healthy subjects, the mean (\pm SD) plasma half-life was 1.5 (\pm 1.0) hours. Both C_{max} and AUC are diminished by about 50% if the drug is given 30 minutes after food as opposed to the fasting condition. There is no significant food effect if the drug is given before meals.

Distribution

Lansoprazole is 97% bound to plasma proteins. Plasma protein binding is constant over the concentration range of 0.05 to 5.0 mcg/mL.

Metabolism

Lansoprazole is extensively metabolized in the liver. Two metabolites have been identified in measurable quantities in plasma (the hydroxylated sulfinyl and sulfone derivatives of lansoprazole). These metabolites have very little or no anti-secretory activity. Lansoprazole is thought to be transformed into two active species which inhibit acid secretion by (H^+ , K^+)-ATPase within the parietal cell canaliculus, but are not present in the systemic circulation. The plasma elimination half-life of lansoprazole does not reflect its duration of suppression of gastric acid secretion. Thus, the plasma elimination half-life is less than two hours while the acid inhibitory effect lasts more than 24 hours.

Elimination

Following single-dose oral administration of lansoprazole, virtually no unchanged lansoprazole was excreted in the urine. In one study, after a single oral dose of ^{14}C -lansoprazole, approximately one-third of the administered radiation was excreted in the urine and two-thirds was recovered in the feces. This implies a significant biliary excretion of the metabolites of lansoprazole.

Special Populations

Geriatric

The clearance of lansoprazole is decreased in the elderly, with elimination half-life increased approximately 50% to 100%. Because the mean half-life in the elderly remains between 1.9 to 2.9 hours, repeated once daily dosing does not result in accumulation of lansoprazole. Peak plasma levels were not increased in the elderly.

(2)

Geriatric

The clearance of lansoprazole is decreased in the elderly, with elimination half-life increased approximately 50% to 100%. Because the mean half-life in the elderly remains between 1.9 to 2.9 hours, repeated once daily dosing does not result in accumulation of lansoprazole. Peak plasma levels were not increased in the elderly.

Pediatric

The pharmacokinetics of lansoprazole has not been investigated in patients <18 years of age.

Gender

In a study comparing 12 male and six female human subjects, no gender differences were found in pharmacokinetics and intragastric pH results (also see Use in Women).

Renal Insufficiency

In patients with severe renal insufficiency, plasma protein binding decreased by 1.0%-1.5% after administration of 60 mg of lansoprazole. Patients with renal insufficiency had a shortened elimination half-life and decreased total AUC (free and bound). AUC for free lansoprazole in plasma, however, was not related to the degree of renal impairment, and C_{max} and T_{max} were not different from subjects with healthy kidneys.

Hepatic Insufficiency

In patients with various degrees of chronic hepatic disease, the mean plasma half-life of the drug was prolonged from 1.5 hours to 3.2-7.2 hours. An increase in mean AUC of up to 500% was observed at steady state in hepatically-impaired patients compared to healthy subjects. Dose reduction in patients with severe hepatic disease should be considered.

Race

The pooled pharmacokinetic parameters of lansoprazole from twelve U.S. Phase I studies (N=513) were compared to the mean pharmacokinetic parameters from two Asian studies (N=20). The mean AUCs of lansoprazole in Asian subjects are approximately twice that seen in pooled U.S. data, however the inter-individual variability is high. The C_{max} values are comparable.

PHARMACODYNAMICS

Mechanism of action

Lansoprazole belongs to a class of antisecretory compounds, the substituted benzimidazoles, that do not exhibit anticholinergic or histamine H₂-receptor antagonist properties, but that suppress gastric acid secretion by specific inhibition of the (H⁺,K⁺)-ATPase enzyme system at the secretory surface of the gastric parietal cell. Because this enzyme system is regarded as the acid (proton) pump within the parietal cell, lansoprazole has been characterized as a gastric acid-pump inhibitor, in that it blocks the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated gastric acid secretion irrespective of the stimulus.

Antisecretory activity

After oral administration, lansoprazole was shown to significantly decrease the basal acid output and significantly increase the mean gastric pH and percent of time the gastric pH was >3 and >4. Lansoprazole also significantly reduced meal-stimulated gastric acid output and secretion volume, as well as pentagastrin-stimulated acid output. In patients with hypersecretion of acid, lansoprazole significantly reduced basal and pentagastrin-stimulated gastric acid secretion. Lansoprazole inhibited the normal increases in secretion volume, acidity and acid output induced by insulin.

In a crossover study comparing lansoprazole 15 and 30 mg with omeprazole 20 mg for five days, the following effects on intragastric pH were noted:

Mean Antisecretory Effects after Single and Multiple Daily Dosing

Parameter	Baseline Value	PREVACID				Omeprazole	
		15 mg Day 1	15 mg Day 5	30 mg Day 1	30 mg Day 5	20 mg Day 1	20 mg Day 5
Mean 24-Hour pH	2.1	2.7*	4.0*	3.6*	4.9*	2.5	4.2*
Mean Nighttime pH	1.9	2.4	3.0*	2.6	3.8*	2.2	3.0*
% Time Gastric pH >3	18	33*	59*	51*	72*	30*	61*
% Time Gastric pH >4	12	22*	49*	41*	66*	19	51*

NOTE: An intragastric pH of >4 reflects a reduction in gastric acid by 99%. *(<0.05) versus baseline, lansoprazole 15 mg and omeprazole 20 mg. *(p<0.05) versus baseline only.

After the initial dose in this study, increased gastric pH was seen within 1-2 hours with lansoprazole 30 mg, 2-3 hours with lansoprazole 15 mg, and 3-4 hours with omeprazole 20 mg. After multiple daily dosing, increased gastric pH was seen within the first hour postdosing with lansoprazole 30 mg and within 1-2 hours postdosing with lansoprazole 15 mg and omeprazole 20 mg.

The inhibition of gastric acid secretion as measured by intragastric pH returns gradually to normal over two to four days after multiple doses. There is no indication of rebound gastric acidity.

Enterochromaffin-like (ECL) cell effects

During lifetime exposure of rats with up to 150 mg/kg/day of lansoprazole dosed seven days per week, marked hypergastrinemia was observed followed by ECL cell proliferation and formation of carcinoid tumors, especially in female rats (see PRECAUTIONS, Carcinogenesis, Mutagenesis, and Fertility).

Gastric biopsy specimens from the body of the stomach from approximately 150 patients treated continuously with lansoprazole for at least one year have not shown evidence of ECL cell effects similar to those seen in rat studies. Longer term data are needed to rule out the possibility of an increased risk of the development of gastric tumors in patients receiving long-term therapy with lansoprazole.

Other gastric effects in humans

Lansoprazole did not significantly affect mucosal blood flow in the fundus of the stomach. Due to the normal physiologic effect caused by the inhibition of gastric acid secretion, a decrease of about 17% in blood flow in the antrum, pylorus and duodenal bulb was seen. Lansoprazole significantly slowed the gastric emptying of digestible solids. Lansoprazole increased serum pepsinogen levels and decreased pepsin activity under basal conditions and in response to meal stimulation or insulin injection. As with other agents that elevate intragastric pH, increases in gastric pH were associated with increases in nitrate-reducing bacteria and elevation of nitrite concentration in gastric juice in patients with gastric ulcer. No significant increase in nitrosamine concentrations was observed.

Serum gastrin effects

In over 2100 patients, median fasting serum gastrin levels increased 50% to 100% from baseline, but remained within normal range after treatment with lansoprazole given orally in doses of 15 mg to 60 mg. These elevations reached a plateau within two months of therapy and returned to pre-

concentration in gastric juice in patients with gastric ulcer. No significant increase in nitrosamine concentrations was observed.

Serum gastrin effects

In over 2100 patients, median fasting serum gastrin levels increased 50% to 100% from baseline, but remained within normal range after treatment with lansoprazole given orally in doses of 15 mg to 60 mg. These elevations reached a plateau within two months of therapy and returned to pre-treatment levels within four weeks after discontinuation of therapy.

Endocrine effects

Human studies for up to one year have not detected any clinically significant effects on the endocrine system. Hormones studied include testosterone, luteinizing hormone (LH), follicle stimulating hormone (FSH), sex hormone binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEA-S), prolactin, cortisol, estradiol, insulin, aldosterone, parathormone, glucagon, thyroid stimulating hormone (TSH), triiodothyronine (T₃), thyroxine (T₄), and somatotrophic hormone (STH). Lansoprazole in oral doses of 15 to 60 mg for up to one year, had no clinically significant effect on sexual function. In addition, lansoprazole in oral doses of 15 to 60 mg for two to eight weeks had no clinically significant effect on thyroid function.

In 24-month carcinogenicity studies in Sprague-Dawley rats with daily dosages up to 150 mg/kg, proliferative changes in the Leydig cells of the testes, including benign neoplasm, were increased compared to control rates.

Other effects

No systemic effects of lansoprazole on the central nervous system, lymphoid, hematopoietic, renal, hepatic, cardiovascular or respiratory systems have been found in humans. No visual toxicity was observed among 56 patients who had extensive baseline eye evaluations, were treated with up to 180 mg/day of lansoprazole and were observed for up to 58 months. Other rat-specific findings after lifetime exposure included focal pancreatic atrophy, diffuse lymphoid hyperplasia in the thymus, and spontaneous retinal atrophy.

CLINICAL STUDIES

Duodenal Ulcer

In a U.S. multicenter, double-blind, placebo-controlled, dose-response (15, 30, and 60 mg of PREVACID once daily) study of 284 patients with endoscopically documented duodenal ulcer, the percentage of patients healed after two and four weeks was significantly higher with all doses of PREVACID than with placebo. There was no evidence of a greater or earlier response with the two higher doses compared with PREVACID 15 mg. Based on this study and the second study described below, the recommended dose of PREVACID in duodenal ulcer is 15 mg per day.

Week	PREVACID			Placebo (N=72)
	15 mg qd (N=68)	30 mg qd (N=74)	60 mg qd (N=70)	
2	42.4%*	35.6%*	39.1%*	11.3%
4	89.4%*	91.7%*	89.9%*	46.1%

* (p<0.001) versus placebo.

PREVACID 15 mg was significantly more effective than placebo in relieving day and nighttime abdominal pain and in decreasing the amount of antacid taken per day.

In a second U.S. multicenter study, also double-blind, placebo, dose-comparison (15 and 30 mg of PREVACID once daily), and including a comparison with ranitidine, in 280 patients with endoscopically documented duodenal ulcer, the percentage of patients healed after four weeks was significantly higher with both doses of PREVACID than with placebo. There was no evidence of a greater or earlier response with the higher dose of PREVACID. Although the 15 mg dose of PREVACID was superior to ranitidine at 4 weeks, the lack of significant difference at 2 weeks and the absence of a difference between 30 mg of PREVACID and ranitidine leaves the comparative effectiveness of the two agents undetermined.

Duodenal Ulcer Healing Rates

Week	PREVACID		Ranitidine	Placebo (N=41)
	15 mg qd (N=80)	30 mg qd (N=77)	300 mg hs (N=82)	
2	35.0%	44.2%	30.5%	34.2%
4	92.3%**	80.3%*	70.5%*	47.5%

* (p<0.05) versus placebo.

** (p<0.05) versus placebo and ranitidine.

Long-Term Maintenance Treatment of Duodenal Ulcers
PREVACID has been shown to prevent the recurrence of duodenal ulcers. Two independent, double-blind, multicenter, controlled trials were conducted in patients with endoscopically confirmed healed duodenal ulcers. Patients remained healed significantly longer and the number of recurrences of duodenal ulcers was significantly less in patients treated with PREVACID than in patients treated with placebo over a 12-month period.

Endoscopic Remission Rates

Trial	Drug	Percent in Endoscopic Remission			
		No. of Pts.	0-3 mo.	0-6 mo.	0-12 mo.
#1	PREVACID				
	15 mg qd	86	90%*	87%*	84%*
	Placebo	83	49%	41%	39%
#2	PREVACID				
	30 mg qd	18	94%*	94%*	85%*
	15 mg qd	15	87%*	79%*	70%*
	Placebo	15	33%	0%	0%

%=Life Table Estimate

* (p<0.001) versus placebo

In trial #2, no significant difference was noted between PREVACID 15 mg and 30 mg in maintaining remission.

Gastric Ulcer

In a U.S. multicenter, double-blind, placebo-controlled study of 253 patients with endoscopically documented gastric ulcer, the percentage of patients healed at four and eight weeks was significantly higher with PREVACID 15 mg and 30 mg once a day than with placebo.

Gastric Ulcer Healing Rates

Week	PREVACID			Placebo (N=64)
	15 mg qd (N=65)	30 mg qd (N=65)	60 mg qd (N=61)	
4	64.6%*	58.1%*	53.3%*	37.5%
8	92.2%*	96.8%*	93.2%*	76.7%

* (p<0.05) versus placebo.

Patients treated with any PREVACID dose reported significantly less day and night abdominal pain along with fewer days of antacid use and fewer antacid tablets used per day than the placebo group.

Independent substantiation of the effectiveness of PREVACID 30 mg was provided by a meta-analysis of published and unpublished data.

Erosive Esophagitis

In a U.S. multicenter, double-blind, placebo-controlled study of 269 patients entering with an endoscopic diagnosis of esophagitis with mucosal grading of 2 or more and grades 3 and 4 signifying erosive disease, the percentages of patients with healing were as follows:

once daily), and including a comparison with ranitidine, in 280 patients with endoscopically documented duodenal ulcer, the percentage of patients healed after four weeks was significantly higher with both doses of PREVACID than with placebo. There was no evidence of a greater or earlier response with the higher dose of PREVACID. Although the 15 mg dose of PREVACID was superior to ranitidine at 4 weeks, the lack of significant difference at 2 weeks and the absence of a difference between 30 mg of PREVACID and ranitidine leaves the comparative effectiveness of the two agents undetermined.

Week	PREVACID		Ranitidine	Placebo
	15 mg qd (N=80)	30 mg qd (N=77)	300 mg hs (N=82)	(N=41)
2	35.0%	44.2%	30.5%	34.2%
4	92.3%**	80.3%*	70.5%*	47.5%

* (p<0.05) versus placebo.
** (p<0.05) versus placebo and ranitidine.

Long-Term Maintenance Treatment of Duodenal Ulcers
PREVACID has been shown to prevent the recurrence of duodenal ulcers. Two independent, double-blind, multicenter, controlled trials were conducted in patients with endoscopically confirmed healed duodenal ulcers. Patients remained healed significantly longer and the number of recurrences of duodenal ulcers was significantly less in patients treated with PREVACID than in patients treated with placebo over a 12-month period.

Trial	Drug	No. of Pts.	Percent in Endoscopic Remission		
			0-3 mo.	0-6 mo.	0-12 mo.
#1	PREVACID				
	15 mg qd	86	90%*	87%*	84%*
	Placebo	83	49%	41%	39%
#2	PREVACID				
	30 mg qd	18	94%*	94%*	85%*
	15 mg qd	15	87%*	79%*	70%*
	Placebo	15	33%	0%	0%

%=Life Table Estimate
* (p<0.001) versus placebo

In trial #2, no significant difference was noted between PREVACID 15 mg and 30 mg in maintaining remission.

Gastric Ulcer

In a U.S. multicenter, double-blind, placebo-controlled study of 253 patients with endoscopically documented gastric ulcer, the percentage of patients healed at four and eight weeks was significantly higher with PREVACID 15 mg and 30 mg once a day than with placebo.

Week	PREVACID			Placebo
	15 mg qd (N=65)	30 mg qd (N=63)	60 mg qd (N=61)	(N=64)
4	64.6%*	58.1%*	53.3%*	37.5%
8	92.2%*	96.8%*	93.2%*	76.7%

* (p<0.05) versus placebo.

Patients treated with any PREVACID dose reported significantly less day and night abdominal pain along with fewer days of antacid use and fewer antacid tablets used per day than the placebo group.

Independent substantiation of the effectiveness of PREVACID 30 mg was provided by a meta-analysis of published and unpublished data.

Erosive Esophagitis

In a U.S. multicenter, double-blind, placebo-controlled study of 269 patients entering with an endoscopic diagnosis of esophagitis with mucosal grading of 2 or more and grades 3 and 4 signifying erosive disease, the percentages of patients with healing were as follows:

Week	PREVACID			Placebo
	15 mg qd (N=69)	30 mg qd (N=65)	60 mg qd (N=72)	(N=63)
4	67.6%*	81.3%**	80.6%**	32.8%
6	87.7%*	95.4%*	94.3%*	52.5%
8	90.9%*	95.4%*	94.4%*	52.5%

* (p<0.001) versus placebo.
** (p<0.05) versus PREVACID 15 mg and placebo.

In this study, all PREVACID groups reported significantly greater relief of heartburn and less day and night abdominal pain along with fewer days of antacid use and fewer antacid tablets taken per day than the placebo group.

Although all doses were effective, the earlier healing in the higher two doses suggest 30 mg qd as the recommended dose.

PREVACID was also compared in a U.S. multicenter, double-blind study to a low dose of ranitidine in 242 patients with erosive reflux esophagitis. PREVACID at a dose of 30 mg was significantly more effective than ranitidine 150 mg bid as shown below.

Week	PREVACID	Ranitidine
	30 mg qd (N=115)	150 mg bid (N=127)
2	66.7%*	38.7%
4	82.5%*	52.0%
6	93.0%*	67.8%
8	92.1%*	69.9%

* (p<0.001) versus ranitidine.

In addition, patients treated with PREVACID reported less day and nighttime heartburn and took less antacid tablets for fewer days than patients taking ranitidine 150 mg bid.

Although this study demonstrates effectiveness of PREVACID in healing erosive esophagitis, it does not represent an adequate comparison with ranitidine because the recommended ranitidine dose for esophagitis is 150 mg qid, twice the dose used in this study.

In the two trials described and in several smaller studies involving patients with moderate to severe erosive esophagitis, PREVACID produced healing rates similar to those shown above.

In a U.S. multicenter, double-blind, active-controlled study, 30 mg of PREVACID was compared with ranitidine 150 mg bid in 151 patients with erosive reflux esophagitis that was poorly responsive to a minimum of 12 weeks of treatment with at least one H₂-receptor antagonist given at the dose indicated for symptom relief or greater, namely cimetidine 800 mg/day, ranitidine 300 mg/day, famotidine 40 mg/day or nizatidine 300 mg/day. PREVACID 30 mg was more effective than ranitidine 150 mg bid in healing reflux esophagitis and the percentage of patients with healing were as follows. This study does not constitute a comparison of the effectiveness of histamine H₂-receptor antagonists with PREVACID as all patients had demonstrated unresponsiveness to the histamine H₂-receptor antagonist mode of treatment. It does indicate, however, that PREVACID may be useful in patients failing on a histamine H₂-receptor antagonist.

Reflux Esophagitis Healing Rates in Patients Poorly Responsive to Histamine H₂-Receptor Antagonist Therapy

Week	PREVACID 30 mg qd (N=100)	Ranitidine 150 mg bid (N=51)
4	74.7%*	42.6%
8	83.7%*	32.0%

* (p<0.001) versus ranitidine.

Long-Term Maintenance Treatment of Erosive Esophagitis
Two independent, double-blind, multicenter, controlled trials were conducted in patients with endoscopically confirmed healed esophagitis. Patients remained in remission significantly longer and the number of recurrences of erosive esophagitis was significantly less in patients treated with PREVACID than in patients treated with placebo over a 12-month period.

Endoscopic Remission Rates

Trial	Drug	No of Pts.	Percent in Endoscopic Remission		
			0-3 mo.	0-6 mo.	0-12 mo.
#1	PREVACID 15 mg qd	59	83%*	81%*	79%*
	PREVACID 30 mg qd	56	93%*	93%*	90%*
	Placebo	55	31%	27%	24%
#2	PREVACID 15 mg qd	50	74%*	72%*	67%*
	PREVACID 30 mg qd	49	75%*	72%*	55%*
	Placebo	47	16%	13%	13%

% = Life Table Estimate

* (p<0.001) versus placebo

Regardless of initial grade of erosive esophagitis, PREVACID 15 mg and 30 mg were similar in maintaining remission.

Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome

In open studies of 57 patients with pathological hypersecretory conditions, such as Zollinger-Ellison (ZE) syndrome with or without multiple endocrine adenomas, PREVACID significantly inhibited gastric acid secretion and controlled associated symptoms of diarrhea, anorexia and pain. Doses ranging from 15 mg every other day to 180 mg per day maintained basal acid secretion below 10 mEq/hr in patients without prior gastric surgery, and below 5 mEq/hr in patients with prior gastric surgery.

Initial doses were titrated to the individual patient need, and adjustments were necessary with time in some patients (see DOSAGE AND ADMINISTRATION). PREVACID was well tolerated at these high dose levels for prolonged periods (greater than four years in some patients). In most ZE patients, serum gastrin levels were not modified by PREVACID. However, in some patients serum gastrin increased to levels greater than those present prior to initiation of lansoprazole therapy.

INDICATIONS AND USAGE

Short-Term Treatment of Active Duodenal Ulcer

PREVACID Delayed-Release Capsules are indicated for short-term treatment (up to 4 weeks) for healing and symptom relief of active duodenal ulcer.

Maintenance of Healed Duodenal Ulcers

PREVACID Delayed-Release Capsules are indicated to maintain healing of duodenal ulcers. Controlled studies do not extend beyond 12 months.

Short-Term Treatment of Active Benign Gastric Ulcer

PREVACID Delayed-Release Capsules are indicated for short-term treatment (up to 8 weeks) for healing and symptom relief of active benign gastric ulcer.

Short-Term Treatment of Erosive Esophagitis

PREVACID Delayed-Release Capsules are indicated for short-term treatment (up to 8 weeks) for healing and symptom relief of all grades of erosive esophagitis.

For patients who do not heal with PREVACID for 8 weeks (5-10%) it may be helpful to give an additional 8 weeks of treatment.

If there is a recurrence of erosive esophagitis an additional 8 week course of PREVACID may be considered.

Maintenance of Healing of Erosive Esophagitis

PREVACID Delayed-Release Capsules are indicated to maintain healing of erosive esophagitis. Controlled studies do not extend beyond 12 months.

Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome

PREVACID Delayed-Release Capsules are indicated for the long-term treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome.

CONTRAINDICATIONS

PREVACID Delayed-Release Capsules are contraindicated in patients with known hypersensitivity to any component of the formulation.

PRECAUTIONS

General

Symptomatic response to therapy with lansoprazole does not preclude the presence of gastric malignancy.

Information for Patients

PREVACID Delayed-Release Capsules should be taken before eating.

For patients who have difficulty swallowing capsules, PREVACID Delayed-Release Capsules can be opened, and the intact granules contained within can be sprinkled on one tablespoon of applesauce and swallowed immediately. The granules should not be chewed or crushed. For patients who have a nasogastric tube in place, PREVACID Delayed-Release Capsules can be opened and the intact granules mixed in 40 mL of apple juice and injected through the nasogastric tube into the stomach. After administering the granules, the nasogastric tube should be flushed with additional apple juice to clear the tube.

Drug Interactions

Lansoprazole is metabolized through the cytochrome P450 system, specifically through the CYP3A and CYP2C19 isozymes. Studies have shown that lansoprazole does not have clinically significant interactions with other drugs metabolized by the cytochrome P450 system, such as warfarin, antipyrine, indomethacin, ibuprofen, phenytoin, propranolol, prednisone, diazepam, clarithromycin, or terfenadine in healthy subjects. These compounds are metabolized through various cytochrome P450 isozymes including CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A. When lansoprazole was administered concomitantly with theophylline (CYP1A2, CYP3A), a minor increase (10%) in the clearance of theophylline was seen. Because of the small magnitude and the direction of the effect on theophylline clearance, this interaction is unlikely to be of clinical concern. Nonetheless, individual patients may require additional titration of their theophylline dosage when lansoprazole is started or stopped to ensure clinically effective blood levels.

Lansoprazole has also been shown to have no clinically significant interaction with amoxicillin.

In a single-dose crossover study examining lansoprazole 30 mg and omeprazole 20 mg each administered alone and

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started or stopped to ensure clinically effective blood levels. Lansoprazole has also been shown to have no clinically significant interaction with amoxicillin.

In a single-dose crossover study examining lansoprazole 30 mg and omeprazole 20 mg each administered alone and concomitantly with sucralfate 1 gram, absorption of the proton pump inhibitors was delayed and their bioavailability was reduced by 17% and 16%, respectively, when administered concomitantly with sucralfate. Therefore, proton pump inhibitors should be taken at least 30 minutes prior to sucralfate. In clinical trials, antacids were administered concomitantly with PREVACID Delayed-Release Capsules; this did not interfere with its effect.

Lansoprazole causes a profound and long lasting inhibition of gastric acid secretion; therefore, it is theoretically possible that lansoprazole may interfere with the absorption of drugs where gastric pH is an important determinant of bioavailability (e.g., ketoconazole, ampicillin esters, iron salts, digoxin).

Carcinogenesis, Mutagenesis, and Fertility

In two 24-month carcinogenicity studies, Sprague-Dawley rats were treated orally with doses of 5 to 150 mg/kg/day, about 1 to 40 times the exposure on a body surface (mg/m²) basis, of a 50 kg person of average height (1.46 m² body surface area) given the recommended human dose of 30 mg/day (22.2 mg/m²). Lansoprazole produced dose-related gastric enterochromaffin like (ECL) cell hyperplasia and ECL cell carcinoids in both male and female rats. It also increased the incidence of intestinal metaplasia of the gastric epithelium in both sexes. In male rats, lansoprazole produced a dose-related increase of testicular interstitial cell adenomas. The incidence of these adenomas in rats receiving doses of 15 to 150 mg/kg/day (4 to 40 times the recommended human dose based on body surface area) exceeded the low background incidence (range = 1.4 to 10%) for this strain of rat. Testicular interstitial cell adenoma also occurred in 1 of 30 rats treated with 50 mg/kg/day (13 times the recommended human dose based on body surface area) in a 1-year toxicity study.

In a 24-month carcinogenicity study, CD-1 mice were treated orally with doses of 15 to 600 mg/kg/day, 2 to 80 times the recommended human dose based on body surface area. Lansoprazole produced a dose related increased incidence of gastric ECL cell hyperplasia. It also produced an increased incidence of liver tumors (hepatocellular adenoma plus carcinoma). The tumor incidences in male mice treated with 300 and 600 mg/kg/day (40 to 80 times the recommended human dose based on body surface area) and female mice treated with 150 to 600 mg/kg/day (20 to 80 times the recommended human dose based on body surface area) exceeded the ranges of background incidences in historical controls for this strain of mice. Lansoprazole treatment produced adenoma of rete testis in male mice receiving 75 to 600 mg/kg/day (10 to 80 times the recommended human dose based on body surface area).

Lansoprazole was not genotoxic in the Ames test, the *ex vivo* rat hepatocyte unscheduled DNA synthesis (UDS) test, the *in vivo* mouse micronucleus test or the rat bone marrow cell chromosomal aberration test. It was positive in *in vitro* human lymphocyte chromosomal aberration assays.

Lansoprazole at oral doses up to 150 mg/kg/day (40 times the recommended human dose based on body surface area) was found to have no effect on fertility and reproductive performance of male and female rats.

Pregnancy

Teratogenic Effects. Pregnancy Category B

Teratology studies have been performed in pregnant rats at oral doses up to 150 mg/kg/day (40 times the recommended human dose based on body surface area) and pregnant rabbits at oral doses up to 30 mg/kg/day (16 times the recommended human dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to lansoprazole.

There are, however, no adequate or well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Lansoprazole or its metabolites are excreted in the milk of rats. It is not known whether lansoprazole is excreted in human milk. Because many drugs are excreted in human milk, because of the potential for serious adverse reactions in nursing infants from lansoprazole, and because of the potential for tumorigenicity shown for lansoprazole in rat carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in children have not been established.

Use in Women

Over 800 women were treated with lansoprazole. Ulcer healing rates in females are similar to those in males. The incidence rates of adverse events are also similar to those seen in males.

Use in Elderly Patients

Ulcer healing rates in elderly patients are similar to those in a younger age group. The incidence rates of adverse events and laboratory test abnormalities are also similar to those seen in younger patients. The initial dosing regimen need not be altered for elderly patients, but subsequent doses higher than 30 mg per day should not be administered unless additional gastric acid suppression is necessary.

ADVERSE REACTIONS

Worldwide, over 6100 patients have been treated with lansoprazole in Phase II-III clinical trials involving various dosages and duration of treatment. In general, lansoprazole treatment has been well tolerated in both short-term and long-term trials.

Incidence in Clinical Trials

The following adverse events were reported by the treating physician to have a possible or probable relationship to drug in 1% or more of PREVACID-treated patients and occurred at a greater rate in PREVACID-treated patients than placebo-treated patients:

Body System/Adverse Event	Incidence of Possibly or Probably Treatment-Related Adverse Events in Short-term, Placebo-Controlled Studies	
	PREVACID (N=1457) %	Placebo (N=467) %
Body as a Whole		
Abdominal Pain	1.8	1.3
Digestive System		
Diarrhea	3.6	2.6
Nausea	1.4	1.3

Headache was also seen at greater than 1% incidence but was more common on placebo. The incidence of diarrhea is similar between placebo and lansoprazole 15 mg and 30 mg patients, but higher in the lansoprazole 60 mg patients (2.9%, 1.4%, 4.2%, and 7.4%, respectively).

Treatment-Related Adverse Events in Short-Term, Placebo-Controlled Studies

Body System/Adverse Event	PREVACID (N=1457) %	Placebo (N=467) %
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The most commonly reported possibly or probably treatment-related adverse event during maintenance therapy was diarrhea.

In short-term and long-term studies, the following adverse events were reported in <1% of the lansoprazole-treated patients:

Body as a Whole - asthenia, candidiasis, chest pain (not otherwise specified), edema, fever, flu syndrome, halitosis, infection (not otherwise specified), malaise; *Cardiovascular System* - angina, cerebrovascular accident, hypertension/hypotension, myocardial infarction, palpitations, shock (circulatory failure), vasodilation; *Digestive System* - melena, anorexia, bezoar, cardiospasm, cholelithiasis, constipation, dry mouth/thirst, dyspepsia, dysphagia, eructation, esophageal stenosis, esophageal ulcer, esophagitis, fecal discoloration, flatulence, gastric nodules/fundic gland polyps, gastroenteritis, gastrointestinal hemorrhage, hematemesis, increased appetite, increased salivation, rectal hemorrhage, stomatitis, tenesmus, ulcerative colitis, vomiting; *Endocrine System* - diabetes mellitus, goiter, hyperglycemia/hypoglycemia; *Hematologic and Lymphatic System* - anemia, hemolysis; *Metabolic and Nutritional Disorders* - gout, weight gain/loss; *Musculoskeletal System* - arthritis/arthralgia, musculoskeletal pain, myalgia; *Nervous System* - agitation, amnesia, anxiety, apathy, confusion, depression, dizziness/syncope, hallucinations, hemiplegia, hostility aggravated, libido decreased, nervousness, paresthesia, thinking abnormality; *Respiratory System* - asthma, bronchitis, cough increased, dyspnea, epistaxis, hemoptysis, hiccup, pneumonia, upper respiratory inflammation/infection; *Skin and Appendages* - acne, alopecia, pruritus, rash, urticaria; *Special Senses* - amblyopia, deafness, eye pain, visual field defect, otitis media, taste perversion, tinnitus; *Urogenital System* - abnormal menses, albuminuria, breast enlargement/gynecomastia, breast tenderness, glycosuria, hematuria, impotence, kidney calculus.

Laboratory Values

The following changes in laboratory parameters were reported as adverse events.

Abnormal liver function tests, increased SGOT (AST), increased SGPT (ALT), increased creatinine, increased alkaline phosphatase, increased globulins, increased GGTP, increased/decreased/abnormal WBC, abnormal AG ratio, abnormal RBC, bilirubinemia, eosinophilia, hyperlipemia, increased/decreased electrolytes, increased/decreased cholesterol, increased glucocorticoids, increased LDH, increased/decreased/abnormal platelets, and increased gastrin levels. Additional isolated laboratory abnormalities were reported.

In the placebo controlled studies, when SGOT (AST) and SGPT (ALT) were evaluated, 0.4% (1/250) placebo patients and 0.3% (2/795) lansoprazole patients had enzyme elevations greater than three times the upper limit of normal range at the final treatment visit. None of these patients reported jaundice at any time during the study.

OVERDOSAGE

Oral doses up to 5000 mg/kg in rats (approximately 1300 times the recommended human dose based on body surface area) and mice (about 675.7 times the recommended human dose based on body surface area) did not produce deaths or any clinical signs.

Lansoprazole is not removed from the circulation by hemodialysis. In one reported case of overdose, the patient consumed 600 mg of lansoprazole with no adverse reaction.

DOSAGE AND ADMINISTRATION

Treatment of Duodenal Ulcer

The recommended adult oral dose is 15 mg once daily for 4 weeks. (See INDICATIONS AND USAGE).

Maintenance of Healed Duodenal Ulcers

The recommended adult oral dose is 15 mg once daily. (See CLINICAL STUDIES).

Treatment of Gastric Ulcer

The recommended adult oral dose is 30 mg once daily for up to eight weeks (see CLINICAL STUDIES).

Treatment of Erosive Esophagitis

The recommended adult oral dose is 30 mg once daily for up to 8 weeks. For patients who do not heal with PREVACID for 8 weeks (5-10%) it may be helpful to give an additional 8 weeks of treatment. (See INDICATIONS AND USAGE).

If there is a recurrence of erosive esophagitis, an additional 8 week course of PREVACID may be considered.

Maintenance of Healing of Erosive Esophagitis

The recommended adult oral dose is 15 mg once daily (See CLINICAL STUDIES).

Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome

The dosage of PREVACID in patients with pathologic hypersecretory conditions varies with the individual patient. The recommended adult oral starting dose is 60 mg once a day. Doses should be adjusted to individual patient needs and should continue for as long as clinically indicated. Dosages up to 90 mg bid have been administered. Daily dosages of greater than 120 mg should be administered in divided doses. Some patients with Zollinger-Ellison syndrome have been treated continuously with PREVACID for more than four years.

No dosage adjustment is necessary in patients with renal insufficiency or the elderly. For patients with severe liver disease, dosage adjustment should be considered.

PREVACID Delayed-Release Capsules should be taken before eating. In the clinical trials, antacids were used concomitantly with PREVACID. For patients who have difficulty swallowing capsules, PREVACID Delayed-Release Capsules can be opened, and the intact granules contained within can be sprinkled on one tablespoon of applesauce and swallowed immediately. The granules should not be chewed or crushed. For patients who have a nasogastric tube in place, PREVACID Delayed-Release Capsules can be opened and the intact granules mixed in 40 mL of apple juice and injected through the nasogastric tube into the stomach. After administering the granules, the nasogastric tube should be flushed with additional apple juice to clear the tube.

HOW SUPPLIED

PREVACID Delayed-Release Capsules, 15 mg, are opaque, hard gelatin, colored pink and green. The 30 mg are opaque, hard gelatin, pink and black colored capsules. They are available as follows:

NDC 0300-1541-30

Unit of use bottles of 30: 15 mg capsules

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HOW SUPPLIED

PREVACID Delayed-Release Capsules, 15 mg, are opaque, hard gelatin, colored pink and green. The 30 mg are opaque, hard gelatin, pink and black colored capsules. They are available as follows:

NDC 0300-1541-30

Unit of use bottles of 30: 15 mg capsules

NDC 0300-1541-13

Bottles of 100: 15 mg capsules

NDC 0300-1541-19

Bottles of 1000: 15 mg capsules

NDC 0300-1541-11

Unit dose package of 100: 15 mg capsules

NDC 0300-3046-13

Bottles of 100: 30 mg capsules

NDC 0300-3046-19

Bottles of 1000: 30 mg capsules

NDC 0300-3046-11

Unit dose package of 100: 30 mg capsules

Storage: PREVACID capsules should be stored in a tight container protected from moisture.

Store between 59°F and 86°F.

Caution: Federal (USA) law prohibits dispensing without a prescription.

U.S. Patent Nos. 4,628,098; 4,689,333; 5,013,743; 5,026,560 and 5,045,321.

TR Manufactured for
TAP Pharmaceuticals Inc.
Deerfield, Illinois 60015-1595, U.S.A.
by Takeda Chemical Industries Limited,
Osaka, Japan 541

®—Registered Trademark

03-4793-R7-Rev. May, 1997
(Nos. 1541, 3046)
PREVACID[®]
(pre-va-sid)
(lansoprazole)
Delayed-Release Capsules



034793

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
20-406/S009

MEDICAL REVIEW(S)

42.1

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW OF NDA SUPPLEMENT

FEB 20 1997

NDA: 20-406
SLR-009 (terfenadine, other drug interactions)

SPONSOR: TAP Holdings Inc.
2355 Waukegan Road, Deerfield, IL 60015

DATE OF SUBMISSION: 15 April 1996

DATE OF RECEIPT: 16 April 1996 (to biopharmaceutics, 25 April)

ASSIGNED FOR REVIEW: 15 January 1997 (medical concurrence)

DRUG: Lansoprazole (PREVACID®) delayed-release capsules;
[gastric parietal cell proton pump inhibitor]

ROUTE OF ADMINISTRATION: Oral, 30 mg capsule

PROPOSED INDICATIONS: Labeling changes for administration with other drugs

MATERIAL REVIEWED: Submission of 18 volumes as SLR-009 to NDA 20-406 dated 15 April 1996; biopharmaceutics consultation review by Drs. H-R Choi and R. Pradhan received 18 November and final report of 19 December 1996.

REVIEWER: John R. Senior, M.D./ 11 February 1997

Background

The sponsor submitted on 15 April 1996 additional information on assessment of the pharmacokinetic interaction between lansoprazole and terfenadine (Study M94-167, Volumes 2-4), steady state clarithromycin levels during lansoprazole administration (Study M93-063, Volumes 5-7), effects of concomitant amoxicillin and lansoprazole administration (Study M94-168, Volumes 8 and 9), and assessment of effects of sucralfate on bioavailability of both lansoprazole and omeprazole (Study M94-237, Volume 10). These studies were carried out in normal subjects. In addition, an integrated summary of safety in Phase I interactions was provided (Volume 11), case report tabulations for these four studies (Volumes 12-17), and individual case reports for deaths (none) and for dropouts from the four studies (Volume 18).

On the basis of the new information provided by these four studies, the sponsor wishes to amend the labeling as follows:

Insert: *"Add terfenadine and clarithromycin to the list of compounds metabolized through the cytochrome P-450 system with which lansoprazole has been demonstrated to have no clinically significant interactions. Lansoprazole has also been shown to have no clinically significant interaction with amoxicillin."*

Delete: "Coadministration of lansoprazole with sucralfate delayed absorption and reduced lansoprazole bioavailability by approximately 30%."

Add: *"In a single-dose crossover study comparing lansoprazole 30 mg and omeprazole 20 mg, each administered alone and concomitantly with sucralfate 1 gram, absorption of the proton pump inhibitors was delayed and their absorption reduced by 17% and 16%, respectively, when administered concomitantly with sucralfate."*

Since the issues addressed were primarily biopharmaceutic, the submission was initially directed to the Office of Clinical Pharmacology and Biopharmaceutics, Division II, where it was reviewed by Drs. Hae-Ryun Choi and Rajendra S. Pradhan (see their review, dated 13 November 1996). It was their conclusion that the data supported the requested labeling changes, provided that additional review of the corrected QT electrocardiographic intervals (QTc) from individual subjects in Study M94-167 were submitted, and that medical review concurred. The individual QTc data were provided by the sponsor quite promptly, and were found by Dr. Pradhan to be acceptable in his review dated 19 December 1996, if the medical opinion agreed that there was no clinically significant difference induced by lansoprazole in patients taking terfenadine.

Brief Summary of Studies Done

Four studies were carried out in support of the requested labeling changes:

1. Study M94-167: Lansoprazole and Terfenadine

"Assessment of the Pharmacokinetic Interaction Between Lansoprazole and Terfenadine"

This study was done to assess whether lansoprazole might increase the plasma levels or cardiac toxicity of terfenadine (torsades de pointes, as first reported in 1990 by Monahan, et al., and in 1991 by Matthews, et al., for concomitant ketoconazole administration with terfenadine, and subsequently for concomitant erythromycin administration by Honig, et al. in 1992). These effects were later shown by Woosley et al., and by Honig and colleagues in 1993 to be caused by inhibition of the hepatic cytochrome P450 enzyme CYP3A4 that metabolizes terfenadine (Yun, et al., 1992), allowing toxic concentrations to accumulate in the plasma. Although lansoprazole is not known to inhibit CYP 3A4 activity, these studies were done to assure the safety of giving both drugs at once.

In this randomized crossover study, 16 healthy young men (mean age, 31 years; mean weight, 172 pounds) were given 60 mg of terfenadine (Seldane®, Marion Merrell Dow) every 12 hours for 7 days and either lansoprazole 30 mg t.i.d. (at 8 a.m., 1 and 6 p.m.) at least 30 minutes before meals for 9 days or matching placebo, half of the participants randomly assigned to each regimen. After at least 14 days of "washout" on no medications, subjects were given the other placebo/lansoprazole regimen, along with the same dose and regimen of terfenadine. Blood samples were to be taken for

pharmacokinetic analyses on Day 7, before the morning dosing, and at 0.5, 1, 2, 4, 4, 6, 8, 10, 12, 12.5, 13, 14, 15, 16, 18, 20, 22, 24, 36, 48, and 72 hours. In addition, blood samples were to be taken before the morning dosing for assay of terfenadine and its acid metabolite on Days 1 to 6 of each of the two periods, with and without added lansoprazole. Electrocardiograms (ECGs) were to be done at the initial screening within 3 weeks before the study to exclude subjects with abnormalities of any sort, especially of QTc interval, <440 msec (corrected for heart rate using the Bazett [1920] formula, $0.37 \times \sqrt{[R-R]}$ for males) or TU morphology. Repeated ECGs were done at 0, 1, 2, 3, 4, 6, 8, 12, 13, 14, 15, 16, and 24 hours after 8:00 a.m. on the day before the first medication was given, and on the 7th day of medication, in steady state. In addition, ECGs were to be done daily about 30 minutes before dosing on Days 1 to 7. The studies were carried out by Dr. Dennis Schenck at the Abbott Clinical Pharmacology Research Unit in Waukegan, IL in August-September 1994.

One participant, #13, A.J.S., a 30-year-old white man, complained of intermittent palpitations on Day 7 of the second crossover period while taking terfenadine and placebo. Telemetric monitoring showed at 9:37 a.m. a 12-beat run of unsustained ventricular tachycardia, without change in the QTc or TU morphology, concurrent with 15 seconds of palpitations (see Volume 18, pages 285-335). He was not given the second or third doses at 1 and 6 p.m. that day of "lansoprazole" (really placebo), nor the second and final dose of terfenadine at 8 p.m., and was removed from the study, but did finish his observations and was followed closely. He had no recurrence, and showed a normal tracing on Day 32. Retrospectively, the investigator elicited a history of previous palpitations not revealed at screening (see Volume 2, page 59).

Results of the Study showed slight (about 12%) but not statistically significant mean increases in C_{max} , and AUC_{12} for plasma terfenadine levels while on lansoprazole. Individual subjects #2 and #5 showed more than doubling of C_{max} and AUC_{12} of terfenadine when lansoprazole had been given, however. Mean terfenadine T_{max} was increased by about 32% by lansoprazole, significant for the evening dose of terfenadine on Day 7, and for carboxyterfenadine after the morning dose of terfenadine on Day 7. There were no clinically significant prolongations of the mean QTc by lansoprazole in subjects receiving terfenadine, and subsequent submission of individual data also showed no effect. There was, notably, no QTc prolongation even in the two subjects #2 and #5, who had the most marked effect of lansoprazole on terfenadine levels, nor in subject #11, who showed a tendency to accumulate terfenadine, with or without lansoprazole, to levels 2 to 3 times those of the mean for the other 15 subjects (see Volume 3, pages 30-33; and Appendix I [Individual QTc data] in Biopharmaceutics Review of 19 December 1996). The Study was summarized and reported by C.J. Eason and P. Linnen (Volumes 2 to 4).

It does not appear that there is any clinically significant effect of lansoprazole on QTc intervals, nor on any aspect of the ECGs, in subjects taking terfenadine. In fact the QTc values appeared to be unaffected by lansoprazole in subjects, within the probable errors of measuring R-R intervals (it is likely that calculation of QTc intervals to two decimal places of milliseconds is false precision, and rounding to the nearest millisecond approaches the limit of measurement by the Bazett method). Therefore, the conclusions of the biopharmaceutics reviewers appear to be medically acceptable as well, with respect to lansoprazole and terfenadine.

2. Study M93-063: Lansoprazole and Clarithromycin

“The Effect of Lansoprazole on Steady State Clarithromycin Plasma Concentrations Following Concomitant Oral Administration of Both Drugs in Normal Subjects”

This study was done to investigate whether lansoprazole and clarithromycin, which together appear to be synergistic in eradicating *Helicobacter pylori* (Hp) infection from the gastroduodenal mucosa in patients with peptic ulcer disease (Logan, et al., 1992), might have any effects on each others' metabolism, plasma levels, or pharmacodynamic effects. Lansoprazole alone (Iwahi, et al. 1991) and clarithromycin alone (Peterson, et al, 1993) have some but insufficient effect. Similar effect of the combination of amoxicillin and omeprazole had been observed (Labenz, et al., 1993; Hunt, 1993), and the omeprazole-clarithromycin interaction had been explored (Gustavson, et al., 1994).

This study was designed as a three-period, randomized, crossover investigation in 24 healthy male volunteer non-smokers negative for Hp antibodies. Study drugs included lansoprazole 30 mg capsules (L30) or placebo (L-P), and clarithromycin 0.5 g tablets (C.5) or placebo (C-P), each to be given t.i.d. at 8 a.m., 1 and 6 p.m. Random sets I to VI were established for all of the six possible sequences for each subject to receive lansoprazole alone (A), clarithromycin alone (C), or both (B): I) L30/C-P, L30/C.5, L-P/C.5; II) L30/C.5, L-P/C.5, L30/C-P; III) L-P/C.5, L30/C-P, L30/C.5; IV) L30/C-P, L-P/C.5, L30/C.5; V) L-P/C.5, L30/C.5, L30/C-P; VI) L30/C.5, L30/C-P, L-P/C.5 and six blocks of four subjects were randomized to each sequence. The clarithromycin or placebo was to be taken for five days (30 minutes after the lansoprazole) and the lansoprazole or placebo for six (30 minutes before meals). Periods for washout between study periods of at least 10 days were scheduled, and subjects were to be confined to the study center for one week in each period.. Plasma samples for lansoprazole and clarithromycin, whether or not assigned to placebo, were to be done on Day 5 and 6 of each period. Gastric pH monitoring for 24 hours was to be done before the study and on Day 5 of each period, and meals were to be standardized those days. The study was carried out in November-December 1993 by Dr. Paul Litka.

b(4)

Four subjects did not complete the study: #24 (Group II) because he was found to discard clarithromycin tablets in the garbage on Day 4 of Period 1 (on B); #3 (Group VI) quit after Period 1 (on B), and subjects #11 (Group III, just prior to Period 3, had had C and A) and #6 (Group V, on Day 5 of Period 3, had had C, B, A) were discontinued by the investigator because of skin rashes. Subject #19 (Group VI: B, A, C) developed flank/suprapubic colic and hematuria on 15 December, after completing the study, diagnosed as urethrolithiasis thought unrelated to study medications.

b(4)

Concurrent C.5 caused small increases in the plasma lansoprazole C_{max}, T_{max}, and AUC, and no effect on intragastric pH levels raised by L30, while L30 caused almost no effect on levels of clarithromycin or its metabolite, 14-[R]-OH-clarithromycin. Medically, these very small changes would not be expected to have any discernible clinical effects.

3. Study M94-168: Lansoprazole and Amoxicillin

“Effect of Concomitant Administration of Lansoprazole and Amoxicillin in Normal Subjects”

This study was done to investigate whether lansoprazole and amoxicillin, which have been used together in treatment of Hp infection, might have any effects on each others' pharmacokinetics or effects.

This study utilized a similar design, randomized, double-blind, three-period, crossover administration of lansoprazole 30 mg t.i.d. alone (A), amoxicillin 1 g t.i.d. alone (C), or both together (B) for five days to 17 men and 7 women, with 9 days “washout” between periods. The 24 subjects were assigned randomly to six groups of four subjects, for each of the possible sequences of regimens: ABC, BCA, CAB, ACB, BAC, and CBA. At each dosing, 8 a.m., 1 and 6 p.m., subjects received one capsule of 30 mg lansoprazole or placebo, plus four capsules of 250 mg amoxicillin or placebo. Blood (heparinized) sampling of 7 mL each time was done on Days 5-6, at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 5.5, 6, 6.5, 7, 7.5, 8, 9, 10, 10.5, 11, 11.5, 12, 12.5, 13, 14, 15, 16, 18, 20, 22, and 24 hours. Plasma samples were frozen until just before analysis at ~~_____~~

~~_____~~ The participants were cared for and observed by Dr. John H. Cavanaugh, at the Abbott Laboratories Clinical Pharmacology Research Unit in Waukegan IL, in July-August 1994. None of the subjects dropped out because of adverse events. b(4)

Results showed no effect of amoxicillin on lansoprazole plasma levels, C_{max}, T_{max}, or AUC, but lansoprazole administration somewhat slowed uptake of amoxicillin, reducing the C_{max} by up to 20% and prolonging the T_{max} by up to 44%, with little or no change in the AUC until after the third dose when a 13% mean increase was seen. The biopharmaceutical conclusion was that the effects of lansoprazole on amoxicillin pharmacokinetics were clinically insignificant, with which I concur.

4. Study M94-168: Lansoprazole and Sucralfate

“Assessment of the Effect of a Dose of Sucralfate on the Bioavailability of Lansoprazole and Omeprazole”

Sucralfate, a sulfated disaccharide aluminum complex, used for treatment of duodenal ulcers, may reduce the extent of absorption of various other medications, apparently by binding to the other medication in the gastrointestinal lumen. Because both lansoprazole and omeprazole are indicated also for healing duodenal ulcers, it was the aim of this study to assess the effect of simultaneous administration of sucralfate on the bioavailability of lansoprazole and omeprazole. The design was a randomized, sequential single-dose administration of either lansoprazole 30 mg capsule or omeprazole (PRILOSEC®, Astra Merck) 20 mg, with or without sucralfate (CARAFATE®, Marion Merrell Dow) 1 g tablet, with 180 mL of water, to fasting subjects. A set of 24 healthy volunteers,

19 men and 5 women, ranging in age from 23 to 53 years (mean 38); they were randomized into four groups of six subjects to receive omeprazole first, half with half without sucralfate, then omeprazole with the reverse a week later, followed by lansoprazole with or without sucralfate on the two following weeks. Blood samples were collected in heparinized tubes, 7 mL at each time, at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, and 12 hours on each of the four days after dosing. This study was also carried out by Dr. Cavanaugh at the Abbott Laboratories in Waukegan in October-November 1994. Plasma was frozen, and sent to _____ for single batch assay of omeprazole and lansoprazole by high pressure liquid chromatography using ultraviolet light detection, limited to about 10 ng/mL from 0.5 mL plasma samples. Two male subjects were unable to complete the study: #5, a 45-year-old man, developed slight anemia (hemoglobin from 14.7 to 13.0 g/dL) as a result of the blood sampling, and was removed after the two omeprazole administrations, and #12 participated only in periods 1 and 3, after omeprazole alone and lansoprazole alone because of elevated alanine aminotransferase levels (from 33 to 56 and 59 units, upper limit of normal, 35 units). Both subjects recovered normal blood levels after removal from the study, and had no symptomatic problems.

b(4)

Results showed a very significant effect of sucralfate 1 g on reducing the Cmax and AUCs for both lansoprazole and omeprazole, amounting to about 17% reduction in AUC for lansoprazole and 16% for omeprazole. The lansoprazole Cmax was reduced about 21%, and that for omeprazole by about 39%, but the elimination half-time for omeprazole was increased by 38% while that for lansoprazole was barely affected. It was noted by the biopharmaceutical reviewer that 2 g of sucralfate (twice the recommended dose) had reduced lansoprazole bioavailability by 32% (for AUC).

Conclusions and Recommendations

The results of the four drug interaction studies appear to justify the labeling changes requested by the sponsor, which were acceptable to the biopharmaceutical reviewers. There were no findings in these studies that raise medical concerns, and I concur that the labeling changes are acceptable.

John R. Senior MD

11 Feb '97

John R. Senior, M.D., Medical Officer

date

Division of GI & Coagulation Drug Products

cc: NDA 20-406/SLR-009

HFD-180

HFD-180/SFredd

HFD-180/JSenior

HFD-180/JChoudary

HFD-180/EDuffy

HFD-181/CSO

HFD-870/LKaus

MED/N/20406702.OJS

2/20/97
JMS

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Study M94-167

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
20-406/S009

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

DEC 19 1996

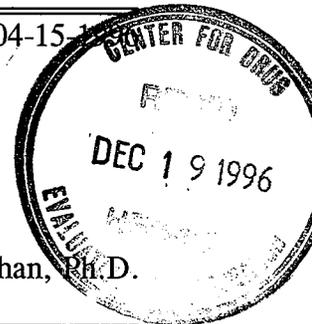
Clinical Pharmacology and Biopharmaceutics Review

NDA 20-406/SLR009

Submission Date 04-15-1996

Lansoprazole, 15 and 30 mg Delayed-Release Capsule
PREVACID®

TAP Holdings Inc.
2355 Waukegan Road
Deerfield, IL 60015



Reviewer: Rajendra S. Pradhan, Ph.D.

Type of Submission: Labeling Change

Background: The firm had submitted this supplement to make changes to the approved PREVACID® (lansoprazole) Delayed-Release Capsules labeling. The Division of Pharmaceutical Evaluation II (DPE-II), OCPB reviewed this supplement on 11-13-1996. The following comment was conveyed to the sponsor as in absence of the requested information proper safety assessment of lansoprazole-terfenidine drug interaction could not be completed.

Comment: The sponsor is requested to submit the individual Qtc along with individual Qtc maxs and Qtc AUCs for the two treatments for study M94-167.

The sponsor has responded to the Agency's request for this additional information. After reviewing the individual Qtc data for the two treatments, viz. lansoprazole 30 mg tid + terfenidine 60 mg bid and lansoprazole placebo tid + terfenidine 60 mg bid, it was concluded that coadministration of lansoprazole with terfenidine did not cause the Qtc to change in any meaningful way. Two subjects in particular, #2 and #5, who had shown more than doubling of Cmax and AUC₁₂ when terfenidine was administered with lansoprazole, did not show any difference in Qtc between the two treatments.

Recommendations:

The sponsor has addressed the Qtc safety issue for the study M94-167 raised by the Division of Pharmaceutical Evaluation-II (DPE-II). The sponsor's proposal (of adding terfenidine to the list of compounds metabolized through cytochrome P-450 system with which lansoprazole has been demonstrated to have no clinically significant interactions) is acceptable to the DPE-II, OCPB. However, the DPE-II's conclusion is contingent on the Medical Officer's (HFD-180) safety assessment of the difference between the Qtc intervals between the two treatments.

 12-18-96

Rajendra S. Pradhan, Ph.D.

Division of Pharmaceutical Evaluation II

FT initialed by Lydia Kaus, Ph.D. LCK 12/19/96

cc: NDA 20-406, HFD-180, HFD-870 (MChen, Kaus, Pradhan), HFD-850 (Lesko), HFD-340 (Viswanathan), HFD-850 (Chron, Drug, Reviewer), HFD-205 (FOI), Drug File (Clearance Bott)

12/24/96


Appendix I
(Individual Qtc data)

8 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

NOV 13 1996

NDA 20-406/SLR009

SUBMISSION DATE: Apr. 15, 1996

Lansoprazole, 15 & 30 mg Delayed-Release Capsules

PREVACID®

TAP Holdings Inc.

2355 Waukegan Road

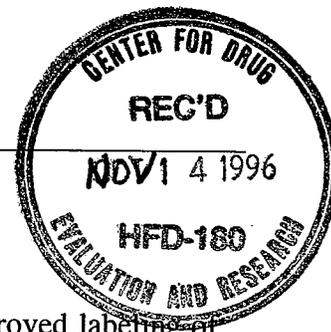
Deerfield IL 60015

REVIEWER: Hae-Ryun Choi, Ph.D.

Rajendra Pradhan, Ph.D.

PRIORITY: 1 S

TYPE OF SUBMISSION: NDA Supplement (labeling Change)



BACKGROUND:

The firm has submitted this supplement to make following changes to the approved labeling of PREVACID® (lansoprazole) Delayed-Release Capsules under Precautions: Drug Interactions section:

1. Add terfenadine and clarithromycin to the list of compounds metabolized through the cytochrome P-450 system with which lansoprazole has been demonstrated to have no clinically significant interactions.

2. Add:

"Lansoprazole has also been shown to have no clinically significant interaction with amoxicillin."

3. Delete:

"Coadministration of lansoprazole with sucralfate delayed absorption and reduced lansoprazole bioavailability by approximately 30%."

Add:

"In a single-dose crossover study comparing lansoprazole 30 mg and omeprazole 20 mg each administered alone and concomitantly with sucralfate 1 gram, absorption of the proton pump inhibitors was delayed and their bioavailability was reduced by 17% and 16%, respectively when administered concomitantly with sucralfate."

In addition, the sponsor wants to replace "lansoprazole" with "proton pump inhibitors" to read:

"Therefore, proton pump inhibitors should be taken at least 30 minutes prior to sucralfate."

In this application the sponsor has provided the following four drug interaction studies to support their labeling claim:

11/18/96

Assessment of the Pharmacokinetic Interaction Between Lansoprazole (Prevacid®) and Terfenadine

Study: M94-167

Investigator and Site: Dennis W. Schneck, M.D.
Victory Memorial Hospital
Waukegan, Illinois 60085

Objectives:

This study was designed to: 1. assess the potential interaction effect of lansoprazole (LN) on terfenadine (TF) pharmacokinetics (PK); 2. compare the effects of terfenadine alone and the combination of lansoprazole and terfenadine on the ECG morphology of the TU complex and the duration of the QTc interval

Study Design:

This Phase I, randomized, double-blind, two-period, complete cross-over study compared the effects of LN 30 mg versus placebo for LN, when given three times daily for nine consecutive days in combination with TF 60 mg BID given for seven days, in healthy adult male subjects. Crossover periods were separated by at least a 14-day wash-out period.

Subjects:

Sixteen subjects (11 caucasian, 2 black, 2 hispanic and 1 mixed) with average weight 172.0 lb and average age 30.9 yr entered this study. Fifteen subjects finished the study. One subject was discontinued from the study due to adverse effects.

Specimens:

A daily 10 ml blood sample for determination of terfenadine and it's acid metabolite concentration was obtained immediately prior to the 8:00AM dosing on day 1 through day 6 of each period. Ten ml blood samples was also collected from each subject immediately prior to the 8:00 AM dosing (0 hour) of Day 7 and at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 12.5, 13, 14, 15, 16, 18, 20, 22, 24, 36, 48 and 72 hours after administration of the Day 7 8:00 AM dosing during both periods.

All subjects had a 12-lead ECG with recording performed at screening daily (ECG was obtained approximately 30 minutes prior to the 8:00 AM dosing on study days 1 through 7), and according to the following time schedule:

ECG Profile: Period 1 and 2	Hours relative to TF dose
Day -1	0*, 1, 2, 3, 4, 6, 8, 12, 13, 14, 15, 16, 24
Day 7	0*, 1, 2, 3, 4, 6, 8, 12, 13, 14, 15, 16, 24
* Approximately 30 min prior to 8:00 AM dosing A sig. prolongation of $\geq 25\%$ in QTc interval from the day -1 baseline for a predose ECG on days 1-7 meant no further drug administration	

Data Analysis:

Pharmacokinetic: Cmax, Tmax, AUC12 and t1/2 were analyzed using ANOVA (included sequence, subjects within sequence, period and treatment as sources of variation, with effects for subjects random and all other effects fixed).

Pharmacodynamic: For the daytime dose interval of Day 7, the maximum observed QTc interval was determined and the area under the QTc interval versus time curve was calculated using the trapezoidal rule for the entire 12 hours. Also, for the first four hours following each of the two terfenadine doses on Day 7, the maximum observed QTc interval was determined, and the area under the QTc interval versus time curve was calculated with the trapezoidal rule. The corresponding Day -1 variables were also computed for each period. An ANOVA similar to that employed for analysis of pharmacokinetic data was performed for the Day -1 and Day 7 variables.

Assay:

TF:

Method: HPLC/MS

Linearity: 50 pg/ml to 5000 pg/ml, satisfactory.

Specificity: Not provided

Precision: Interday precision ranged from 11.8% at 150 pg/ml to 5.1% at 3500 pg/ml.

Accuracy: Interday accuracy ranged from 3.3% at 150 pg/ml to 1.4 % at 3500 pg/ml.

Carboxy-TF

Method: HPLC/fluorescence

Linearity: 10 ng/ml to 500 ng/ml, satisfactory.

Specificity: Not provided

Precision: Interday precision ranged from 6.3% at 30 pg/ml to 4.4% at 390 ng/ml.

Accuracy: Interday accuracy ranged from 0.9% at 30 pg/ml to 5.5 % at 390 ng/ml.

Results:

Dropouts: Subject #13, a 30 year old caucasian male, experienced intermittent palpitations on Day 7 of crossover period 2 (study day 31), during the TF/placebo regimen. The palpitation lasted for 15 seconds, and an assessment of telemetry monitored simultaneously indicated a 12-

beat run of nonsustained ventricular tachycardia. The event was considered to be mild and possibly related to study medication. As a result of the adverse event the subject was prematurely discontinued from the study. At follow-up on study day 32, the subject had no ST-T wave, QTc interval or TU morphology abnormalities upon ECG examination.

Mean pharmacokinetic parameters for the last day (day 7th) are summarized in the following table.

Terfenadine				
	Dose 1		Dose 2	
Parameters	+ Placebo	+ Lansoprazole	+ Placebo	+ Lansoprazole
C _{max} (pg/ml)	2560 ± 1266	2905 ± 1509	2788 ± 1213	3104 ± 1419
T _{max} (h)	1.6 ± 1.0	2.1 ± 0.8	2.1 ± 1.0	2.8 ± 1.2†
AUC ₁₂ * (pg.h/ml)	20430 ± 12937	23007 ± 13831	22504 ± 11626	25167 ± 14255
t _{1/2} ** (h)	-	-	17.19 ± 4.24	15.06 ± 3.84
Carboxyterfenadine				
	Dose 1		Dose 2	
Parameter	+ Placebo	+ Lansoprazole	+ Placebo	+ Lansoprazole
C _{max} (pg/ml)	252.6 ± 30.9	239.1 ± 50.4	224.7 ± 67.9	230.5 ± 56.0
T _{max} (h)	1.6 ± 0.5	2.1 ± 0.8†	2.7 ± 1.0	2.9 ± 1.0
AUC ₁₂ * (pg.h/ml)	1517.2 ± 233.4	1559.6 ± 349.4	1469.2 ± 355.1	1578.1 ± 369.6†
t _{1/2} ** (h)	-	-	9.64 ± 2.76	8.53 ± 2.38
AUC ₁₂ *: AUC ₀₋₁₂ (Dose 1) and AUC ₁₂₋₂₄ (Dose 2) †: Statistically different p ≤ 0.05 **: Harmonic Mean				

Even though the mean PK parameters showed little difference between the two regimens, subject # 2 and 5 clearly showed a more than doubling of C_{max} and AUC₁₂ when TF was administered with LN. Fig. 1 and 2 show the mean plasma TF and carboxyterfenadine concentration versus time plot on day 7.

The least square mean QTc interval parameters for the subjects who completed the study are listed in the following table:

Parameter	Dose	N	TF + Placebo		TF + LN	
			Day -1	Day 7	Day -1	Day 7
QTc _{max 0-12} (msec)	1	16	397.6	402.2	401.7	400.3
QTc _{max0-4} (msec)	1	16	393.8	394.0	394.5	395.4
QTc _{max0-4} (msec)	2	15*	389.1	394.0	389.6	398.8
QTc AUC ₀₋₁₂ (msec*h)	1	16	4568	4648	4609	4628
QTc AUC ₀₋₄ (msec*h)	1	16	1524	1539	1530	1533
QTc AUC ₀₋₄ (msec*h)	2	15*	1515	1537	1526	1546

*: Excluding subject 13 who did not receive the second dose on Day 7 in period 2 (TF + placebo)

In attachment 1 all the submitted data on QTc is presented. The sponsor has not presented the individual QTc data for comparison. Thus, it is difficult to evaluate as to exactly who (which subject) showed a specific difference. In other words it is not possible to link the changes seen in individual's TF plasma concentrations (due to drug interaction) to his QTc changes. In absence of this information it will be difficult to evaluate clinical significance of difference in QTc in each subject.

Conclusions:

Small mean increases in C_{max} and AUC₀₋₁₂ of TF was observed (< 15%) at the steady state when TF (60 mg BID) was administered with LN (30 mg TID). On individual subject level the maximum increase in C_{max} and AUC₀₋₁₂ seen was less than 3 fold increase. This is less in comparison to 16 to 73 fold increases in TF AUC seen in case of ketoconazole (CYP3A4 inhibitor) coadministration.

The mean QTc differences (max and AUC) between the two treatments (TF+LN and TF+Placebo) were small (< 5%). However, sponsor has not provided the individual QTc (max and AUC) and therefore determining clinical importance for individual change is not possible.

Comments (to be sent to the Sponsor):

The sponsor is requested to submit the individual QTcs along with individual QTc maxs and QTc AUCs for the two treatments for study M94-167.

Figure 1. Mean \pm Standard Error Plasma Terfenadine Concentrations on Day 7 from Study M94-167

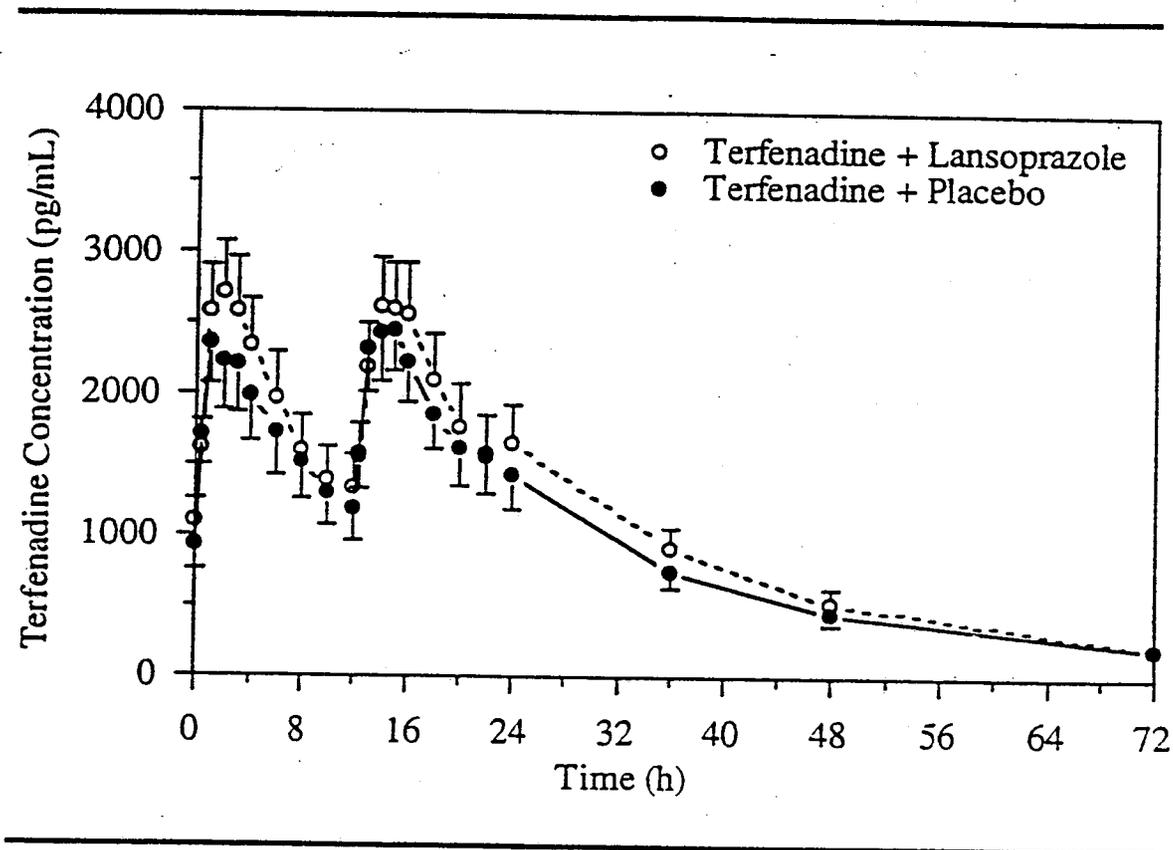
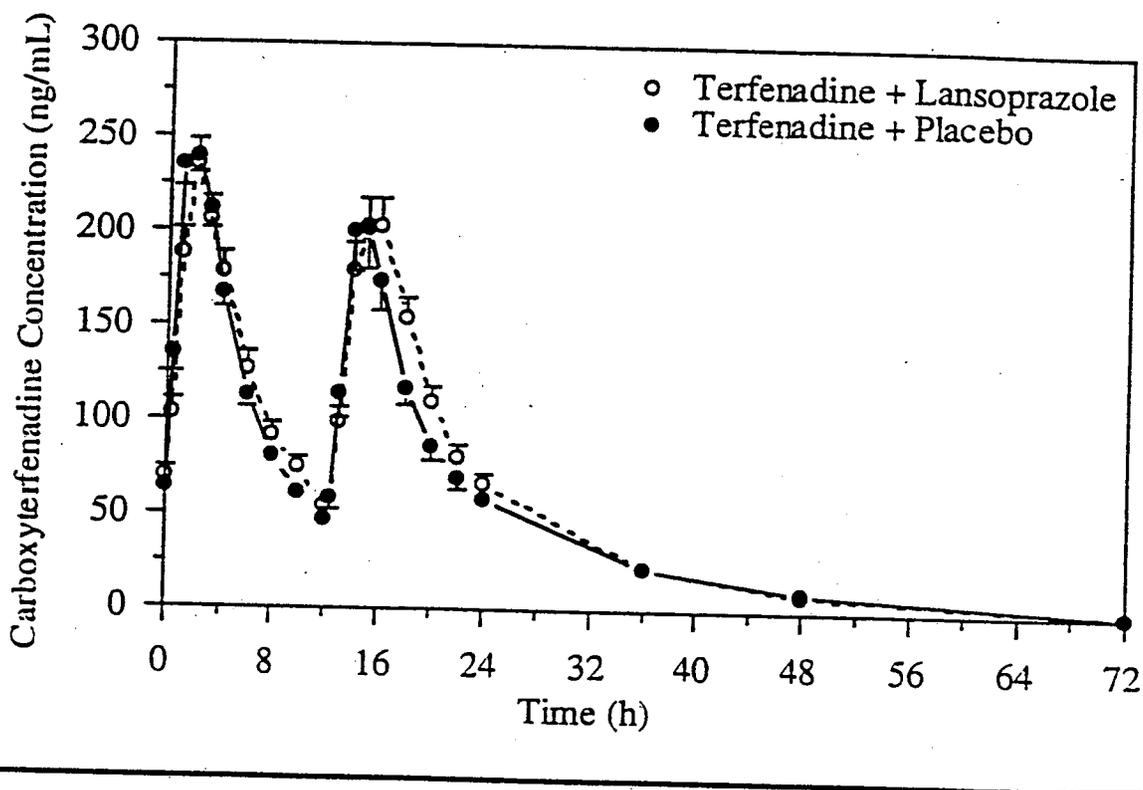


Figure 2. Mean \pm Standard Error Plasma Carboxyterfenadine Concentrations on Day 7 from Study M94-167



The Effect of Lansoprazole on Steady-State Clarithromycin Plasma Concentrations Following Concomitant Oral Administration of Both Drugs in Normal Subjects

Study: M93-063

Investigator and Site: Paul A. Litka, M.D.

b(4)

Objectives:

1. To determine the effect of lansoprazole (LN) on steady state plasma concentrations of clarithromycin (CL) and 14-R-hydroxy-clarithromycin (CLM).
2. To determine the effect of clarithromycin on steady state lansoprazole pharmacokinetics and pharmacodynamics as measured by gastric pH.

Study Design:

This was a double-blind, randomized, placebo-controlled, three-period, complete cross-over, single center interaction study of LN and CL in healthy adult male and female subjects.

The subjects were divided in 6 sequences in receiving three treatments.

Treatment A: One 30 mg LN capsule followed one-half hour later by placebo for CL TID on Days 1 to 5 and one 30 mg LN capsule TID on day 6. (Placebo for CL will not be administered on Day 6) All LN doses will be administered 30 min prior to any meal.

Treatment B: One 30 mg LN capsule followed one-half hour later by one 500 mg CL tablet three times daily on Days 1 to 5 and one 30 mg LN capsule TID on day 6. (CL was not administered on day 6). All LN doses will be administered 30 minutes prior to any meal.

Treatment C: One placebo for 30 mg LN capsule followed one-half hour later by one 500 mg CL tablet TID on Days 1 to 5 and one placebo for LN TID on day 6. (CL was not administered on day 6). All LN doses will be administered 30 minutes prior to any meal.

There was at least a 10 day wash-out between each periods. In periods 1, 2 and 3, all subjects underwent 24-hour gastric pH monitoring.

Intragastric pH Monitoring: Ambulatory 24-hour intragastric pH monitoring was performed beginning on the day prior to crossover Period 1 for a baseline recording and beginning of Day 5 of each crossover period. Measurements were made using a Sandhill one channel RMS-II Datalogger pH assessment system with a graphite/antimony pH and pressure sensor probe that was accurately calibrated. The pH probe was inserted nasogastrically and placed in the gastric antrum. Placement was determined using a Sandhill LES Locator™ which locates the lower esophageal sphincter (LES) by

manometry, and then placing the probe 15 to 18 cm below the LES. Monitoring began at approximately 7:30 AM, and the probe was removed after completion of 24 hours of monitoring.

Specimens:

Blood samples were collected on Day 5 for LN or LN placebo at 0, 1, 1.5, 2, 3 and 5 hours after the first dose and again at 0, 1, 1.5, 2, 3, 5, 7, 9 and 12 hours following the third dose. Samples for CL and CLM were drawn prior to the first and third doses at 0 and at 1, 1.5, 2.5 and 5 hours after the first dose and at 0, 1, 1.5, 2.5, 5, 6.5, 8.5, 11.5, 14, 18, 24 and 36 hours after the third dose.

Assay:

LN:

Method: HPLC

Limit of Detection: 10 ng/ml

Linearity: 10 to 4000 ng/ml, Satisfactory.

Precision: Inter-day precision ranged from 10.5% at 30 ng/ml to 5.4% at 400 ng/ml.

Accuracy: Inter-day accuracy ranged from 8.0% at 30 ng/ml to 2.3% at 400 ng/ml.

Specificity: Not provided

CL:

Method: HPLC with electrochemical detection

Limit of Detection: 15.6 ng/ml

Linearity: 15.6 to 8000 ng/ml, Satisfactory.

Precision: Inter-day precision ranged from 7.0% at 65 ng/ml to 4.0% at 2000 ng/ml.

Accuracy: Inter-day precision ranged from 0.8% at 65 ng/ml to 4.1% at 2000 ng/ml.

CLM:

Method: HPLC with electrochemical detection

Limit of Detection: 15.6 ng/ml

Linearity: 15.6 to 8000 ng/ml, Satisfactory.

Precision: Inter-day precision ranged from 7.2% at 65 ng/ml to 4.7% at 2000 ng/ml.

Accuracy: Inter-day precision ranged from 0.9% at 65 ng/ml to 5.5% at 2000 ng/ml.

Results:

CL dosing resulted in a significant (at $P < 0.05$) increase in the AUC of LN for both dosing intervals. The only other significant change was to the AUC for the metabolite of CL, CLM, in the presence of LN during the third dose of the Dosing Day 5.

The following table summarizes the pharmacokinetic parameters, mean (SD).

Lansoprazole							
Cmax (ng/ml)		Tmax (h)		AUC (ng.h/ml)*		t1/2 (h)‡	
Dose 1	Dose 3	Dose 1	Dose 3	Dose 1	Dose 3	Dose 1	Dose 3
Regimen: Lansoprazole + Placebo							
698 (375)	919 (443)	1.48 (0.62)	1.17 (0.29)	1712 (1171)	2726 (2465)	1.34 (0.65)	1.05 (0.50)
Regimen: Lansoprazole + Clarithromycin							
727 (423)	975 (535)	1.78 (0.82)	1.26 (0.50)	1911 (1463)	3180 (3638)	1.24 (0.63)	1.07 (0.55)
Clarithromycin							
Cmax (ng/ml)		Tmax (h)		AUC (ng.h/ml)*		t1/2 (h)‡	
Dose 1	Dose 3	Dose 1	Dose 3	Dose 1	Dose 3	Dose 1	Dose 3
Regimen: Clarithromycin + Placebo							
3.78 (1.19)	4.60 (1.37)	1.55 (0.92)	1.27 (0.59)	15.15 (4.97)	37.55 (11.47)	ND	6.60 (1.66)
Regimen: Clarithromycin + Lansoprazole							
3.64 (0.94)	4.56 (0.97)	1.65 (0.55)	1.35 (0.44)	14.50 (4.09)	38.52 (10.85)	ND	6.72 (1.53)
14-[R]-OH-Clarithromycin							
Cmax (ng/ml)		Tmax (h)		AUC (ng.h/ml)*		t1/2 (h)‡	
Dose 1	Dose 3	Dose 1	Dose 3	Dose 1	Dose 3	Dose 1	Dose 3
Regimen: Clarithromycin + Placebo							
1.06 (0.19)	1.17 (0.21)	1.82 (1.19)	1.45 (0.77)	4.68 (0.81)	12.22 (2.18)	ND	ND
Regimen: Clarithromycin + Lansoprazole							
1.13 (0.24)	1.32 (0.34)	1.65 (0.61)	1.52 (0.91)	5.02 (1.18)	13.89 (3.52)	ND	ND

*: AUC for Dose 1 is calculated as AUC₀₋₅ and for Dose 3 as AUC₀₋₁₄

‡: Harmonic mean

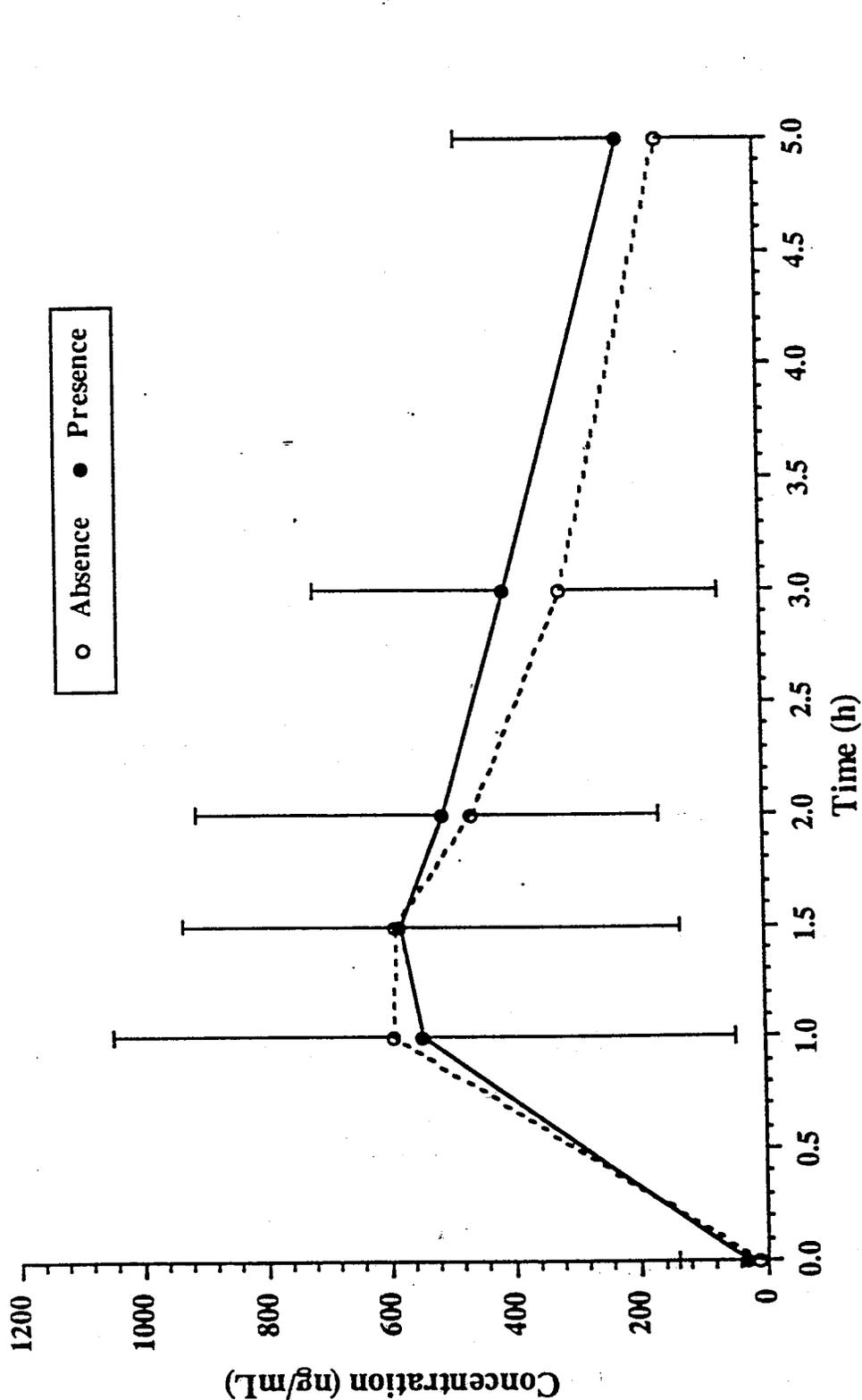
Figure 1 to 6 show mean concentration versus time curves for LN, CL and CLM. Figure 7 show mean

intra-gastric pH levels over 24 hour period for all the treatments in this study. There was no difference between LN/CL and LN alone in increasing gastric pH.

Conclusion:

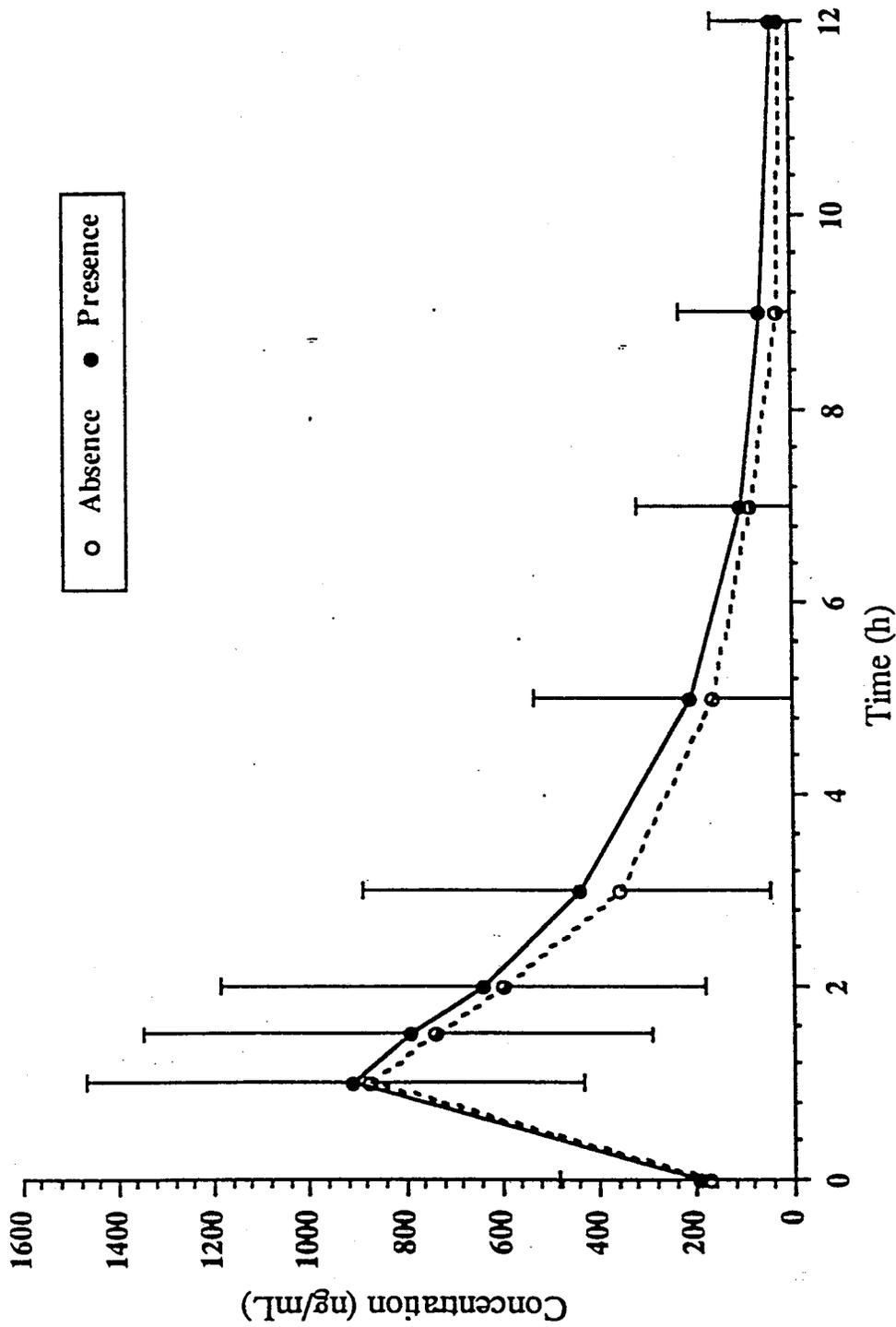
Coadministration of LN and CL resulted in an increase in the AUC of LN for the first (12%) and the third dose (17%) at the steady state. LN had no clinically meaningful effect on any of the absorption or disposition parameters of CL. However, there was about 14% increase in AUC after the third daily dose in the AUC of CLM. These results show that the interaction between CL and LN is small, and therefore, may be considered clinically insignificant.

Figure 1. Mean \pm SD Concentrations of Lansoprazole in the Absence and Presence of Clarithromycin (Morning Dose)

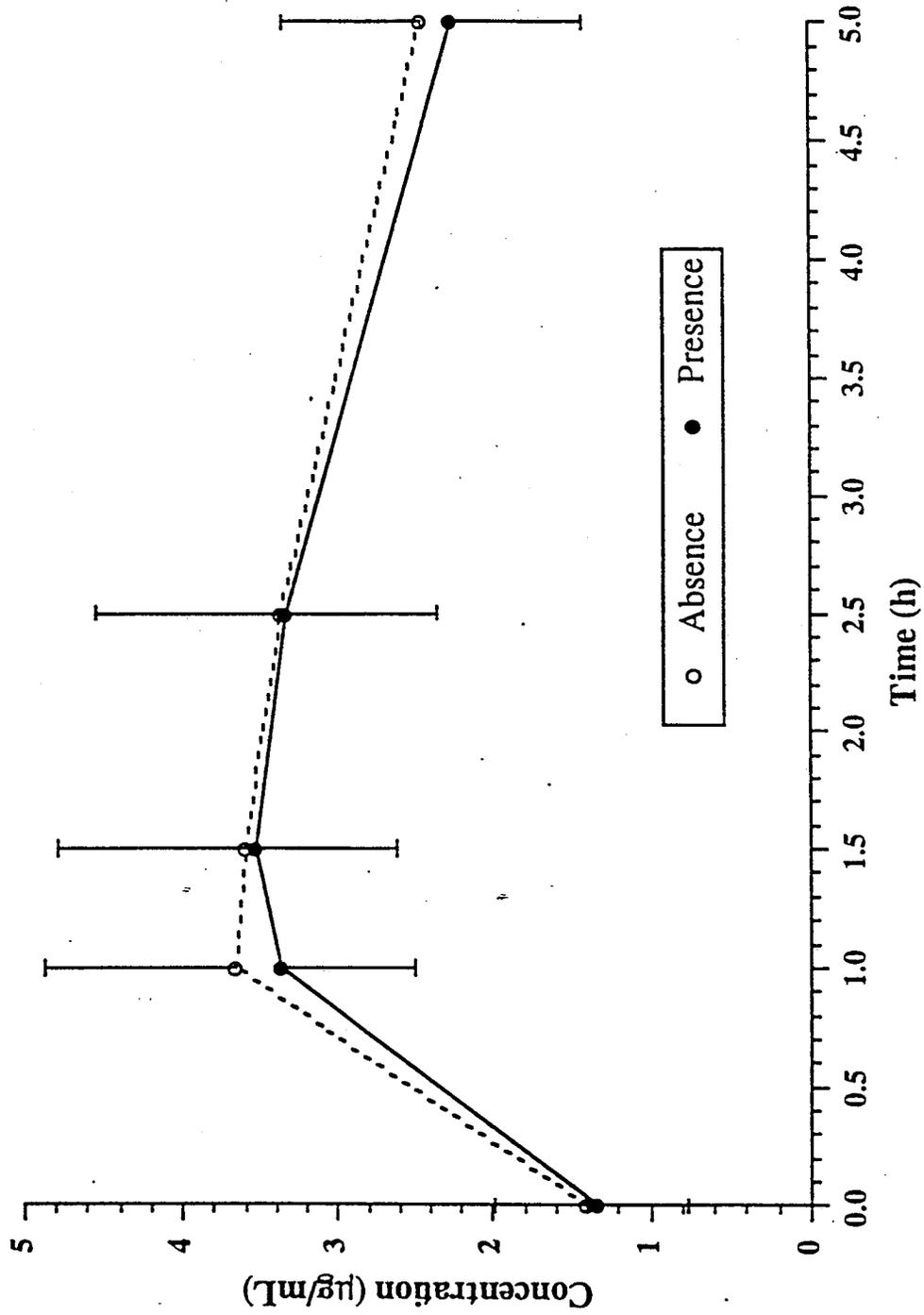


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Figure 2. Mean \pm SD Concentrations of Lansoprazole in the Absence and Presence of Clarithromycin (Evening Dose)



3 **Figure 8. Mean \pm SD Concentration of Clarithromycin in the Absence and Presence of Lansoprazole (Morning Dose)**



4 Figure 9. Mean \pm SD Concentration of Clarithromycin in the Absence and Presence of Lansoprazole (Evening Dose)

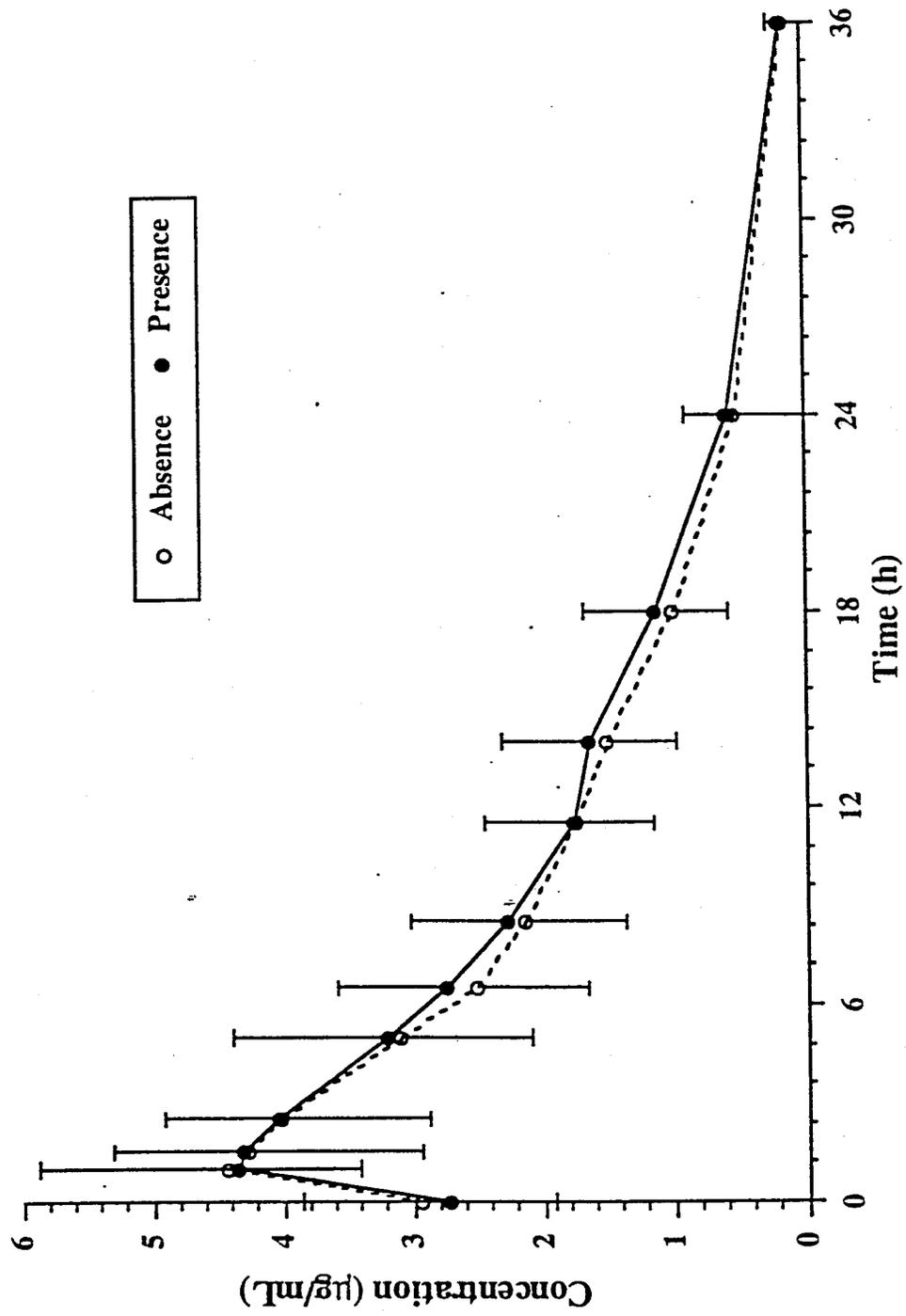


Figure 45. Mean \pm SD Concentration of 14[R]-Hydroxy-Clarithromycin in the Absence and Presence of Lansoprazole (Morning Dose)

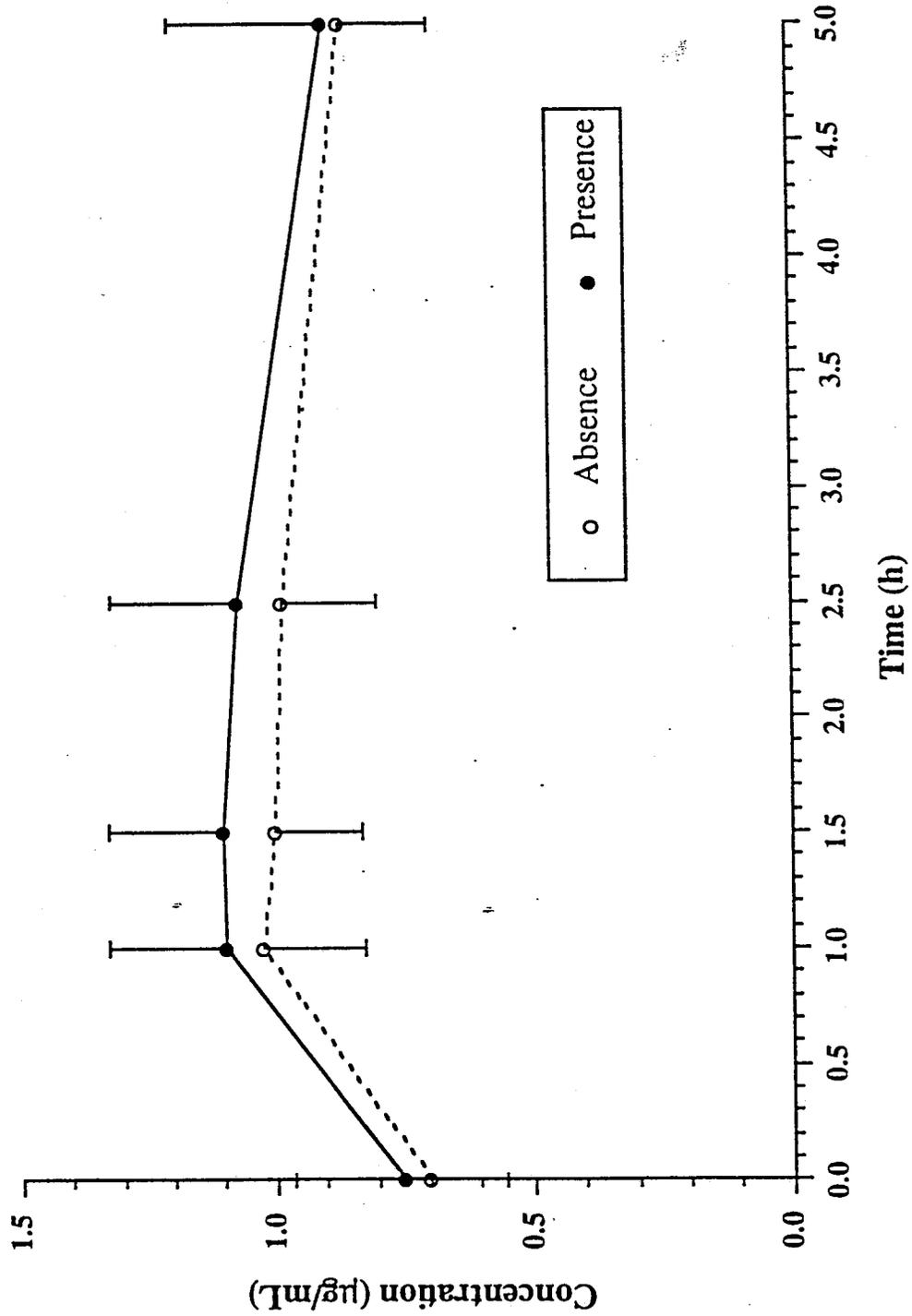
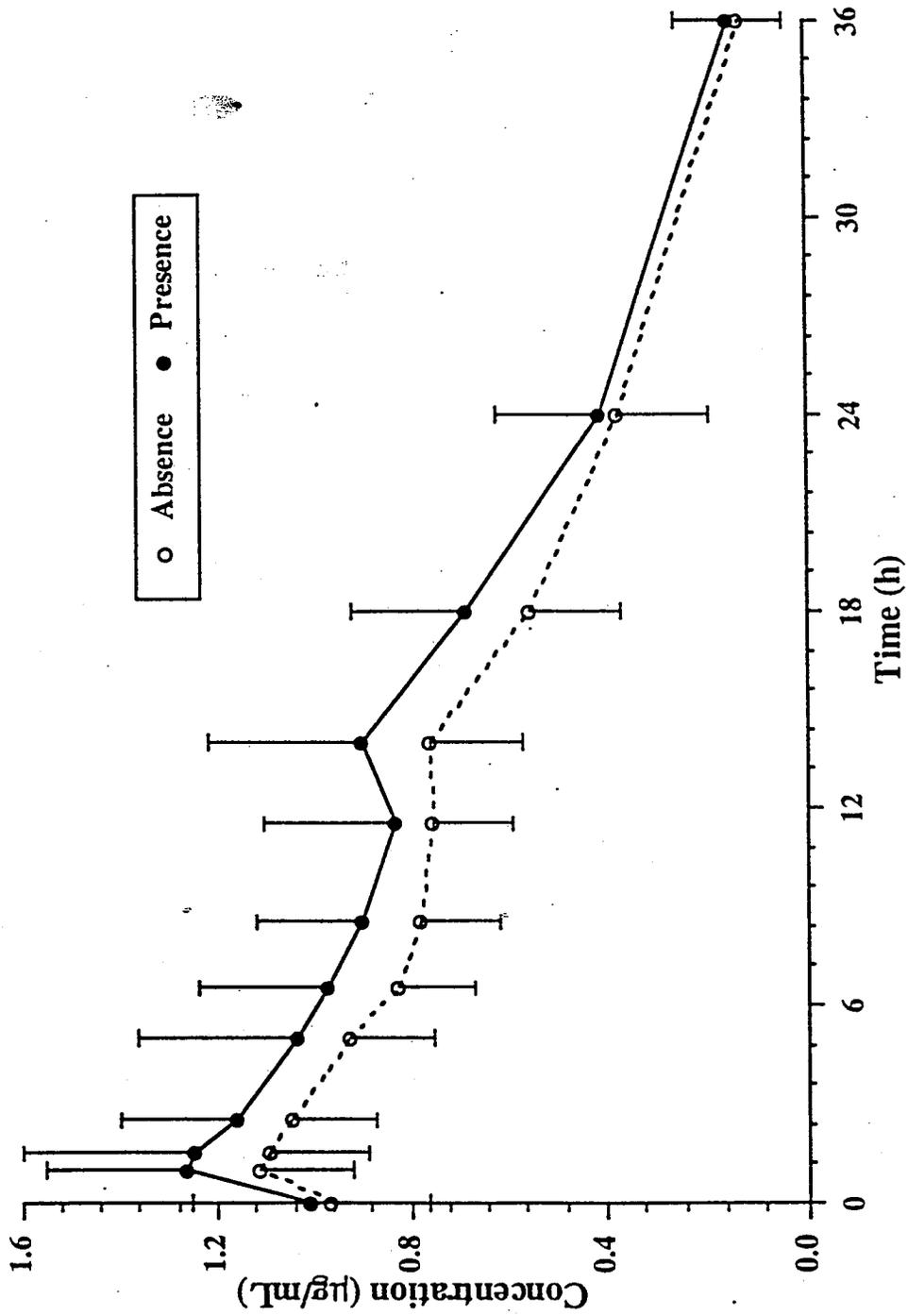
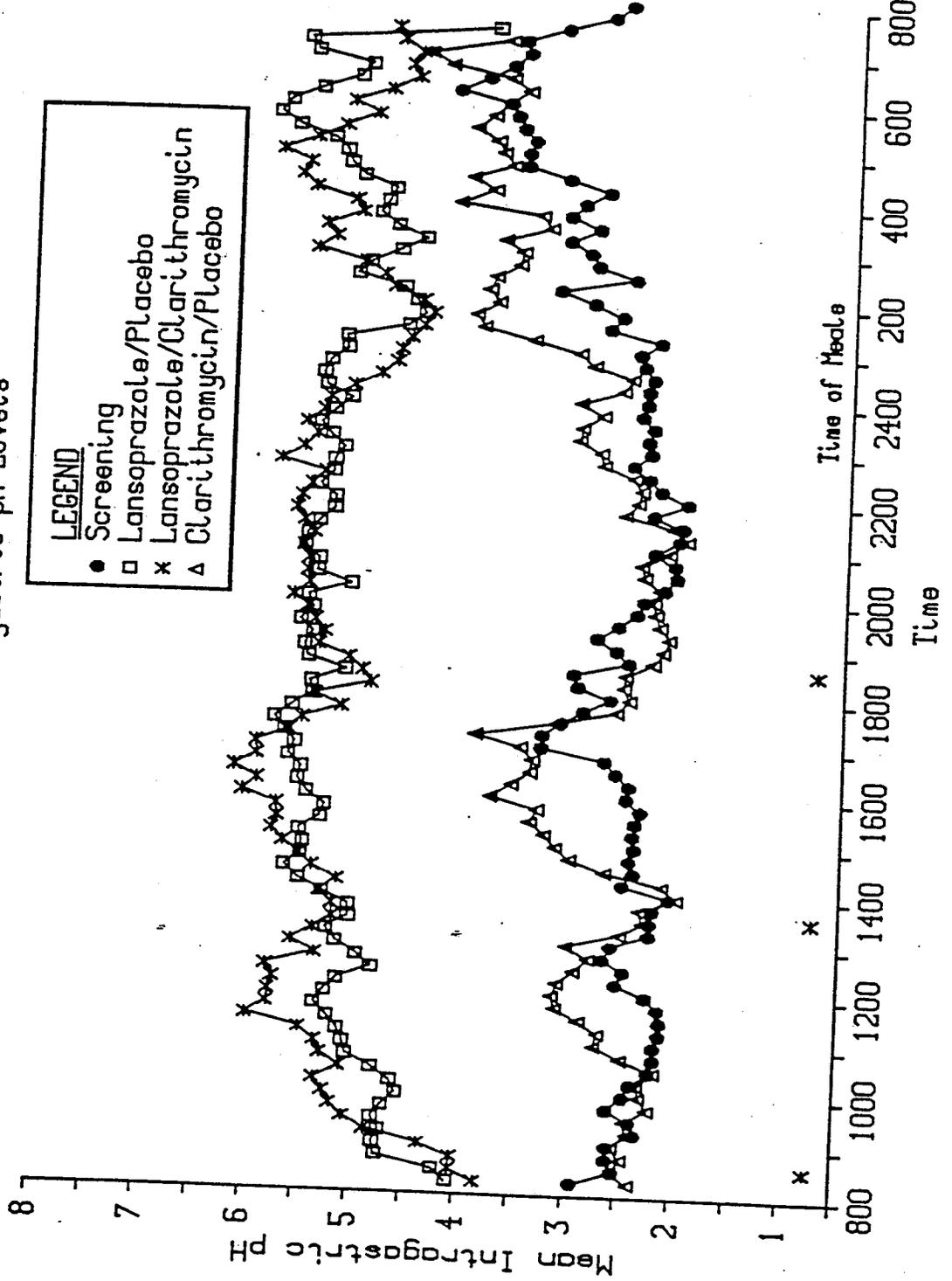


Figure #6. Mean \pm SD Concentration of 14[R]-Hydroxy-Clarithromycin in the Absence and Presence of Lansoprazole (Evening Dose)



(1)

Figure 7
Mean Intra-gastric pH Levels



LANSOPRAZOLE AND AMOXICILLIN DRUG INTERACTION STUDY

Title: The effect of concomitant administration of lansoprazole and amoxicillin in normal subjects

Study No.: M94-168

Investigator and Site: J.H. Cavanaugh, Ph.D., M.D.
Abbott Laboratories
Clinical Pharmacology Research Unit
Victory Memorial Hospital
Waukegan, Illinois 60085

Study Dates: July 18, 1994 - August 20, 1994

Objective: To determine the pharmacokinetics and assess the safety of concomitant administration of lansoprazole and amoxicillin.

Study Design: This was a Phase I, double-blind, randomized, placebo-controlled, three-period, crossover, single-center interaction study comparing lansoprazole 30 mg TID, lansoprazole 30 mg TID plus amoxicillin 1000 mg TID, and amoxicillin 100 mg TID for five days. Twenty-four healthy subjects (17 males and 7 females, mean age: 29.5 years, mean weight: 167 lb) were randomly assigned in equal numbers to one of the six possible sequences for the three treatment regimens. All 24 subjects completed the study. Crossover periods were separated by at least 9-day washout interval. Doses were given at approximately 8:00 AM, 1:00 PM, and 6:00 PM on Days 1 through 5. Each dose was given one-half hour prior to any meal.

Formulations:

- A: Lansoprazole capsules, 30 mg NPRO 6089R, Lot 81-447-AR (TAP Pharmaceuticals, Inc., Deerfield, IL).
- B: Amoxicillin capsules, 250 mg amoxicillin as the trihydrate, Lot WT1026 (Amoxil[®], SmithKline Beecham Pharmaceuticals, Philadelphia, PA).

Regimens:

- A: One 30 mg lansoprazole capsule three times daily plus placebo for amoxicillin capsules three times daily on Days 1-5.
- B: One placebo for lansoprazole capsule three times daily plus four 250 mg amoxicillin capsules three times daily on Days 1-5.

C: One 30 mg lansoprazole capsule three times daily plus four 250 mg amoxicillin capsules three times daily on Days 1-5.

Specimens: Seven-mL blood samples were collected at following times: prior to the first day of dosing (predose), immediately prior to the first dose (0 hr) on Day 5 and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5 (just prior to the 1300 hr dose), 5.5, 6, 6.5, 7, 7.5, 8, 9, 10 (just prior to the 1800 hr dose), 10.5, 11, 11.5, 12, 12.5, 13, 14, 15, 16, 18, 20, 22 and 24 hours after the first dose on Day 5 of each study period.

Assay: Venous plasma samples were analyzed for lansoprazole and amoxicillin by HPLC with UV detection at _____ b(4)

Lansoprazole:

Linearity: 20 ng/ml to 4000 ng/ml, satisfactory.

Precision: Interassay precision (%CV) ranged from 2.57% at 50 ng/ml to 1.82% at 2000 ng/ml.

Accuracy: Interassay accuracy ranged from 104% at 50 ng/ml to 109% at 2000 ng/ml.

Sensitivity: LOQ - 20 ng/ml from 0.5 ml of plasma.

Amoxicillin:

Linearity: 0.50 µg/ml to 15.0 µg/ml, satisfactory.

Precision: Interassay precision (%CV) ranged from 12.4% at 1.0 µg/ml to 6.06% at 10.0 µg/ml.

Accuracy: Interassay accuracy ranged from 98.4% at 1.0 µg/ml to 101% at 10.0 µg/ml.

Sensitivity: LOQ - 0.5 µg/ml from 0.5 ml of plasma.

Data Analysis: The following pharmacokinetic parameters were evaluated for lansoprazole and amoxicillin for each of the three doses of Day 5: C_{max}, T_{max}, C_{min}, AUC_{int} (AUC for the dose interval). In addition, AUC₀₋₂₄ on Day 5 and t_{1/2} after the Day 5 evening dose were evaluated.

Pharmacokinetic parameters were analyzed using an ANOVA which included subject, period and regimen as sources of variation. For C_{max} and AUC a logarithmic transformation was employed. In addition, for C_{max} and AUC of lansoprazole and amoxicillin, a 95% confidence interval was obtained for the combination of lansoprazole and amoxicillin (Regimen C) relative to that of each single drug (Regimens A and B).

Results: Mean (\pm SD) lansoprazole pharmacokinetic parameters are summarized in the following table:

Parameter	Dose 1*		Dose 2*		Dose 3	
	Alone	+ Amoxicillin	Alone	+ Amoxicillin	Alone	+ Amoxicillin
Cmax (ng/ml)	769 \pm 318	817 \pm 371	909 \pm 515	887 \pm 627	671 \pm 399	721 \pm 417
Tmax (hr)	1.5 \pm 0.5	1.3 \pm 0.7	1.3 \pm 0.8	1.6 \pm 1.2	1.5 \pm 0.6	1.5 \pm 0.8
Cmin** (ng/ml)	128 \pm 167	94 \pm 147	122 \pm 175	133 \pm 170	7.3 \pm 35.8	7.7 \pm 31.8
AUCint*** (ng.hr/ml)	1656 \pm 938	1609 \pm 937	1913 \pm 1398*	1790 \pm 1563* (-14%)	1996 \pm 1872	2122 \pm 2019
t1/2 (hr)	N.D.	N.D.	N.D.	N.D.	1.21 \pm 0.41	1.17 \pm 0.44
Doses 1, 2, and 3						
Parameter	Alone		+ Amoxicillin			
AUC0-24	5565 \pm 4138		5521 \pm 4381			

N=24 subjects except for lansoprazole β determined in the presence of amoxicillin, for which N=23.

*Statistically significant ($p \leq 0.05$) difference between lansoprazole alone and lansoprazole + amoxicillin. Parenthetical value represents percent difference in central values. For Cmax and AUC, central values were computed from the least square means of analysis of logarithms with back transformation.

**Statistical test not performed for dose interval 3.

***AUCint denotes AUC from time of the indicated dose to the next dose. These are AUC0-5, AUC5-10, and AUC10-24, and represent the AUC values from the time of Doses 1, 2, and 3, to the next dose, respectively.

N.D. not determined.

Mean (\pm SD) amoxicillin pharmacokinetic parameters are summarized in the following table:

Parameter	Dose 1*		Dose 2*		Dose 3	
	Alone	+ Lansoprazole	Alone	+ Lansoprazole	Alone	+ Lansoprazole
Cmax (ng/ml)	15.3 \pm 6.3	13.9 \pm 4.8	14.9 \pm 5.2*	12.6 \pm 5.1* (-16%)	16.9 \pm 6.1*	13.6 \pm 5.2* (-20%)
Tmax (hr)	1.5 \pm 0.4*	1.8 \pm 0.6* (+20%)	1.8 \pm 0.8	2.1 \pm 1.1	1.6 \pm 0.5*	2.3 \pm 0.8* (+44%)
Cmin** (ng/ml)	2.0 \pm 0.9	2.2 \pm 1.1	2.7 \pm 1.4*	4.3 \pm 3.8* (+59%)	0.0 \pm 0.0	0.0 \pm 0.0
AUCint*** (ng.hr/ml)	34.5 \pm 11.8	34.7 \pm 11.3	38.6 \pm 11.5	36.5 \pm 8.6	44.7 \pm 14.4*	51.2 \pm 20.5* (+13%)
t1/2 (hr)	N.D.	N.D.	N.D.	N.D.	1.22 \pm 0.22*	1.45 \pm 0.36* (+18%)
Doses 1, 2, and 3						
Parameter	Alone		+ Lansoprazole			
AUC0-24	117.8 \pm 35.8		122.4 \pm 34.4			

N=24 subjects

*Statistically significant ($p \leq 0.05$) difference between amoxicillin alone and amoxicillin + lansoprazole. Parenthetical value represents percent difference in central values (C_{max} and AUC) or means (T_{max}, C_{min} and t_{1/2}). For C_{max} and AUC, central values were computed from the least square means of analysis of logarithms with back transformation.

**Statistical test not performed for dose interval 3.

***AUC_{int} denotes AUC from time of the indicated dose to the next dose. These are AUC₀₋₅, AUC₅₋₁₀, and AUC₁₀₋₂₄, and represent the AUC values from the time of Doses 1, 2, and 3, to the next dose, respectively.

N.D. not determined.

Fig. 1 and 2 show the mean lansoprazole and amoxicillin plasma concentration versus time plots, respectively.

The 95% confidence intervals for lansoprazole and amoxicillin relative bioavailability in terms of C_{max} and AUC are given in the following pages.

A total of 84 adverse events were reported by 19 subjects. Of these 84 events, the investigator judged one to be probably, 50 to be possibly, and 33 to be not related to study drug. It was reported the proportion of subjects reporting adverse events were similar during three regimens; 40% for amoxicillin/placebo regimen, 58% for the lansoprazole/amoxicillin regimen, and 63% for the lansoprazole/placebo regimen.

The most frequently reported adverse events were headache, diarrhea, dry mouth, and rhinitis.

Comments:

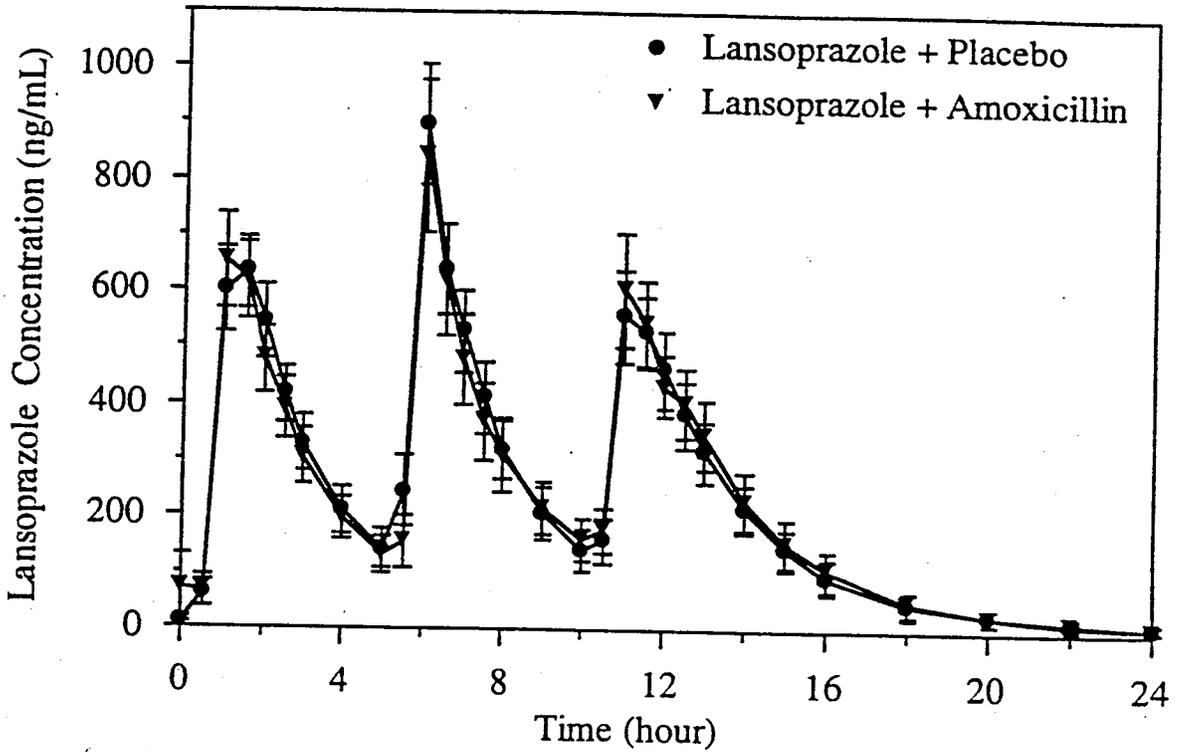
1. High doses of lansoprazole were administered in this study to ensure that the maximum interaction which might occur with doses being taken for H. pylori eradication would be detected.
2. The dose was given before a meal, as labeled for lansoprazole.
3. Amoxicillin is stable in the presence of gastric acid and may be given without regard to timing of meals. However, amoxicillin degrades in acid and has diminished solubility at pHs in the range of 3.5 to 6.
4. The ANOVA model used by the sponsor includes terms for subject, period and regimen as factors instead of using the model which contains terms for sequence, subject(nested within the sequence), period and regimen.

Conclusions:

- For lansoprazole, there was no statistically significant difference in mean pharmacokinetic parameters due to amoxicillin, with an exception of a 14% reduction in AUC after the second dose. Lansoprazole AUC over the 24 hour period for the two regimens was not statistically significantly different.

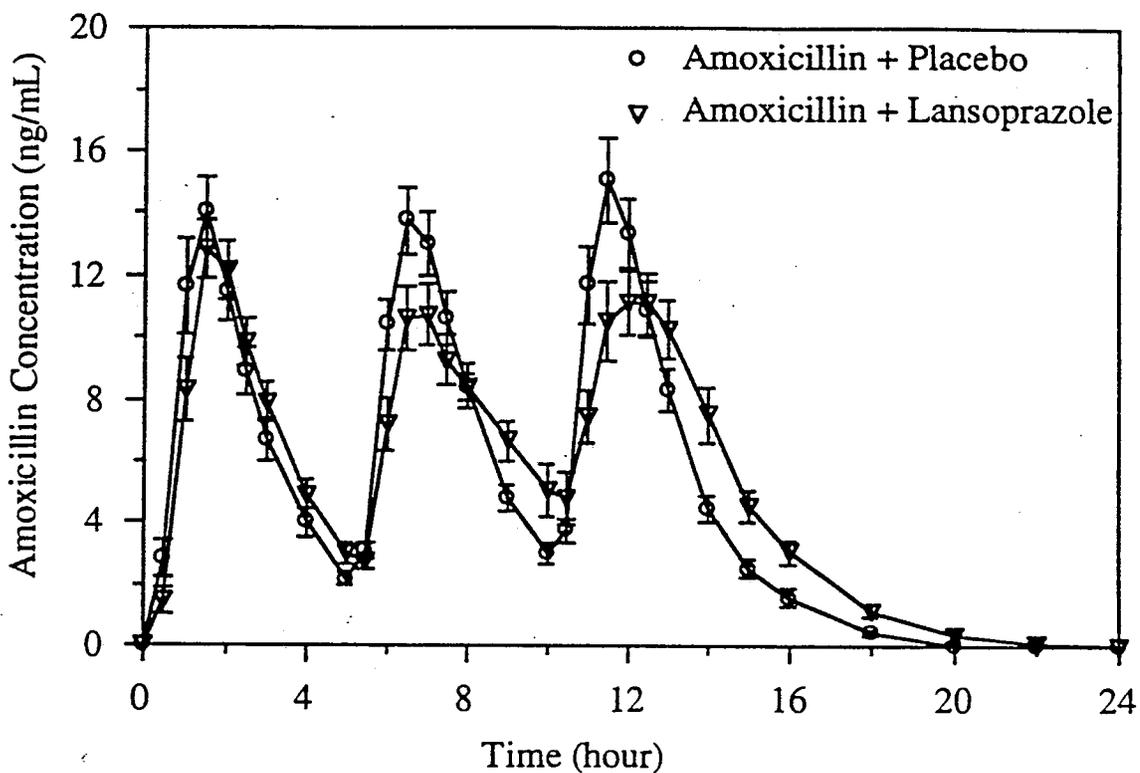
- For amoxicillin, a statistically significant lowering of C_{max} values following the second and third doses, and statistically significantly greater T_{max} values for Dose 1 and Dose 3 were observed with concurrent dosing of lansoprazole. For Dose 2, amoxicillin C_{max} was diminished by 16% and for Dose 3 it was lower by 20%. Amoxicillin mean T_{max} for Dose 1 was 20% greater with lansoprazole and for Dose 3 it was 44% greater. Amoxicillin mean AUC after the third dose was significantly increased by 13%. A statistically significant increase in mean C_{min} by 59% associated with the second dose was observed. Amoxicillin AUC over the 24 hour period for the two regimens was not statistically significantly different.
- The results showed that the pharmacokinetic interaction between lansoprazole and amoxicillin is small, therefore, may be considered clinically insignificant.

Figure 1. Mean \pm Standard Error Lansoprazole Plasma Concentrations



n = 24 Subjects.

Figure 2. Mean \pm Standard Error Amoxicillin Plasma Concentrations



n = 24 Subjects.

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 STUDY M94-168
 R41D/95/281

APPENDIX PAGE 1
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APPENDIX D.4

The 95% Confidence Intervals for Comparison of Amoxicillin Bioavailabilities on Day 5 With and Without Lansoprazole from Natural Logarithms of Cmax and AUC

B: Placebo*Amoxi; C: Lanso*Amoxi

Variable	Regimens Test Reference	Estimate of Test		Logarithm Means	95% Confidence Interval		Relative Bioavailability
		Mean	Mean		for Difference of Means	Point Estimate	
Cmax after morning dose	C B	2.5817	2.6700	-	-0.2111 - 0.0344	0.915	0.810 - 1.035
AUC after morning dose	C B	3.5017	3.4937	-	-0.0821 - 0.0979	1.008	0.921 - 1.103
Cmax after 1300 hour dose	C B	2.4695	2.6495	-	-0.2981 - -0.0619	0.835	0.742 - 0.940
AUC after 1300 hour dose	C B	3.5690	3.6169	-	-0.1583 - 0.0624	0.953	0.854 - 1.064
Cmax after evening dose	C B	2.5436	2.7724	-	-0.3737 - -0.0837	0.796	0.688 - 0.920
AUC after evening dose	C B	3.8788	3.7548	-	0.0391 - 0.2089	1.132	1.040 - 1.232
AUC0-24 hours	C B	4.7760	4.7320	-	-0.0036 - 0.0917	1.045	0.996 - 1.096

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APPENDIX PAGE 1
 LAST APPENDIX PAGE

APPENDIX D.2

The 95% Confidence Intervals for Comparison of Lansoprazole Bioavailabilities on Day 5 With and Without Amoxicillin
 from Natural Logarithms of Cmax and AUC

A: Lanso+Placebo; C: Lanso+Amoxi

Variable	Regimens Test Reference	Logarithm Means		Relative Bioavailability		
		Estimate of Test Mean	Estimate of Reference Mean	95% Confidence Interval for Difference of Means	Point Estimate	95% Confidence Interval
Cmax after morning dose	C A	6.5807	6.5337	-.1369 - 0.2308	1.048	0.872 - 1.260
AUC after morning dose	C A	7.2445	7.2660	-.1190 - 0.0759	0.979	0.888 - 1.079
Cmax after 1300 hour dose	C A	6.5106	6.6093	-.3431 - 0.1457	0.906	0.710 - 1.157
AUC after 1300 hour dose	C A	7.1656	7.3133	-.2879 - -.0075	0.863	0.750 - 0.993
Cmax after evening dose	C A	6.3894	6.3253	-.2387 - 0.3668	1.066	0.788 - 1.443
AUC after evening dose	C A	7.3731	7.2925	-.1086 - 0.2699	1.084	0.897 - 1.310
AUC0-24 hours.	C A	8.4069	8.4076	-.0902 - 0.0890	0.999	0.914 - 1.093

PROTONS PUMP INHIBITORS AND SUCRALFATE DRUG INTERACTION STUDY

Title: Assessment of the effect of a dose of sucralfate on the bioavailability of lansoprazole and omeprazole

Study No.: M94-237

Investigator and Site: J.H. Cavanaugh, Ph.D., M.D.
Abbott Laboratories
Clinical Pharmacology Research Unit
Victory Memorial Hospital
Waukegan, Illinois 60085

Study Dates: Subjects were administered omeprazole or omeprazole with sucralfate on October 27 and November 3, 1994. Lansoprazole or lansoprazole with sucralfate was administered on November 10 and November 17, 1994.

Objective: To determine the effect of simultaneous administration of sucralfate on the bioavailability of lansoprazole and omeprazole.

Study Design: This was a single-dose, fasting, open-label, four-period, crossover study. The first two study periods constituted a crossover of omeprazole with and without sucralfate, and Periods 3 and 4 were a crossover study of lansoprazole with and without sucralfate. One week separated the doses of successive study periods. Twenty-four healthy adult male (nineteen) and female (five) subjects participated in the study and twenty-two subjects completed all study periods. The average age and weight of the 24 subjects were 38 years and 179 lb, respectively.

Formulations:

- A: Lansoprazole capsules, 30 mg, NPRO 6626, Lot 93-631-S2 (TAP Pharmaceuticals, Inc., Deerfield, IL).
- B: Omeprazole capsules, 20 mg, Lot A4525 (Prilosec®, Merck & Co., Inc., West Point, PA).
- C: Sucralfate tablets, 1 gram per tablet, Lot K24111, (Carafate®, Marion Merrell Dow Inc., Kansas City, MO).

Regimens:

- A: One 30 mg lansoprazole capsule administered under fasting conditions (breakfast served two hours after dosing).

B: One 30 mg lansoprazole capsule and one 1 gram tablet of sucralfate administered under fasting conditions (breakfast served two hours after dosing).

C: One 20 mg omeprazole capsule administered under fasting conditions (breakfast served two hours after dosing).

D: One 30 mg omeprazole capsule and one 1 gram tablet of sucralfate administered under fasting conditions (breakfast served two hours after dosing).

Specimens: Blood samples for the drug assays (lansoprazole or omeprazole) were collected at following times: prior to dosing (0 hour) and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, and 12 hours after the dose.

Assay: Plasma samples were analyzed for lansoprazole or omeprazole by HPLC with UV detection at ~~7~~ ^{b(4)}

Lansoprazole:

Linearity: 10 ng/ml to 4000 ng/ml, satisfactory.

Precision: Interassay precision (%CV) ranged from 13.11% at 30 ng/ml to 5.15% at 3000 ng/ml.

Accuracy: Interassay accuracy ranged from 1.67% at 30 ng/ml to -4.30% at 3000 ng/ml.

Sensitivity: LOQ - 10 ng/ml from 0.5 ml of plasma.

Omeprazole:

Linearity: 10 ng/ml to 2000 ng/ml, satisfactory.

Precision: Interassay precision (%CV) ranged from 7.09% at 30 ng/ml to 3.97% at 1500 ng/ml.

Accuracy: Interassay accuracy ranged from -1.33% at 30 ng/ml to 2.47% at 1500 ng/ml.

Sensitivity: LOQ - 10 ng/ml from 0.5 ml of plasma.

Data Analysis: C_{max}, T_{max}, AUC₀₋₁₂, AUC_{0-∞}, β, and t_{1/2} were analyzed using ANOVA which included sequence, subject nested within sequence, period and regimen as sources of variation, with effects for subject random and all other effects fixed. Separate two-period crossover analyses were performed for lansoprazole data and omeprazole data.

Due to the extent of nonnormality probability distributions, nonparametric tests corresponding to those of the ANOVA were performed for omeprazole. On the basis of each of log transformed C_{max} and AUC for both lansoprazole and omeprazole, a 97% confidence interval for bioavailability with sucralfate relative to that without sucralfate was obtained.

Results: Mean pharmacokinetic parameters for lansoprazole and omeprazole are summarized in the following table:

Parameter	Lansoprazole†		Omeprazole‡	
	Alone	with Sucralfate	Alone	with Sucralfate
C _{max} (ng/ml)	840.7 ± 326.9	643.2 ± 212.2	323.7 ± 168.3	219.8 ± 145.7
T _{max} (hr)	1.8 ± 0.7	2.3 ± 0.4	2.3 ± 1.8	3.1 ± 2.0
AUC ₀₋₁₂ (ng.hr/ml)	2210.3 ± 1128.3	1829.6 ± 934.8	534.0 ± 322.4	487.2 ± 362.7
AUC _{0-∞} (ng.hr/ml)	2245.1 ± 1174.0	1857.6 ± 971.9	535.6 ± 328.3	501.0 ± 365.8
β (1/hr)	0.578 ± 0.183	0.561 ± 0.165	1.191 ± 0.428	0.863 ± 0.392
t _{1/2} (hr)*	1.20 ± 0.32	1.24 ± 0.37	0.58 ± 0.26	0.80 ± 0.37

Results presented as mean ± standard deviation.

*Harmonic mean ± pseudo-standard deviation.

† n=22, ‡ n=23.

The relative bioavailability of lansoprazole and omeprazole with sucralfate relative to that without sucralfate is summarized in the following table:

Parameter	Drug	Relative Bioavailability		
		Point Estimate	97%*** Confidence Interval	P***- value for Sucralfate Effect
C _{max}	Lansoprazole	0.788	0.653 - 0.952	0.0079*
	Omeprazole	0.610	0.538 - 0.696	0.0008*
AUC ₀₋₁₂	Lansoprazole	0.832	0.739 - 0.937	0.0018*
	Omeprazole	0.840	0.761 - 0.932	0.0121*
AUC _{0-∞}	Lansoprazole	0.832	0.740 - 0.936	0.0016*
	Omeprazole	0.840	0.770 - 0.953	0.0121*

**The statistical tests were performed on the logarithms of the PK variables using a crossover design analysis.

*Statistically significant.

***95% confidence intervals for lansoprazole were 0.666 - 0.933, 0.748 - 0.925, and 0.750 - 0.924, for C_{max}, AUC₀₋₁₂, and AUC_{0-∞}, respectively. 95% confidence intervals for omeprazole were not calculable due to the discreteness of nonparametric statistic that was used.

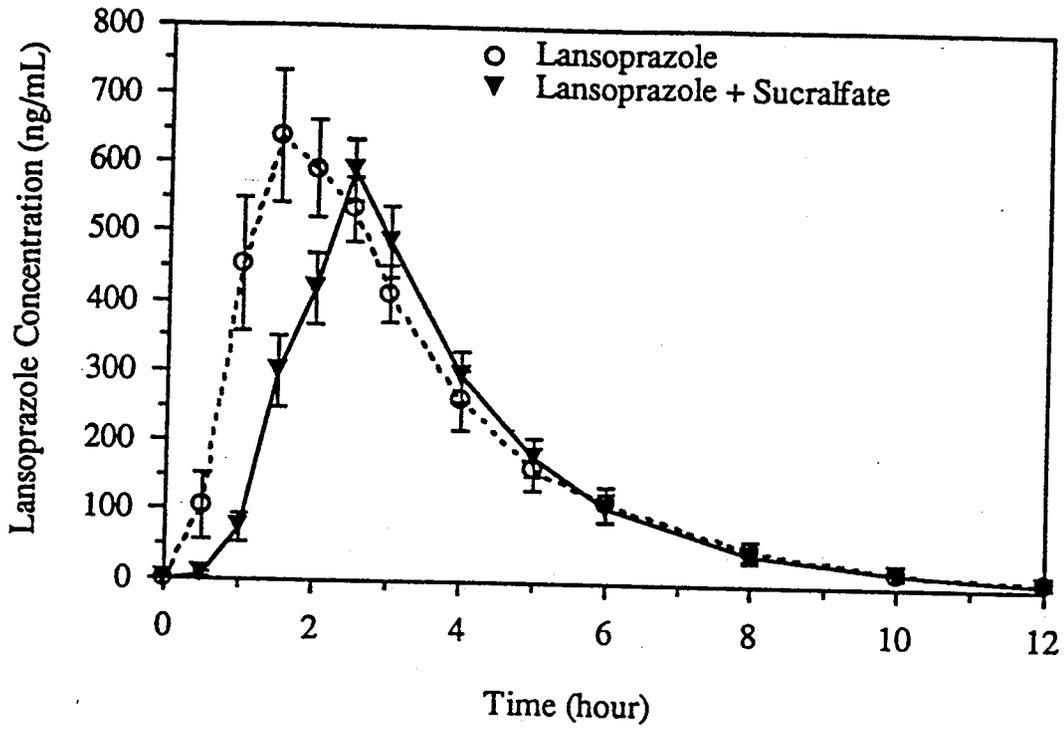
Fig. 1 and 2 show the mean plasma concentration versus time plots for lansoprazole and omeprazole, respectively.

Two subjects (# 5 and #12) did not complete the study, both premature terminations due to adverse effects.

Comments: In a previous study, lansoprazole AUC and Cmax means were reduced by 32% and 55%, respectively, when lansoprazole was coadministered with 2 gram sucralfate. In this study, lansoprazole AUC and Cmax means were reduced by 17% and 21%, respectively, when coadministered with 1 gram sucralfate. This effect is half of that seen in a previous study. The recommended sucralfate single dose is 1 gram.

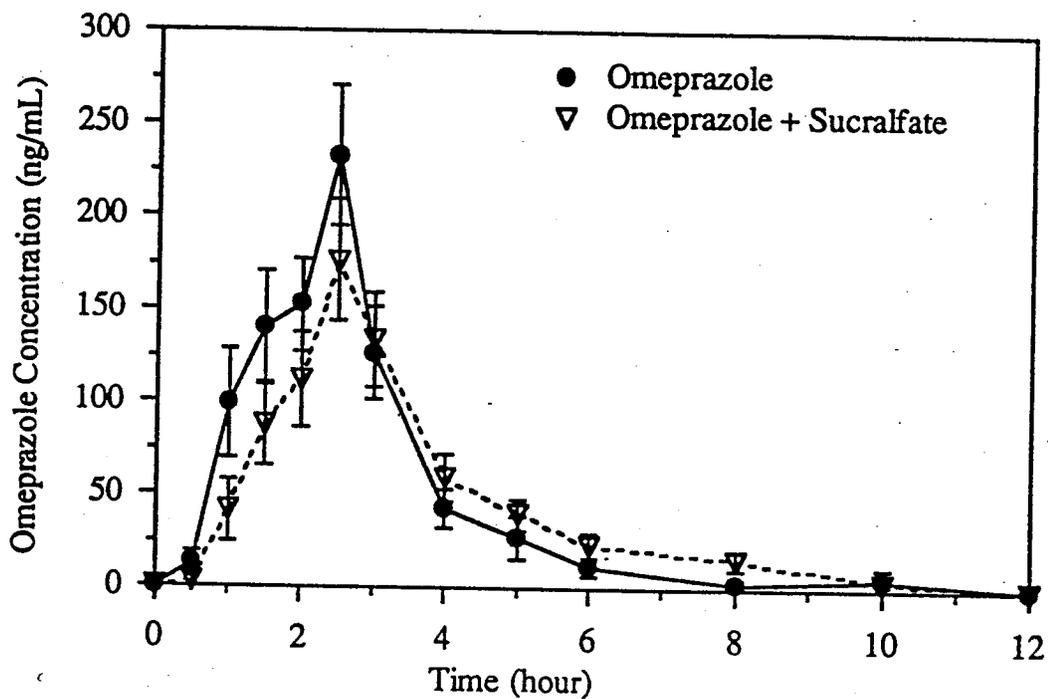
Conclusions: Administration of 1 gram sucralfate with either proton pump inhibitor (PPI), lansoprazole or omeprazole reduced the bioavailability of the PPI. AUC and Cmax values for lansoprazole were diminished by 17% and 21%, respectively, as a result of coadministration of sucralfate. AUC and Cmax values for omeprazole were also diminished by 16% and 39%, respectively.

Figure 1. Mean \pm Standard Error Lansoprazole Plasma Concentrations



n=22 subjects, excluding Subject 5 and Subject 12

Figure 2. Mean \pm Standard Error Omeprazole Plasma Concentrations



n=23 subjects, excluding Subject 12.

COMMENTS (to be sent to the firm):

1. The sponsor is requested to submit the individual QTcs along with individual QTc maxs and QTc AUCs for the two treatments for Study M94-167.

RECOMMENDATIONS:

The submission dated 04/15/96 has been reviewed by the Division of Pharmaceutical Evaluation II. The Medical Officer(s) in HFD-180 is requested to go over the "Integrated Summary of Safety - Phase I Interaction" (Vol. 11-18) of this application. If the Medical Officer(s) has no specific concerns, Study M93-063, M94-168, and M94-237 are acceptable.

Comment 1 should be forwarded to the sponsor.

Labeling recommendation for terfenadine to wait pending submission of data.

Hae Ryun Choi 11/13/96
Hae-Ryun Choi, Ph.D.
Division of Pharmaceutical Evaluation II

Rajendra Pradhan 11-13-96
Rajendra Pradhan, Ph.D.
Division of Pharmaceutical Evaluation II

RD/FT initialed by Lydia Kaus, Ph.D. *LCK* 11/13/96.

cc: NDA 20-406/SLR009, HFD-180, HFD-870 (M. Chen, Kaus, Choi, Pradhan), HFD-340 (Viswanathan), HFD-870 (Chron, Drug, Reviewer).

Attachment 1

Table 9.1

Summary of Statistical Analysis of Day -1 QTc Interval Area Under the Curve and Maximum

Pharmacodynamic Parameter ^a	N	Adjusted Means* Terfenadine with Lansoprazole	Terfenadine with Placebo	Difference of Means Estimate	95% Confidence Interval
Dose 1 ECG QTc AUC 0-4 hrs (msec x hr)	16	1529.9	1524.0	5.9	-14.9 - 26.7
Dose 2 ECG QTc AUC 0-4 hrs (msec x hr)	16	1526.0	1515.1	10.9	-9.7 - 31.6
Dose 1 ECG QTc AUC 0-12 hrs (msec x hr)	16	4609.0	4567.6	41.3	-22.0 - 104.6
Dose 1 Max. QTc 0-4 hrs (msec)	16	394.5	393.8	0.7	-5.9 - 7.3
Dose 2 Max. QTc 0-4 hrs (msec)	16	389.6	389.0	0.6	-5.1 - 6.3
Dose 1 Max. QTc 0-12 hrs (msec)	16	401.7	397.6	4.1	-2.2 - 10.3

* Means are adjusted for possibility of period effects. Since the number of subjects was the same for the two sequences of regimens, the adjusted means are the same as the unadjusted means.
^a No dose was administered on Day -1. The dose numbers in the parameter names identify the corresponding range of time on Day 7 for which the parameter was determined.

Table 9.2

Summary of Statistical Analysis of QTc Interval Area Under the Curve and Maximum for Comparison of Regimens (Day 7)

Pharmacodynamic Parameter	N	Adjusted Means* Terfenadine with Lansoprazole	Terfenadine with Placebo	Difference of Means Estimate	95% Confidence Interval
Dose 1 ECG QTc AUC 0-4 hrs (msec x hr)	16	1533.3	1538.6	-5.3	-21.2 - 10.5
Dose 2 ECG QTc AUC 0-4 hrs (msec x hr)	15	1449.9	1441.4	8.4	-6.8 - 23.7
Dose 1 ECG QTc AUC 0-12 hrs (msec x hr)	16	4628.0	4647.6	-19.6	-66.1 - 26.8
Dose 1 Max. QTc 0-4 hrs (msec)	16	395.4	394.0	1.4	-3.5 - 6.4
Dose 2 Max. QTc 0-4 hrs (msec)	15	398.8	394.0	4.8	-2.0 - 11.7
Dose 1 Max. QTc 0-12 hrs (msec)	16	400.3	402.1	-1.8	-7.3 - 3.7

* Means are adjusted for possibility of period effects. Since for Dose 2 the number of subjects was slightly different for the two sequences of regimens, the adjusted means differed some from the unadjusted means.

Table 9.3

Summary of Investigator Assessments of ECG Changes from Pre-regimen Evaluation

		----- For Individual ECGs Measurements on Days 1 Through 8 of Each Period -----		
	N*	Unchanged	Not Clinically Significant	Changed Clinically Significant
Terfenadine with Lansoprazole	296	188(63.5%)	108(36.5%)	0(0 %)
Terfenadine with Placebo	296	208(70.3%)	88(29.7%)	0(0 %)
Total	592	396(66.9%)	196(33.1%)	0(0 %)

		----- Counts of Subjects Classified By Greatest Change During Days 1 Through 8 of Each Regimen -----		
	N	Unchanged	Not Clinically Significant	Changed Clinically Significant
Terfenadine with Lansoprazole	16	1(6.3%)	15(93.8%)	0(0 %)
Terfenadine with Placebo	16	2(12.5%)	14(87.5%)	0(0 %)

* Number of individual ECGs after first dose of regimen across all subjects

01APR96 <tu167morphsCHANGED.sas linnenp>
 ABT-006 (LASOPRAZOLE)
 STUDY M94-167
 R&D/95/634 - CLINICAL/STATISTICAL
 Table Page 1 - Last Table Page

Table 9.4
 Summary of Investigator Assessments of TU Morphology Changes from Pre-regimen Evaluation

----- For Individual TU Morphology Measurements Days 1 Through 8 of Each Period -----				
	N*	Unchanged	Changed Not Clinically Significant	Changed Clinically Significant
Terfenadine with Lansoprazole	296	282(95.3%)	8(2.7%)	6(2.0%)
Terfenadine with Placebo	296	282(95.3%)	7(2.4%)	7(2.4%)
Total	592	564(95.3%)	15(2.5%)	13(2.2%)
----- Counts of Subjects Classified By Greatest Change During Days 1 Through 8 of Each Regimen -----				
	N	Unchanged	Changed Not Clinically Significant	Changed Clinically Significant
Terfenadine with Lansoprazole	16	13(81.3%)	1(6.3%)	2(12.5%)
Terfenadine with Placebo	16	13(81.3%)	0(0.0%)	3(18.8%)

* Number of individual TU morphology assessments after first dose of regimen across all subjects

Table 9.5

Descriptive Statistics for QTC Interval (msec) for Each Time of Measurement

Day Time*	N	Terfenadine with Lansoprazole			Terfenadine with Placebo						
		Mean	S.D.	Maximum	Mean	S.D.	Maximum				
-1 APPROX. 7:30 AM	16	381.6	22.7	335	385.9	429	377.2	18.7	341	375.3	411
-1 APPROX. 9:00 AM	16	387.7	17.2	353	388.7	420	384.5	22.2	344	387.3	418
-1 APPROX. 10:00 AM	16	388.0	21.3	353	387.8	431	383.6	21.4	343	384.0	420
-1 APPROX. 11:00 AM	16	375.9	20.1	337	377.2	406	380.5	17.8	348	379.2	410
-1 APPROX. 12:00 NOON	16	385.2	20.8	335	378.9	417	373.3	17.6	348	372.4	411
-1 APPROX. 2:00 PM	16	385.2	19.8	343	388.5	415	377.4	19.9	338	378.5	411
-1 APPROX. 4:00 PM	16	383.9	17.4	341	383.4	427	382.5	21.7	351	383.7	413
-1 APPROX. 8:00 PM	16	390.9	18.8	360	389.4	428	384.1	16.0	353	390.2	410
-1 APPROX. 9:00 PM	16	385.0	16.1	364	383.1	415	381.8	19.9	344	382.4	417
-1 APPROX. 10:00 PM	16	380.8	23.2	337	385.3	419	376.3	26.1	321	376.8	416
-1 APPROX. 11:00 PM	16	377.5	19.2	343	376.4	424	375.1	22.4	321	381.8	413
-1 APPROX. 12:00 MIDNIGHT	16	374.5	20.2	325	374.1	409	379.6	21.1	338	376.6	421
1 APPROX. 7:30 AM	16	382.4	19.2	349	384.3	424	381.1	23.2	336	387.6	428
3 APPROX. 7:30 AM	16	379.2	19.9	329	384.5	403	387.9	19.8	342	392.0	419
3 APPROX. 7:30 AM	16	376.0	19.2	335	375.5	412	374.3	20.6	348	370.5	420
5 APPROX. 7:30 AM	16	380.4	18.1	344	382.0	412	379.9	22.7	339	382.5	415
6 APPROX. 7:30 AM	16	381.9	20.5	335	383.5	422	372.6	17.9	346	370.0	405
7 APPROX. 7:30 AM	16	379.3	20.1	343	380.8	409	380.6	21.6	340	386.5	412
7 1 HOUR AFTER MORNING DOSE	16	389.3	20.9	348	386.0	431	386.6	22.0	350	384.5	419
7 2 HOURS AFTER MORNING DOSE	16	382.7	20.9	339	381.6	417	389.6	22.4	350	384.1	423
7 3 HOURS AFTER MORNING DOSE	16	383.1	20.5	343	386.0	409	381.7	24.5	343	381.3	417
7 4 HOURS AFTER MORNING DOSE	16	377.1	21.3	333	382.5	414	378.6	24.7	331	374.5	417
7 5 HOURS AFTER MORNING DOSE	16	391.8	18.2	368	388.9	433	390.2	23.1	349	394.3	425
7 6 HOURS AFTER MORNING DOSE	16	385.1	19.3	341	385.2	412	387.7	19.7	353	393.6	416
7 7 HOURS AFTER MORNING DOSE	16	389.3	21.8	349	389.4	431	393.5	25.9	352	398.4	428
7 8 HOURS AFTER MORNING DOSE	16	385.3	23.0	348	390.2	416	386.9	20.9	342	391.2	417
7 9 HOURS AFTER MORNING DOSE	15	390.0	23.2	347	390.3	421	380.2	17.8	352	384.3	402
7 10 HOURS AFTER MORNING DOSE	15	381.1	24.1	333	385.6	411	379.6	21.0	338	383.1	407
7 11 HOURS AFTER MORNING DOSE	15	389.2	20.9	354	387.7	434	386.5	26.7	341	381.3	430
8 APPROX. 7:30 AM	15	385.3	24.0	337	388.7	423	383.3	26.2	337	388.2	424

* For Day -1, the times of measurement corresponded to those of Day 7 for 1 to 16 hours after the morning dose.

Table 9.6

Descriptive Statistics for Difference of QTC Intervals (msec) Between Terfenadine with Lansoprazole and Terfenadine with Placebo for Each Time of Measurement

Day Time*	N	Mean	S.D.	Minimum	Median	Maximum
-1 APPROX. 7:30 AM	16	4.4	16.3	-27	4.2	31
-1 APPROX. 9:00 AM	16	3.1	19.7	-40	4.5	40
-1 APPROX. 10:00 AM	16	4.3	21.6	-34	1.8	54
-1 APPROX. 11:00 AM	16	-4.6	18.3	-34	-4.6	28
-1 APPROX. 12:00 NOON	16	1.7	18.5	-34	4.9	38
-1 APPROX. 2:00 PM	16	7.9	17.3	-20	6.1	36
-1 APPROX. 4:00 PM	16	1.4	22.6	-37	-5.2	44
-1 APPROX. 8:00 PM	16	6.8	12.6	-14	5.1	31
-1 APPROX. 9:00 PM	16	3.2	14.3	-22	2.7	31
-1 APPROX. 10:00 PM	16	4.5	15.5	-31	4.9	28
-1 APPROX. 11:00 PM	16	2.3	17.5	-32	5.6	31
-1 APPROX. 12:00 MIDNIGHT	16	-5.1	12.9	-31	-7.9	15
1 APPROX. 7:30 AM	16	1.3	13.6	-25	0.3	23
2 APPROX. 7:30 AM	16	-8.7	14.4	-33	-12.5	14
3 APPROX. 7:30 AM	16	1.8	17.2	-23	0.0	39
4 APPROX. 7:30 AM	16	-1.3	18.7	-30	-1.0	45
5 APPROX. 7:30 AM	16	7.8	19.0	-25	9.0	47
6 APPROX. 7:30 AM	16	1.3	28.8	-42	-5.0	56
7 APPROX. 7:30 AM	16	-3.3	8.4	-18	-3.9	16
7 1 HOUR AFTER MORNING DOSE	16	2.7	16.2	-30	-1.6	37
7 2 HOURS AFTER MORNING DOSE	16	-7.0	14.4	-30	-5.3	20
7 3 HOURS AFTER MORNING DOSE	16	1.3	14.1	-20	0.9	29
7 4 HOURS AFTER MORNING DOSE	16	-1.5	11.8	-21	-3.3	22
7 6 HOURS AFTER MORNING DOSE	16	1.6	21.3	-36	3.0	39
7 8 HOURS AFTER MORNING DOSE	16	-2.6	13.0	-18	-6.4	27
7 12 HOURS AFTER MORNING DOSE	16	-4.2	13.8	-26	-4.9	25
7 13 HOURS AFTER MORNING DOSE	15	-1.6	13.5	-24	2.8	22
7 14 HOURS AFTER MORNING DOSE	15	9.8	16.0	-29	12.3	33
7 15 HOURS AFTER MORNING DOSE	15	1.5	15.4	-29	0.2	35
7 16 HOURS AFTER MORNING DOSE	15	2.8	14.3	-28	4.1	33
8 APPROX. 7:30 AM	15	2.0	16.9	-24	3.0	32

* For Day -1, the times of measurement corresponded to those of Day 7 for 1 to 16 hours after the morning dose.

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-406/S009

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

DEC 19 1996

Application Number: NDA 20-406/SLR-009

Name of Drug: Prevacid (lansoprazole) Delayed-Release Capsules

Sponsor: TAP Holdings, Inc.

Material Reviewed

Submission Date(s): April 15, 1996

Receipt Date(s): April 16, 1996

Background and Summary Description: The sponsor submitted SLR-009 on April 15, 1996 with draft labeling. The supplement provides for revisions to the PRECAUTIONS, Drug Interactions section of the package insert.

REVIEW

The submitted draft labeling was compared to the currently approved labeling, identified as "03-4662-R4-Rev. February, 1996" approved April 8, 1996 in supplement 002. The following differences were noted.

PRECAUTIONS, Drug Interactions:

1. Terfenadine and clarithromycin were added to the list of compounds metabolized through the cytochrome P-450 system with which lansoprazole has been demonstrated to have no clinically significant interactions.
2. The following statement was added:
"Lansoprazole has also been shown to have no clinically significant interaction with amoxicillin."
3. The following statement was deleted:
"Coadministration of lansoprazole with sucralfate delayed absorption and reduced lansoprazole bioavailability by approximately 30%."
4. The following paragraph was added:
"In a single-dose crossover study comparing lansoprazole 30 mg and omeprazole 20 mg each administered alone and concomitantly with sucralfate 1 gram, absorption of the proton pump inhibitors was delayed and their bioavailability was reduced by 17% and 16%, respectively

when administered concomitantly with sucralfate."

5. "Lansoprazole" was replaced with "proton pump inhibitors" in the following statement:

"Therefore, proton pump inhibitors should be taken at least 30 minutes prior to sucralfate."

THE BIOPHARMACEUTICS REVIEW, DATED 11/13/96, RECOMMENDS CONSIDERATION OF THE "INTEGRATED SUMMARY OF SAFETY" - PHASE I INTERACTION" (VOLS. 11-18) BY THE MEDICAL OFFICER. IF THE MEDICAL OFFICER HAS NO SPECIFIC CONCERNS, THE LABELING REVISIONS REGARDING CLARITHROMYCIN, AMOXICILLIN, AND SUCRALFATE ARE ACCEPTABLE BY BIOPHARMACEUTICS.

REGARDING THE LABELING REVISION FOR TERFENADINE, THE BIOPHARMACEUTICS REVIEW, DATED 12/13/96, RECOMMENDS CONSIDERATION OF THE Qtc INTERVALS BETWEEN THE TWO TREATMENTS IN STUDY M94-167. IF THE MEDICAL OFFICER HAS NO CONCERNS, THE LABELING REVISION REGARDING TERFENADINE IS ACCEPTABLE BY BIOPHARMACEUTICS.

CONCLUSION

The medical officer should review the proposed revisions to the PRECAUTIONS, Drug Interaction section of the package insert in light of the biopharmaceutics reviews.

Maria R. Walsh 12/19/96
Maria R. Walsh, Project Manager

cc:
Orig NDA 20-406/S-009
HFD-180/Division file
HFD-180/J.Senior
S.Fredd
HFD-181/M.Walsh
Final: M.Walsh 12/19/96
C:\wpfiles\cso\n\20406S09.RMW

12/29/96
JF

NDA 20-406/S-009

NOV 21 1996

TAP Holdings, Inc.
Attention: Judy Decker Wargel
2355 Waukegan Road
Deerfield, IL 60015

Dear Ms. Wargel:

Please refer to your April 15, 1996 supplemental new drug application submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prevacid (lansoprazole) Delayed-Release Capsules.

We are reviewing your submission, and have the following request:

Please submit the individual QTcs along with the individual QTc maxs and QTc AUCs for the two treatments for Study M94-167.

If you have any questions, please contact:

Maria R. Walsh
Regulatory Health Project Manager
(301) 443-0487

Sincerely yours,

Stephen B. Fredd, M.D.
Director
Division of Gastrointestinal
and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:

Orig NDA 20-406/S-009
HFD-180/Division file
HFD-180/J.Senior
HFD-181/M.Walsh
HFD-870/L.Kaus
H. Choi

Drafted: M.Walsh 11/18/96

R/D init: S.Fredd 11/19/96

Final: M.Walsh

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INFORMATION REQUEST

63-1

NDA NDA 20-406/S-009, S-010, S-011

TAP Holdings Inc.
Attention: Judy Decker Wargel
2355 Waukegan Road
Deerfield, IL 60015

JUN 17 1997

Dear Ms. Wargel:

We acknowledge the receipt of your June 3, 1997 submissions containing final printed labeling in response to our February 25, April 17, and May 8, 1997 letters approving your supplemental new drug applications for Prevacid (lansoprazole) Delayed-Release Capsules.

Supplement 009 provides for revisions to the PRECAUTIONS, Drug Interactions sections of the package insert. Supplement 010 provides for a new indication: maintenance of healing of duodenal ulcer. Supplement 011 provides for a new indication: acute treatment of active benign gastric ulcer.

We have reviewed the labeling that you have submitted in accordance with our February 25, April 17, and May 8, 1997 letters, and we find it acceptable.

Sincerely yours,

LT 6-16-97

Lilia Talarico, M.D.
Acting Director
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

NDA NDA 20-406/S-009, S-010, S-011
Page 2

cc:

Original NDA 20-406/SLR-009
SE1-010
SE1-011

HFD-180/Div. Files
HF-2/Medwatch (with labeling)
HFD-103/Office Director (with labeling)
HFD-180/CSO/M. Walsh
HFD-40/DDMAC (with labeling)
HFD-92/DDM-DIAB (with labeling)
HFD-613/OGD (with labeling)
HFD-735/DPE (with labeling)

final: M. Walsh 6/16/97
filename: 20406706.A&R

ACKNOWLEDGE AND RETAIN (AR)

63-1

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: NDA 20-406/SLR-009
SE1-010
SE1-011

JUN 16 1997

Name of Drug: Prevacid (lansoprazole) Delayed-Release Capsules

Sponsor: TAP Holdings, Inc.

Material Reviewed

Submission Date(s): June 3, 1997

Receipt Date(s): June 4, 1997

Background and Summary Description: The sponsor submitted final printed labeling (FPL) for supplements 009, 010, and 011, approved on draft on February 25, 1997, April 17, 1997, and May 8, 1997, respectively. Supplement 009 provides for revisions to the PRECAUTIONS, Drug Interactions sections of the package insert. Supplement 010 provides for a new indication: maintenance of healing of duodenal ulcer. Supplement 011 provides for a new indication: acute treatment of active benign gastric ulcer.

Review

The submitted FPL, identified as "03-4793-R7-Rev. May, 1997," was compared to the approved draft labeling for supplements 009, 010, and 011 and the currently approved labeling, identified as "03-4742-R5-Rev. December, 1996," approved in supplements 008 and 012 on December 24, 1996. All approved revisions to the labeling were incorporated into the submitted FPL and no other differences were noted.

Conclusions

The submitted FPL is acceptable and will be acknowledged and retained.

Maria R. Walsh 6/16/97
Maria R. Walsh, M.S., Project Manager

NDA 20-406/SLR-009

SE1-010

SE1-011

Page 2

cc:

Original NDA 20-406/S-009

S-010

S-011

HFD-180/Div. Files

HFD-180/M. Walsh

HFD-180/Lilia Talarico, M.D. *lt 6-16-97*

final: M. Walsh 6/16/97

filename: 20406706.rev

CSO REVIEW

NDA 20-406/S-009

42-1
APR 22 1996

TAP Holdings Inc.
Attention: Ms. Judy Decker Wargel
2355 Waukegan Road
Deerfield, IL 60015

Dear Ms. Wargel:

We acknowledge receipt of your supplemental application for the following:

Name of Drug Product: Prevacid (lansoprazole) Delayed-Release Capsules

NDA Number: NDA 20-406

Supplement Number: S-009

Therapeutic Classification: Standard

Date of Supplement: April 15, 1996

Date of Receipt: April 16, 1996

This supplement provides for revisions to the PRECAUTIONS: Drug Interactions section of the package insert.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on June 15, 1996 in accordance with 21 CFR 314.101(a).

All communications concerning this supplemental application should be addressed as follows:

Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products,
HFD-180
Attention: DOCUMENT CONTROL ROOM
5600 Fishers Lane
Rockville, Maryland 20857

NDA 20-406/S-009

Page 2

Should you have any questions, please contact me at (301) 443-0487.

Sincerely yours,

Maria R. Walsh
Regulatory Health Project Manager
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:

Original NDA 20-406/S-009

HFD-180/Div. Files

HFD-180/CSO/M. Walsh

DISTRICT OFFICE

MW 4/19/96

Final: MRW 4/19/96

SUPPLEMENT ACKNOWLEDGEMENT



TAP HOLDINGS INC.
parent of TAP Pharmaceuticals Inc.

Bannockburn Lake Office Plaza
2355 Waukegan Rd.
Deerfield, IL 60015



*SUR/FA
009*

June 3, 1997

Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Document Control Room 6B-24
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Attn: Lilia Talarico, M.D.

**RE: PREVACID® (lansoprazole) Delayed-Release Capsules
NDA 20-406
Supplement 009
Final Printed Labeling for Approved Supplement**

Dear Dr. Talarico:

In Accordance with section 505(b) of the Food, Drug and Cosmetic Act and 21 CFR 314.60, TAP Holdings Inc., submits this correspondence regarding SNDA 009 for PREVACID. This approved supplement added information to the PRECAUTIONS: Drug Interaction section of the PREVACID labeling.

Per your letter of February 25, 1997, enclosed are 20 copies of final printed labeling, ten of which are individually mounted on heavy weight paper. This labeling is identical to that submitted on April 15, 1996, with the following exceptions:

Clinical Studies, Indications and Usage and Dosage and Administration

Information on the maintenance of healed duodenal ulcer was added per the Agency's letter of April 17, 1997, which cleared PREVACID for use in maintenance of healed duodenal ulcer. Please note that Supplement No. 010 was initially submitted to the Agency on April 24, 1996.



Information on gastric ulcer was added per the Agency's letter of May 8, 1997, which cleared PREVACID for the treatment of benign active gastric ulcer. This labeling reflects the changes requested by the Agency on May 6 and 8, 1997. Please note that Supplement No. 011 was initially submitted to the Agency on May 10, 1996.

The Final Printed Labeling incorporating these changes was also submitted to SNDAs 010 and 011 on this date.

Should further information be required, please do not hesitate to contact me.

Sincerely,

Judy Decker Wargel
Associate Director, Regulatory Affairs
Phone: (847) 317-5781
Fax: (847) 317-5795

JDW/jlh



TAP HOLDINGS INC.
parent of TAP Pharmaceuticals Inc.

Bannockburn Lake Office Plaza
2355 Waukegan Rd.
Deerfield, IL 60015

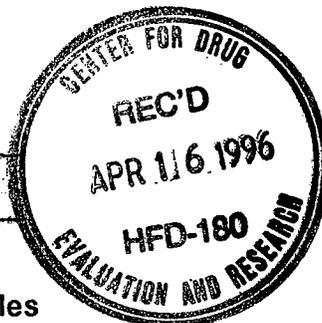
April 15, 1996

Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Document Control Room 6B-24
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA NO. 20406 REF. NO. 009

NDA SUPPL FOR SLR

Attn: Stephen B. Fredd, M.D.



RE: PREVACID® (Lansoprazole) Delayed-Release Capsules
NDA 20-406
Supplemental Application for Labeling Change

SNDA 009

Dear Dr. Fredd:

The sponsor, TAP Holdings Inc., submits this Supplemental Application under the provisions of Section 505 (i) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.70 (b) (3).

This supplement requests changes to the approved labeling for PREVACID® (lansoprazole) Delayed-Release Capsules, NDA 20-406 approved on May 10, 1995. Namely, under Precautions: Drug Interactions, we propose to make the following changes:

1. Add terfenadine and clarithromycin to the list of compounds metabolized through the cytochrome P-450 system with which lansoprazole has been demonstrated to have no clinically significant interactions.

2. Add the following statement:

"Lansoprazole has also been shown to have no clinically significant interaction with amoxicillin."

3. Delete:

"Coadministration of lansoprazole with sucralfate delayed absorption and reduced lansoprazole bioavailability by approximately 30%."

4/21/96 [Signature] 4/24/96 [Signature]



Add:

"In a single-dose crossover study comparing lansoprazole 30 mg and omeprazole 20 mg each administered alone and concomitantly with sucralfate 1 gram, absorption of the proton pump inhibitors was delayed and their bioavailability was reduced by 17% and 16%, respectively when administered concomitantly with sucralfate."

In addition, replace "lansoprazole" with "proton pump inhibitors" to read:

"Therefore, proton pump inhibitors should be taken at least 30 minutes prior to sucralfate."

Included in this submission is the requisite information needed to support these labeling changes as outlined in the Table of Contents.

If you have any questions or if additional information is needed, please do not hesitate to contact me.

Sincerely,

Judy Decker Wargel
Associate Director, Regulatory Affairs
Phone: (847) 317-5781
Fax: (847) 317-5795

JDW/pjp

8 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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