CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-406/S024

Trade Name: Prevacid Delayed Release Capsules

Generic Name: (lansoprazole)

Sponsor: TAP Holdings Inc

Approval Date: June 23, 1998

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-406/S024

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	X
Approvable Letter	
Labeling	X
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Medical Review(s)	X
Chemistry Review(s)	
Environmental Assessment	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-406/S024

APPROVAL LETTER

NDA 20-406/S-024

TAP Holdings, Inc.
Attention: Gary C. Magistrelli, Ph.D.
2355 Waukegan Road
Deerfield, IL 60015

Dear Dr. Magistrellil:

Please refer to your supplemental new drug application dated January 9, 1998, received January 12, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prevacid (lansoprazole) Delayed-Release Capsules.

The user fee goal date for this application is July 12, 1998.

This supplemental new drug application provides for the following changes to the ADVERSE REACTIONS section of the package insert: Addition of "anaphylactoid-like reaction" under the subheading, *Body as a Whole*, and the substitution of "blurred vision" for "amblyopia" in the subheading, *Special Senses*.

We have completed the review of this supplemental application, as amended, 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 agreed upon labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert dated January 7, 1998). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug. In addition, all previous revisions as reflected in the most currently approved package insert must be included.

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 "FPL for approved supplement NDA 20-406/S-024." Approval of this submission by FDA is not required before the labeling is used.

If additional information relating to the safety or effectiveness of this drug becomes available before we receive the final printed labeling, revision of that labeling may be required.

If a letter communicating important information about this drug product (i.e., a "Dear Healthcare Practitioner" letter) is 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 20857

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, contact Maria R. Walsh, M.S., Project Manager, at (301) 443-0487.

Sincerely,

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

cc:
Archival NDA 20-406
HFD-180/Div. Files
HFD-180/M.Walsh
HFD-180/J.Senior
HFD-180/H.Gallo-Torres
HFD-180/L.Talarcio
HF-2/MedWatch (with labeling)
HFD-002/ORM (with labeling)
HFD-103/ADRA (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-95/DDMS (with labeling)
HFD-820/DNDC Division Director
DISTRICT OFFICE

final: M.Walsh 6/23/98
filename: 20406S24-AP806.doc

APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-406/S024

LABELING

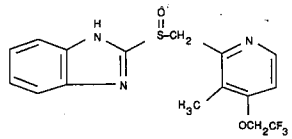
(Nos. 1541, 3046)
03-4891-R11-Rev. June, 1998

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 (± SD) plasma half-life was 1.5 (± 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 µg/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 antisecretory 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 returned to pretreatment 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 (T_3), thyroxine (T_4), and somatotropic 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 PHARMACOLOGY

MICROBIOLOGY

Lansoprazole, clarithromycin and/or amoxicillin have been shown to be active against most strains of *Helicobacter pylori in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section.

Helicobacter

Helicobacter pylori

Pretreatment Resistance

Clarithromycin pretreatment resistance (≥ 2.0 µg/mL) was 9.5% (91/960) by E-test and 11.3% (12/106) by agar dilution in the dual and triple therapy clinical trials (M93-125, M93-130, M93-131, M95-392, and M95-399).

Amoxicillin pretreatment susceptible isolates (≤ 0.25 µg/mL) occurred in 97.8% (936/957) and 98.0% (98/100) of the patients in the dual and triple therapy clinical trials by E-test and agar dilution, respectively. Twenty-one of 957 patients (2.2%) by E-test and 2 of 100 patients (2.0%) by agar dilution had amoxicillin pretreatment MICs of > 0.25 µg/mL. One patient on the 14 day triple therapy regimen had an unconfirmed pretreatment amoxicillin minimum inhibitory concentration (MIC) of > 256 µg/mL by E-test and the patient was eradicated of *H. pylori*.

Clarithromycin Susceptibility Test Results and Clinical/Bacteriological Outcomes[a]

Clarithromycin Pretreatment Results		Clarithromycin Post-treatment Results				
		H. pylori negative–eradicated	*H. pylori* positive–not eradicated			
			Post-treatment susceptibility results			
			S[b]	I[b]	R[b]	No MIC
Triple Therapy 14-Day (lansoprazole 30 mg b.i.d./amoxicillin 1 gm b.i.d./clarithromycin 500 mg b.i.d.) (M95-399, M93-131, M95-392)						
Susceptible[b]	112	105			7	
Intermediate[b]	3	3				
Resistant[b]	17	6		7	4	
Triple Therapy 10-Day (lansoprazole 30 mg b.i.d./amoxicillin 1 gm b.i.d./clarithromycin 500 mg b.i.d.) (M95-399)						
Susceptible[b]	42	40	1	1		

that the 10-day triple therapy was equivalent to the 14-day triple therapy in eradi *H. pylori*.

***H. pylori* Eradication Rates – Triple Therapy**
(PREVACID/amoxicillin/clarithromycin)
Percent of Patients Cured
[95% Confidence Interval]
(Number of patients)

Study	Duration	Triple Therapy Evaluable Analysis*	Triple Therapy Intent-to-Treat Analy
M93-131	14 days	92† [80.0-97.7] (N=48)	86† [73.3-93.5] (N=55)
M95-392	14 days	86‡ [75.7-93.6] (N=66)	83‡ [72.0-90.8] (N=70)
M95-399+	14 days	85 [77.0-91.0] (N=113)	82 [73.9-88.1] (N=126)
	10 days	84 [76.0-89.8] (N=123)	81 [73.9-87.6] (N=135)

*Based on evaluable patients with confirmed duodenal ulcer (active or within one year) and *H. pylori* inf at baseline defined as at least two of three positive endoscopic tests from CLOtest® (Delta West Ltd., B Australia), histology and/or culture. Patients were included in the analysis if they completed the study. Additionally, if patients dropped out of the study due to an adverse event related to the study drug, they included in the evaluable analysis as failures of therapy.

#Patients were included in the analysis if they had documented *H. pylori* infection at baseline as defined a and had a confirmed duodenal ulcer (active or within one year). All dropouts were included as failures of t

†(p<0.05) versus PREVACID/amoxicillin and PREVACID/clarithromycin dual therapy

‡(p<0.05) versus clarithromycin/amoxicillin dual therapy

+The 95% confidence interval for the difference in eradication rates, 10-day minus 14-day is (-10.5, 8.1) evaluable analysis and (-9.7, 9.1) in the intent-to-treat analysis.

***H. pylori* Eradication Rates – 14-Day Dual Therapy**
(PREVACID/amoxicillin)
Percent of Patients Cured
[95% Confidence Interval]
(Number of patients)

Study	Dual Therapy Evaluable Analysis*	Dual Therapy Intent-to-Treat Analysis#
M93-131	77† [62.5-87.2] (N=51)	70† [56.8-81.2] (N=60)
M93-125	66‡ [51.9-77.5] (N=58)	61‡ [48.5-72.9] (N=67)

*Based on evaluable patients with confirmed duodenal ulcer (active or within one year) and *H. pylori* infe baseline defined as at least two of three positive endoscopic tests from CLOtest®, histology and/or cultu Patients were included in the analysis if they completed the study. Additionally, if patients dropped out c study due to an adverse event related to the study drug, they were included in the analysis as failures of #Patients were included in the analysis if they had documented *H. pylori* infection at baseline as defined and had a confirmed duodenal ulcer (active or within one year). All dropouts were included as failures of t

†(p<0.05) versus PREVACID alone.

‡(p<0.05) versus PREVACID alone or amoxicillin alone.

Long-Term Maintenance Treatment of Duodenal Ulcers

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

comparing 12 male and six female human subjects, no gender differences were harmacokinetics and intragastric pH results. (Also see Use in Women.)

ufficiency

: with severe renal insufficiency, plasma protein binding decreased by 1.0%-1.5% nistration of 60 mg of lansoprazole. Patients with renal insufficiency had a short- nation half-life and decreased total AUC (free and bound). AUC for free lansopra- sma, however, was not related to the degree of renal impairment, and C_{max} and : not different from subjects with healthy kidneys.

sufficiency

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

d mean pharmacokinetic parameters of lansoprazole from twelve U.S. Phase 1 stud- 3) were compared to the mean pharmacokinetic parameters from two Asian studies he mean AUCs of lansoprazole in Asian subjects were approximately twice those oled U.S. data; however, the inter-individual variability was high. The C_{max} values parable.

ACODYNAMICS

m of action

:ole belongs to a class of antisecretory compounds, the substituted benzimidazoles, ot exhibit anticholinergic or histamine H_2-receptor antagonist properties, but that gastric acid secretion by specific inhibition of the (H^+,K^+)-ATPase enzyme system at ory surface of the gastric parietal cell. Because this enzyme system is regarded as proton) pump within the parietal cell, lansoprazole has been characterized as a gas- ump inhibitor, in that it blocks the final step of acid production. This effect is dose- d leads to inhibition of both basal and stimulated gastric acid secretion irrespective nulus.

tory activity

administration, lansoprazole was shown to significantly decrease the basal acid out- ignificantly increase the mean gastric pH and percent of time the gastric pH was . Lansoprazole also significantly reduced meal-stimulated gastric acid output and volume, as well as pentagastrin-stimulated acid output. In patients with hypersecre- id, lansoprazole significantly reduced basal and pentagastrin-stimulated gastric acid Lansoprazole inhibited the normal increases in secretion volume, acidity and acid luced by insulin.

ossover study comparing lansoprazole 15 and 30 mg with omeprazole 20 mg for five following effects on intragastric pH were noted:

Mean Antisecretory Effects after Single and Multiple Daily Dosing

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

intragastric pH of >4 reflects a reduction in gastric acid by 99%.
ersus baseline, lansoprazole 15 mg and omeprazole 20 mg.
ersus baseline only.

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

uppression may enhance the effect of antimicrobials in eradicating *Helicobacter . pylori)*. The percentage of time gastric pH was elevated above 5 and 6 was evalu- crossover study of PREVACID given q.d., b.i.d. and t.i.d.

Mean Antisecretory Effects After 5 Days of b.i.d. and t.i.d. Dosing

	PREVACID			
	30 mg q.d.	15 mg b.i.d.	30 mg b.i.d.	30 mg t.i.d.
Gastric pH>5	43	47	59*	77*
Gastric pH>6	20	23	28	45*

ersus PREVACID 30 mg q.d.
ersus PREVACID 30 mg q.d., 15 mg b.i.d. and 30 mg b.i.d.

ition of gastric acid secretion as measured by intragastric pH returns gradually to nor- two to four days after multiple doses. There is no indication of rebound gastric acidity.

romaffin-like (ECL) cell effects

fetime exposure of rats with up to 150 mg/kg/day of lansoprazole dosed seven days , marked hypergastrinemia was observed followed by ECL cell proliferation and for- f carcinoid tumors, especially in female rats. (See PRECAUTIONS, Carcinogenesis, esis, Impairment of Fertility.)

.c biopsy specimens from the body of the stomach from approximately nts treated continuously with lansoprazole for at least one year did not show evi- ECL cell effects similar to those seen in rat studies. Longer term data are needed to the possibility of an increased risk of the development of gastric tumors in patients ; long-term therapy with lansoprazole.

stric effects in humans

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

astrin effects

.100 patients, median fasting serum gastrin levels increased 50% to 100% from base- emained within normal range after treatment with lansoprazole given orally in doses g to 60 mg. These elevations reached a plateau within two months of therapy and with pretreatment amoxicillin MICs of > 0.25 µg/mL, three of six had the *H. pylori* eradicated. A total of 30% (21/70) of the patients failed lansoprazole 30 mg t.i.d./amoxicillin 1 gm t.i.d. dual therapy and a total of 12.8% (22/172) of the patients failed the 10-and-14 day triple therapy regimens. Post-treatment susceptibility results were not obtained on 11 of the patients who failed therapy. Nine of the 11 patients with amoxicillin post-treatment MICs that failed the triple therapy regimen also had clarithromycin resistant *H. pylori* isolates.

Susceptibility Test for *Helicobacter pylori*

The reference methodology for susceptibility testing of *H. pylori* is agar dilution MICs.[1] One to three microliters of an inoculum equivalent to a No. 2 McFarland standard (1×10^7 - 1×10^8 CFU/mL for *H. pylori*) are inoculated directly onto freshly prepared antimicrobial containing Mueller-Hinton agar plates with 5% aged defibrinated sheep blood (≥ 2 weeks old). The agar dilution plates are incubated at 35°C in a microaerobic environment produced by a gas generating system suitable for campylobacters. After 3 days of incubation, the MICs are recorded as the lowest concentration of antimicrobial agent required to inhibit growth of the organism. The clarithromycin and amoxicillin MIC values should be interpreted according to the following criteria:

Clarithromycin MIC (µg/mL)[a]	Interpretation
≤ 0.25	Susceptible (S)
0.5-1.0	Intermediate (I)
≥ 2.0	Resistant (R)
Amoxicillin MIC (µg/mL)[b]	**Interpretation**
≤ 0.25	Susceptible (S)

[a] These are tentative breakpoints for the agar dilution methodology and they should not be used to interpret results obtained using alternative methods.

[b] There were not enough organisms with MICs > 0.25 µg/mL to determine a resistance breakpoint.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard clarithromycin and amoxicillin powders should provide the following MIC values:

Microorganism	Antimicrobial Agent	MIC (µg/mL)[a]
H. pylori ATCC 43504	Clarithromycin	0.015-0.12 mcg/mL
H. pylori ATCC 43504	Amoxicillin	0.015-0.12 mcg/mL

[a] These are quality control ranges for the agar dilution methodology and they should not be used to control test results obtained using alternative methods.

Reference

1. National Committee for Clinical Laboratory Standards. Summary Minutes, Subcommittee on Antimicrobial Susceptibility Testing, Tampa, FL, January 11-13, 1998.

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.

Duodenal Ulcer Healing Rates

	PREVACID			Placebo
	15 mg q.d.	30 mg q.d.	60 mg q.d.	
Week	(N=68)	(N=74)	(N=70)	(N=72)
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-controlled, 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

	PREVACID		Ranitidine	Placebo
	15 mg q.d.	30 mg q.d.	300 mg h.s.	
Week	(N=80)	(N=77)	(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.

***H. pylori* Eradication to Reduce the Risk of Duodenal Ulcer Recurrence**

Randomized, double-blind clinical studies performed in the U.S. in patients with *H. pylori* and duodenal ulcer disease (defined as an active ulcer or history of an ulcer within one year) evaluated the efficacy of PREVACID in combination with amoxicillin capsules and clarithromycin tablets as triple 14-day therapy or in combination with amoxicillin capsules as dual 14-day therapy for the eradication of *H. pylori*. Based on the results of these studies, the safety and efficacy of two different eradication regimens were established:

Triple therapy: PREVACID 30 mg b.i.d./amoxicillin 1 gm b.i.d./clarithromycin 500 mg b.i.d.

Dual therapy: PREVACID 30 mg t.i.d./amoxicillin 1 gm t.i.d.

All treatments were for 14 days. *H. pylori* eradication was defined as two negative tests (culture and histology) at 4-6 weeks following the end of treatment.

Triple therapy was shown to be more effective than all possible dual therapy combinations. Dual therapy was shown to be more effective than both monotherapies. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence.

A randomized, double-blind clinical study performed in the U.S. in patients with *H. pylori* and duodenal ulcer disease (defined as an active ulcer or history of an ulcer within one year) compared the efficacy of PREVACID triple therapy for 10 and 14 days. This study established

%=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

	PREVACID			Placebo
	15 mg q.d.	30 mg q.d.	60 mg q.d.	
Week	(N=65)	(N=63)	(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.

Gastroesophageal Reflux Disease (GERD)

Symptomatic GERD

In a U.S. multicenter, double-blind, placebo-controlled study of 214 patients with frequent GERD symptoms, but no esophageal erosions by endoscopy, significantly greater relief of heartburn associated with GERD was observed with the administration of lansoprazole 15 mg once daily up to 8 weeks than with placebo. No significant additional benefit from lansoprazole 30 mg once daily was observed.

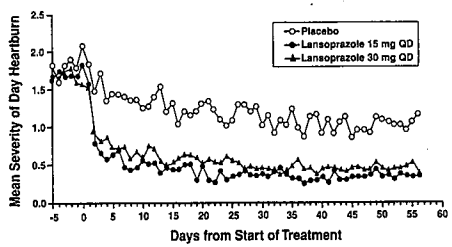
The intent-to-treat analyses demonstrated significant reduction in frequency and severity of day and night heartburn. Data for frequency and severity for the 8-week treatment period were as follows:

Frequency of Heartburn

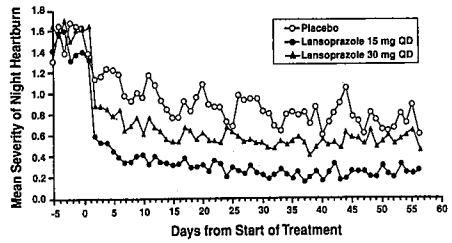
Variable	Placebo (n=43)	PREVACID 15 mg (n=80)	PREVACID 30 mg (n=86)
		Median	
% of Days without Heartburn			
Week 1	0%	71%*	46%*
Week 4	11%	81%*	76%*
Week 8	13%	84%*	82%*
% of Nights without Heartburn			
Week 1	17%	86%*	57%*
Week 4	25%	89%*	73%*
Week 8	36%	92%*	80%*

*(p<0.01) versus placebo.

Mean Severity of Day Heartburn By Study Day For Evaluable Patients (3=Severe, 2=Moderate, 1=Mild, 0=None)



Mean Severity of Night Heartburn By Study Day For Evaluable Patients (3=Severe, 2=Moderate, 1=Mild, 0=None)



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:

measurable quantities in plasma (the hydroxylated sulfinyl and sulfone derivatives of lansoprazole). These metabolites have very little or no antisecretory 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.

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 mean pharmacokinetic parameters of lansoprazole from twelve U.S. Phase 1 studies (N=513) were compared to the mean pharmacokinetic parameters from two Asian studies (N=20). The mean AUCs of lansoprazole in Asian subjects were approximately twice those seen in pooled U.S. data; however, the inter-individual variability was high. The C_{max} values were comparable.

PHARMACODYNAMICS

Mechanism of action

Lansoprazole belongs to a class of antisecretory compounds, the substituted benzimidazoles, that do not exhibit anticholinergic or histamine H_2-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

		PREVACID				Omeprazole	
	Baseline	15 mg		30 mg		20 mg	
Parameter	Value	Day 1	Day 5	Day 1	Day 5	Day 1	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%.
*(p<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.

Acid suppression may enhance the effect of antimicrobials in eradicating *Helicobacter pylori (H. pylori)*. The percentage of time gastric pH was elevated above 5 and 6 was evaluated in a crossover study of PREVACID given q.d., b.i.d. and t.i.d.

Mean Antisecretory Effects After 5 Days of b.i.d. and t.i.d. Dosing

	PREVACID			
Parameter	30 mg q.d.	15 mg b.i.d.	30 mg b.i.d.	30 mg t.i.d.
% Time Gastric pH>5	43	47	59+	77*
% Time Gastric pH>6	20	23	28	45*

+(p<0.05) versus PREVACID 30 mg q.d.
*(p<0.05) versus PREVACID 30 mg q.d., 15 mg b.i.d. and 30 mg b.i.d.

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, Impairment of Fertility.)

Gastric biopsy specimens from the body of the stomach from approximately

Resistant[b]	17	6	7	4
Triple Therapy 10-Day (lansoprazole 30 mg b.i.d./amoxicillin 1 gm b.i.d./clarithromycin 500 mg b.i.d.) (M95-399)				
Susceptible[b]	42	40	1	1
Intermediate[b]				
Resistant[b]	4	1	3	

[a] Includes only patients with pretreatment clarithromycin susceptibility test results

[b] Susceptible (S) MIC ≤ 0.25 µg/mL, Intermediate (I) MIC 0.5 - 1.0 µg/mL, Resistant (R) MIC ≥ 2 µg/mL

Patients not eradicated of *H. pylori* following lansoprazole/amoxicillin/clarithromycin triple therapy will likely have clarithromycin resistant *H. pylori*. Therefore, for those patients who fail therapy, clarithromycin susceptibility testing should be done when possible. Patients with clarithromycin resistant *H. pylori* should not be treated with lansoprazole/amoxicillin/clarithromycin triple therapy or with regimens which include clarithromycin as the sole antimicrobial agent.

Amoxicillin Susceptibility Test Results and Clinical/Bacteriological Outcomes

In the dual and triple therapy clinical trials, 82.6% (195/236) of the patients that had pretreatment amoxicillin susceptible MICs (≤ 0.25 µg/mL) were eradicated of *H. pylori*. Of those with pretreamtent amoxicillin MICs of > 0.25 µg/mL, three of six had the *H. pylori* eradicated. A total of 30% (21/70) of the patients failed lansoprazole 30 mg t.i.d./amoxicillin 1 gm t.i.d. dual therapy and a total of 12.8% (22/172) of the patients failed the 10-and-14 day triple therapy regimens. Post-treatment susceptibility results were not obtained on 11 of the patients who failed therapy. Nine of the 11 patients with amoxicillin post-treatment MICs that failed the triple therapy regimen also had clarithromycin resistant *H. pylori* isolates.

Susceptibility Test for *Helicobacter pylori*

The reference methodology for susceptibility testing of *H. pylori* is agar dilution MICs.[1] One to three microliters of an inoculum equivalent to a No. 2 McFarland standard (1 x 10^7 - 1 x 10^8 CFU/mL for *H. pylori*) are inoculated directly onto freshly prepared antimicrobial containing Mueller-Hinton agar plates with 5% aged defibrinated sheep blood (≥ 2 weeks old). The agar dilution plates are incubated at 35°C in a microaerobic environment produced by a gas generating system suitable for campylobacters. After 3 days of incubation, the MICs are recorded as the lowest concentration of antimicrobial agent required to inhibit growth of the organism. The clarithromycin and amoxicillin MIC values should be interpreted according to the following criteria:

Clarithromycin MIC (µg/mL)[a]	Interpretation
≤ 0.25	Susceptible (S)
0.5-1.0	Intermediate (I)
≥ 2.0	Resistant (R)
Amoxicillin MIC (µg/mL)[b]	**Interpretation**
≤ 0.25	Susceptible (S)

[a] These are tentative breakpoints for the agar dilution methodology and they should not be used to interpret results obtained using alternative methods.

[b] There were not enough organisms with MICs > 0.25 µg/mL to determine a resistance breakpoint.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard clarithromycin and amoxicillin powders should provide the following MIC values:

Microorganism	Antimicrobial Agent	MIC (µg/mL)[a]
H. pylori ATCC 43504	Clarithromycin	0.015-0.12 mcg/mL
H. pylori ATCC 43504	Amoxicillin	0.015-0.12 mcg/mL

[a] These are quality control ranges for the agar dilution methodology and they should not be used to control test results obtained using alternative methods.

Reference

1. National Committee for Clinical Laboratory Standards. Summary Minutes, Subcommittee on Antimicrobial Susceptibility Testing, Tampa, FL, January 11-13, 1998.

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.

Duodenal Ulcer Healing Rates

	PREVACID			Placebo
	15 mg q.d.	30 mg q.d.	60 mg q.d.	
Week	(N=68)	(N=74)	(N=70)	(N=72)
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-controlled, 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

	PREVACID		Ranitidine	Placebo
	15 mg q.d.	30 mg q.d.	300 mg h.s.	
Week	(N=80)	(N=77)	(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.

[illegible] Patients were included in the analysis if they had documented *H. pylori* infection at baseline as defined and had a confirmed duodenal ulcer (active or within one year). All dropouts were included as failures of
†(p<0.05) versus PREVACID alone.
‡(p<0.05) versus PREVACID alone or amoxicillin alone.

Long-Term Maintenance Treatment of Duodenal Ulcers

PREVACID has been shown to prevent the recurrence of duodenal ulcers. Two inde double-blind, multicenter, controlled trials were conducted in patients with endosc confirmed healed duodenal ulcers. Patients remained healed significantly longer and ber of recurrences of duodenal ulcers was significantly less in patients treat PREVACID than in patients treated with placebo over a 12-month period.

Endoscopic Remission Rates

			Percent in Endoscopic Remissio		
Trial	Drug	No. of Pts.	0-3 mo.	0-6 mo.	0-12 m
#1	PREVACID 15 mg q.d.	86	90%*	87%*	84%*
	Placebo	83	49%	41%	39%
#2	PREVACID 30 mg q.d.	18	94%*	94%*	85%*
	PREVACID 15 mg q.d.	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 3 maintaining remission.

Gastric Ulcer

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

Gastric Ulcer Healing Rates

	PREVACID			Placebo
	15 mg q.d.	30 mg q.d.	60 mg q.d.	
Week	(N=65)	(N=63)	(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 nal pain along with fewer days of antacid use and fewer antacid tablets used per day placebo group.

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

Gastroesophageal Reflux Disease (GERD)

Symptomatic GERD

In a U.S. multicenter, double-blind, placebo-controlled study of 214 patients with GERD symptoms, but no esophageal erosions by endoscopy, significantly greater heartburn associated with GERD was observed with the administration of lansoprazol once daily up to 8 weeks than with placebo. No significant additional benefit from la zole 30 mg once daily was observed.

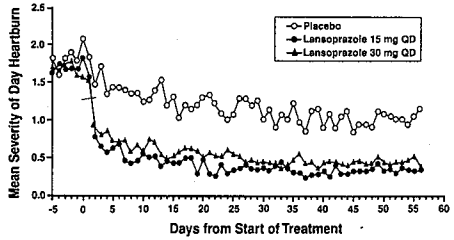
The intent-to-treat analyses demonstrated significant reduction in frequency and of day and night heartburn. Data for frequency and severity for the 8-week treatmen were as follows:

Frequency of Heartburn

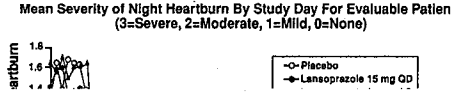
Variable	Placebo (n=43)	PREVACID 15 mg (n=80)	PREVACID (n=8
		Median	
% of Days without Heartburn			
Week 1	0%	71%*	46%*
Week 4	11%	81%*	76%*
Week 8	13%	84%*	82%*
% of Nights without Heartburn			
Week 1	17%	86%*	57%*
Week 4	25%	89%*	73%*
Week 8	36%	92%*	80%*

*(p<0.01) versus placebo.

Mean Severity of Day Heartburn By Study Day For Evaluable Patien (3=Severe, 2=Moderate, 1=Mild, 0=None)



Mean Severity of Night Heartburn By Study Day For Evaluable Patien (3=Severe, 2=Moderate, 1=Mild, 0=None)



...minate a comparison of the effectiveness of histamine H_2-receptor antagonists
'ACID, as all patients had demonstrated unresponsiveness to the histamine
antagonist mode of treatment. It does indicate, however, that
may be useful in patients failing on a histamine H_2-receptor antagonist.

flux Esophagitis Healing Rates in Patients Poorly Responsive to Histamine H_2-Receptor Antagonist Therapy

PREVACID 30 mg q.d. (N=100)	Ranitidine 150 mg b.i.d. (N=51)
74.7%*	42.6%
83.7%*	32.0%

sus ranitidine.

) Maintenance Treatment of Erosive Esophagitis

ndent, double-blind, multicenter, controlled trials were conducted in patients with
lly confirmed healed esophagitis. Patients remained in remission significantly
he number of recurrences of erosive esophagitis was significantly less in patients
PREVACID than in patients treated with placebo over a 12-month period.

Endoscopic Remission Rates

		Percent in Endoscopic Remission		
	No. of Pts.	0-3 mo.	0-6 mo.	0-12 mo.
VACID 15 mg q.d.	59	83%*	81%*	79%*
VACID 30 mg q.d.	56	93%*	93%*	90%*
ebo	55	31%	27%	24%
VACID 15 mg q.d.	50	74%*	72%*	67%*
VACID 30 mg q.d.	49	75%*	72%*	55%*
ebo	47	16%	13%	13%

Estimate
sus placebo.

of initial grade of erosive esophagitis, PREVACID 15 mg and 30 mg were simi-
ining remission.

al Hypersecretory Conditions Including Zollinger-Ellison Syndrome

ies of 57 patients with pathological hypersecretory conditions, such as Zollinger-
syndrome with or without multiple endocrine adenomas, PREVACID signifi-
ited gastric acid secretion and controlled associated symptoms of diarrhea,
pain. Doses ranging from 15 mg every other day to 180 mg per day maintained
ecretion below 10 mEq/hr in patients without prior gastric surgery and below
patients with prior gastric surgery.

ses were titrated to the individual patient need, and adjustments were necessary
some patients. (See DOSAGE AND ADMINISTRATION.) PREVACID was
d at these high dose levels for prolonged periods (greater than four years in some
most ZE patients, serum gastrin levels were not modified by PREVACID. How-
e patients, serum gastrin increased to levels greater than those present prior to ini-
isoprazole therapy.

ONS AND USAGE

Treatment of Active Duodenal Ulcer

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

radication to Reduce the Risk of Duodenal Ulcer Recurrence

py (PREVACID/amoxicillin/clarithromycin)

Delayed-Release Capsules, in combination with amoxicillin plus clarithromycin
apy, are indicated for the treatment of patients with *H. pylori* infection and duo-
disease (active or one-year history of a duodenal ulcer) to eradicate *H. pylori*.
of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence. (See
STUDIES and DOSAGE AND ADMINISTRATION.)

y (PREVACID/amoxicillin)

Delayed-Release Capsules, in combination with amoxicillin as dual therapy, are
the treatment of patients with *H. pylori* infection and duodenal ulcer disease
e-year history of a duodenal ulcer) **who are either allergic or intolerant to clar-
or in whom resistance to clarithromycin is known or suspected.** (See the clar-
ackage insert, MICROBIOLOGY section.) Eradication of *H. pylori* has been
duce the risk of duodenal ulcer recurrence. (See CLINICAL STUDIES and
ND ADMINISTRATION.)

e of Healed Duodenal Ulcers

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

Treatment of Active Benign Gastric Ulcer

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

hageal Reflux Disease (GERD)

reatment of Symptomatic GERD

Delayed-Release Capsules are indicated for the treatment of heartburn and other
sociated with GERD.

Treatment of Erosive Esophagitis

Delayed-Release Capsules are indicated for short-term treatment (up to
healing and symptom relief of all grades of erosive esophagitis.
ts who do not heal with PREVACID for 8 weeks (5-10%), it may be helpful to
ional 8 weeks of treatment.
is a recurrence of erosive esophagitis an additional 8-week course of
may be considered.

e of Healing of Erosive Esophagitis

Delayed-Release Capsules are indicated to maintain healing of erosive esophagi-
d studies did not extend beyond 12 months.

l Hypersecretory Conditions Including Zollinger-Ellison Syndrome

Delayed-Release Capsules are indicated for the long-term treatment of patho-
secretory conditions, including Zollinger-Ellison syndrome.

NDICATIONS

Delayed-Release Capsules are contraindicated in patients with known hypersen-
component of the formulation.
in is contraindicated in patients with a known hypersensitivity to any penicillin.
to full prescribing information for amoxicillin before prescribing.)
ycin is contraindicated in patients with a known hypersensitivity to any
tibiotic, and in patients receiving terfenadine therapy who have preexisting car-
lities or electrolyte disturbances. (Please refer to full prescribing information for
n before prescribing.)

S

**OMYCIN SHOULD NOT BE USED IN PREGNANT WOMEN EXCEPT IN
CIRCUMSTANCES WHERE NO ALTERNATIVE THERAPY IS APPROPRI-
GNANCY OCCURS WHILE TAKING CLARITHROMYCIN, THE PATIENT
APPRISED OF THE POTENTIAL HAZARD TO THE FETUS. (SEE WARN-
ESCRIBING INFORMATION FOR CLARITHROMYCIN.)**

**mbranous colitis has been reported with nearly all antibacterial agents,
rithromycin and amoxicillin, and may range in severity from mild to life
Therefore, it is important to consider this diagnosis in patients who present
a subsequent to the administration of antibacterial agents.**

with antibacterial agents alters the normal flora of the colon and may permit
f clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a
of "antibiotic-associated colitis".
liagnosis of pseudomembranous colitis has been established, therapeutic mea-
be initiated. Mild cases of pseudomembranous colitis usually respond to dis-
of the drug alone. In moderate to severe cases, consideration should be given to
with fluids and electrolytes, protein supplementation, and treatment with an
rug clinically effective against *Clostridium difficile* colitis.
l occasionally fatal hypersensitivity (anaphylactic) reactions have been reported
penicillin therapy. These reactions are more apt to occur in individuals with a
icillin hypersensitivity and/or a history of sensitivity to multiple allergens.
been well documented reports of individuals with a history of penicillin hyper-
actions who have experienced severe hypersensitivity reactions when treated
osporin. Before initiating therapy with any penicillin, careful inquiry should be
ing previous hypersensitivity reactions to penicillins, cephalosporins, and other
n allergic reaction occurs, amoxicillin should be discontinued and the appropri-

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 (eg, ketoconazole, ampicillin esters, iron salts, digoxin).

Carcinogenesis, Mutagenesis, Impairment of 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/m^2) basis, of a 50-kg person of average height (1.46 m^2 body surface area) given the recommended human dose of 30 mg/day (22.2 mg/m^2). 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

Lansoprazole

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.

Clarithromycin

Pregnancy Category C

See WARNINGS (above) and full prescribing information for clarithromycin before using in pregnant women.

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 pediatric patients have not been established.

Use in Women

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

Use in Geriatric 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. For elderly patients, dosage and administration of lansoprazole need not be altered for a particular indication.

ADVERSE REACTIONS

Worldwide, over 6100 patients have been treated with lansoprazole in Phase 2-3 clinical trials involving various dosages and durations of treatment. In general, lansoprazole treatment has been well tolerated in both short-term and long-term 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:

Incidence of Possibly or Probably Treatment-Related Adverse Events in Short-term, Placebo-Controlled Studies

Body System/Adverse Event	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 was similar between patients who received placebo and patients who received lansoprazole 15 mg and 30 mg, but higher in the patients who received lansoprazole 60 mg (2.9%, 1.4%, 4.2%, and 7.4%, respectively).

The most commonly reported possibly or probably treatment-related adverse event during maintenance therapy was diarrhea.

Additional adverse experiences occurring in <1% of patients or subjects in domestic and/or international trials, or occurring since the drug was marketed, are shown below within each body system.

Body as a Whole - anaphylactoid-like reaction, 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** - agranulocytosis, anemia, aplastic anemia, hemolysis, hemolytic anemia, leukopenia, neutropenia, pancytopenia, thrombocytopenia, and thrombotic thrombocytopenic purpura; *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* - blurred vision, deafness, eye pain, visual field defect, otitis media, speech disorder, taste perversion, tinnitus; *Urogenital System* - abnormal menses, albuminuria, breast enlargement/gynecomastia, breast tenderness, glycosuria, hematuria, impotence, kidney calculus, urinary retention.

* The majority of hematologic cases received were foreign-sourced and their relationship to lansoprazole was unclear.

Combination Therapy with Amoxicillin and Clarithromycin

In clinical trials using combination therapy with PREVACID plus amoxicillin and clarithromycin, and PREVACID plus amoxicillin, no adverse reactions peculiar to these drug combinations were observed. Adverse reactions that have occurred have been limited to those that had been previously reported with PREVACID, amoxicillin, or clarithromycin.

H. pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence

Triple Therapy: PREVACID/amoxicillin/clarithromycin

The recommended adult oral dose is 30 mg PREVACID, 1 gram amoxicillin, and 500 mg clarithromycin, all given twice daily (q 12h) for 10 or 14 days. (See INDICATIONS AND USAGE.)

Dual Therapy: PREVACID/amoxicillin

The recommended adult oral dose is 30 mg PREVACID and 1 gram amoxicillin, each given three times daily (q 8h) for 14 days. (See INDICATIONS AND USAGE.)

Please refer to amoxicillin and clarithromycin full prescribing information for CONTRAINDICATIONS and WARNINGS, and for information regarding dosing in elderly and renally-impaired patients.

Maintenance of Healed Duodenal Ulcers

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

Short-Term Treatment of Gastric Ulcer

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

Gastroesophageal Reflux Disease (GERD)

Short-Term Treatment of Symptomatic GERD

The recommended adult oral dose is 15 mg once daily for up to 8 weeks.

Short-Term 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 b.i.d. 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. The granules have also been shown *in vitro* to remain intact when exposed to apple, cranberry, grape, orange, pineapple, prune, tomato, and V-8® vegetable juice and stored for up to 30 minutes.

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 with the TAP logo and "PREVACID 15" imprinted on the capsules. The 30 mg are opaque, hard gelatin, colored pink and black with the TAP logo and "PREVACID 30" imprinted on the 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 15°C and 30°C (59°F and 86°F).

℞ only

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

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

®—Registered Trademark

Erosive Esophagitis Healing Rates

Week	PREVACID 15 mg q.d. (N=69)	PREVACID 30 mg q.d. (N=65)	PREVACID 60 mg q.d. (N=72)	Placebo (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 suggests 30 mg q.d. 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 b.i.d. as shown below.

Erosive Esophagitis Healing Rates

Week	PREVACID 30 mg q.d. (N=115)	Ranitidine 150 mg b.i.d. (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 b.i.d.

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 q.i.d., 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 b.i.d. in 151 patients with erosive reflux esophagitis that was poorly responsive to a minimum of 12 weeks of treatment with at least one H_2-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 b.i.d. 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 H_2-receptor antagonists with PREVACID, as all patients had demonstrated unresponsiveness to the histamine H_2-receptor antagonist mode of treatment. It does indicate, however, that PREVACID may be useful in patients failing on a histamine H_2-receptor antagonist.

Reflux Esophagitis Healing Rates in Patients Poorly Responsive to Histamine H_2-Receptor Antagonist Therapy

Week	PREVACID 30 mg q.d. (N=100)	Ranitidine 150 mg b.i.d. (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 q.d.	59	83%*	81%*	79%*
	PREVACID 30 mg q.d.	56	93%*	93%*	90%*
	Placebo	55	31%	27%	24%
#2	PREVACID 15 mg q.d.	50	74%*	72%*	67%*
	PREVACID 30 mg q.d.	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.

***H. pylori* Eradication to Reduce the Risk of Duodenal Ulcer Recurrence**

Triple Therapy (PREVACID/amoxicillin/clarithromycin)

PREVACID Delayed-Release Capsules, in combination with amoxicillin plus clarithromycin as triple therapy, are indicated for the treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or one-year history of a duodenal ulcer) to eradicate *H. pylori*. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence. (See CLINICAL STUDIES and DOSAGE AND ADMINISTRATION.)

Dual Therapy (PREVACID/amoxicillin)

PREVACID Delayed-Release Capsules, in combination with amoxicillin as dual therapy, are indicated for the treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or one-year history of a duodenal ulcer) **who are either allergic or intolerant to clarithromycin or in whom resistance to clarithromycin is known or suspected.** (See the clarithromycin package insert, MICROBIOLOGY section.) Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence. (See CLINICAL STUDIES and DOSAGE AND ADMINISTRATION.)

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.

Gastroesophageal Reflux Disease (GERD)

Short-Term Treatment of Symptomatic GERD

PREVACID Delayed-Release Capsules are indicated for the treatment of heartburn and other symptoms associated with GERD.

Short-Term Treatment of Erosive Esophagitis

ate therapy instituted.

SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

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. The granules have also been shown *in vitro* to remain intact when exposed to apple, cranberry, grape, orange, pineapple, prune, tomato, and V-8® vegetable juice and stored for up to 30 minutes.

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 P_{450} 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 P_{450} system, such as warfarin, antipyrine, indomethacin, ibuprofen, phenytoin, propranolol, prednisone, diazepam, clarithromycin, or terfenadine in healthy subjects. These compounds are metabolized through various cytochrome P_{450} 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 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 (eg, ketoconazole, ampicillin esters, iron salts, digoxin).

Carcinogenesis, Mutagenesis, Impairment of 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/m^2) basis, of a 50-kg person of average height (1.46 m^2 body surface area) given the recommended human dose of 30 mg/day (22.2 mg/m^2). 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

Lansoprazole

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.

Clarithromycin

Pregnancy Category C

See WARNINGS (above) and full prescribing information for clarithromycin before using in pregnant women.

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 pediatric patients have not been established.

Use in Women

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

Use in Geriatric 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. For elderly patients, dosage and administration of lansoprazole need not be altered for a particular indication.

ADVERSE REACTIONS

Worldwide, over 6100 patients have been treated with lansoprazole in Phase 2-3 clinical trials involving various dosages and durations of treatment. In general, lansoprazole treatment has been well tolerated in both short-term and long-term 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:

Triple Therapy: PREVACID/amoxicillin/clarithromycin

The most frequently reported adverse events for patients who received tr 14 days were diarrhea (7%), headache (6%), and taste perversion (5%). Ther tically significant differences in the frequency of reported adverse events bet 14-day triple therapy regimens. No treatment-emergent adverse events were nificantly higher rates with triple therapy than with any dual therapy regime

Dual Therapy: PREVACID/amoxicillin

The most frequently reported adverse events for patients who received PRE amoxicillin t.i.d. dual therapy were diarrhea (8%) and headache (7%). No tre adverse events were observed at significantly higher rates with PREVACID icillin t.i.d. dual therapy than with PREVACID alone.

For more information on adverse reactions with amoxicillin or clarithr their package inserts, ADVERSE REACTIONS sections.

Laboratory Values

The following changes in laboratory parameters for lansoprazole were rep events:

Abnormal liver function tests, increased SGOT (AST), increased SGPT creatinine, increased alkaline phosphatase, increased globulins, increased C decreased/abnormal WBC, abnormal AG ratio, abnormal RBC, bilirubinen hyperlipemia, increased/decreased electrolytes, increased/decreased chole glucocorticoids, increased LDH, increased/decreased/abnormal platelets, ar trin levels. Additional isolated laboratory abnormalities were reported.

In the placebo controlled studies, when SGOT (AST) and SGPT (ALT) 0.4% (1/250) placebo patients and 0.3% (2/795) lansoprazole patients had ei greater than three times the upper limit of normal range at the final treatme these patients reported jaundice at any time during the study.

In clinical trials using combination therapy with PREVACID plus amo ithromycin, and PREVACID plus amoxicillin, no increased laboratory abno lar to these drug combinations were observed.

For more information on laboratory value changes with amoxicillin o refer to their package inserts, ADVERSE REACTIONS section.

OVERDOSAGE

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

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

DOSAGE AND ADMINISTRATION

Short-Term Treatment of Duodenal Ulcer

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

***H. pylori* Eradication to Reduce the Risk of Duodenal Ulcer Recurr**

Triple Therapy: PREVACID/amoxicillin/clarithromycin

The recommended adult oral dose is 30 mg PREVACID, 1 gram amoxici clarithromycin, all given twice daily (q 12h) for 10 or 14 days. (See IND USAGE.)

Dual Therapy: PREVACID/amoxicillin

The recommended adult oral dose is 30 mg PREVACID and 1 gram amoxi three times daily (q 8h) for 14 days. (See INDICATIONS AND USAGE.)

Please refer to amoxicillin and clarithromycin full prescribing inform TRAINDICATIONS and WARNINGS, and for information regarding dosi renally-impaired patients.

Maintenance of Healed Duodenal Ulcers

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

Short-Term Treatment of Gastric Ulcer

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

Gastroesophageal Reflux Disease (GERD)

Short-Term Treatment of Symptomatic GERD

The recommended adult oral dose is 15 mg once daily for up to 8 weeks.

Short-Term Treatment of Erosive Esophagitis

The recommended adult oral dose is 30 mg once daily for up to 8 weeks. Fc not heal with PREVACID for 8 weeks (5-10%), it may be helpful to g 8 weeks of treatment. (See INDICATIONS AND USAGE.)

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

Maintenance of Healing of Erosive Esophagitis

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

Pathological Hypersecretory Conditions Including Zollinger-Ellison

The dosage of PREVACID in patients with pathologic hypersecretory conc the individual patient. The recommended adult oral starting dose is 60 mg should be adjusted to individual patient needs and should continue for as indicated. Dosages up to 90 mg b.i.d. have been administered. Daily dosag 120 mg should be administered in divided doses. Some patients with Zolli drome have been treated continuously with PREVACID for more than four

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

PREVACID Delayed-Release Capsules should be taken before eating. In antacids were used concomitantly with PREVACID. For patients who hav lowing capsules, PREVACID Delayed-Release Capsules can be opened, ar ules contained within can be sprinkled on one tablespoon of applesauc immediately. The granules should not be chewed or crushed. The granul shown *in vitro* to remain intact when exposed to apple, cranberry, grape, prune, tomato, and V-8® vegetable juice and stored for up to 30 minutes.

For patients who have a nasogastric tube in place, PREVACID Delayed can be opened and the intact granules mixed in 40 mL of apple juice and in nasogastric tube into the stomach. After administering the granules, the should be flushed with additional apple juice to clear the tube.

HOW SUPPLIED

PREVACID Delayed-Release Capsules, 15 mg, are opaque, hard gelatin, green with the TAP logo and "PREVACID 15" imprinted on the capsule opaque, hard gelatin, colored pink and black with the TAP logo and imprinted on the 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 protect

Store between 15°C and 30°C (59°F and 86°F).

℞ only

U.S. Patent Nos. 4,628,098; 4,689,333; 5,013,743; 5,026,560 and 5,045,32

Manufactured for
TAP Pharmaceuticals Inc.
Deerfield, Illinois 60015-1595 U.S.A.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-406/S024

MEDICAL REVIEW(S)

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

NDA:	20-406, SLR-024
SPONSOR:	TAP Holdings Inc. 2355 Waukegan Road, Deerfield, IL 60015
DATE OF SUBMISSION:	9 January 1998
DATE OF RECEIPT:	12 January 1998
ASSIGNED FOR REVIEW:	22 January 1998
DRUG:	Lansoprazole (PREVACID®) delayed-release capsules;
ROUTE OF ADMINISTRATION:	Oral, 15 or 30 mg once daily before eating, for up to a year, (several approved indications for healing and maintenance of healing of duodenal ulcers or erosive esophagitis, gastric ulcer healing, acid hypersecretory conditions, eradication of Helicobacter pylori infections, treatment of heartburn).
PROPOSED LABEL CHANGES:	Substitute "blurred vision" for "amblyopia," and add new adverse reaction: "*Body as a Whole* - anaphylactoid-like reaction."
MATERIAL REVIEWED:	Supplemental application: correspondence, new draft labeling proposed change in labeling
REVIEWER:	John R. Senior, M.D./ 19 June 1998

I. Background and Introduction

Lansoprazole (PREVACID® Delayed-Release Capsules, pronounced pre'-va-sid, AG-1749, TAP Holdings Inc.), has been approved for a number of clinical indications, the first on 10 May 1995 for short-term, up to 4 weeks, treatment by oral dosage of 15 mg once daily before eating for healing of active duodenal ulcer; for doses of 30 mg once daily before eating for up to 8 weeks for healing of erosive esophagitis (plus an additional 8 weeks if not healed or recurrent); and for 60 or more mg/day indefinitely for the Zollinger-Ellison syndrome or other pathological hypersecretory conditions (divided doses are recommended for over 120 mg/day). Other approvals have been granted since then, for use of lansoprazole for maintenance of healing of

erosive esophagitis (as of 8 April 1995), maintenance of healing of duodenal ulcers, 17 April 1997;, healing of gastric ulcer, 8 May 1997; short-term treatment of symptoms of gastroesophageal reflux disease (GERD), 12 March 1998. In addition, lansoprazole was considered "approvable" on 11 May 1998 for eradication of gastric mucosal infection with Helicobacter pylori (Hp) when used along with amoxicillin and clarithromycin.

As a results of these approvals in the United States, and the registration of lansoprazole for treatment of these problems in most of the countries of the world, hundreds of thousands of people, now millions, have been taking the drug, some for periods of more than a year (exact figures not available), and spontaneous reports of adverse effects are accumulating. Among these that have not been previously specified in the ADVERSE REACTIONS section are "blurred vision" in the subsection on *Special Senses*, "anaphylactoid-like reaction" in the subsection on *Body as a Whole*, and pancreatitis in the subsection on *Digestive System*. Concern about these problems was expressed in a letter to the sponsor dated 9 October 1997 making mention of 10 reported cases of anaphylactic and anaphylactoid-type reactions, 4 reported cases of blurred vision, and 4 cases of pancreatitis. The sponsor's reply to that letter is the subject of this submission.

II. Sponsor's Proposed Labeling Changes

The letter of 9 January 1998 from the sponsor proposed that changes be made to the labeling in the ADVERSE REACTIONS section as follows:

1) Add, in subsection on *Body as a Whole*, "anaphylactoid-like reaction;"
2) Substitute "blurred vision" for "amblyopia" in the subsection on *Special Senses*;
3) No addition of "pancreatitis" in the subsection on *Digestive System*.

Justifications were provided in the letter from the sponsor for these proposed changes, in which it was agreed that addition of "anaphylactoid-like reactions" was appropriate, but argued that their analysis of the reported cases of pancreatitis suggested that alcohol abuse, history of chronic pancreatitis, use of other medications were more likely causes than lansoprazole. It was further submitted that the term "blurred vision" was more accurate to describe the symptoms reported as "eyes blurry," "blurry vision," and "blurred vision." They argued that "amblyopia" was a misleading term, in that it implies an event much broader in scope and more severe than the four cases reported.

Comment: Although the cases of acute pancreatitis reported may have been caused by something other than lansoprazole, which the sponsor claims to be the case, this problem will need to be watched carefully. For the moment, it may be reasonable to accept the sponsor's argument that it is not clearly a lansoprazole-induced complication. It is true that vast numbers of people do abuse alcohol, and that in the United States alcohol abuse is the leading cause of both acute and chronic pancreatitis. It will need to be determined if taking lansoprazole induces an increased risk above that in people not taking lansoprazole. This is admittedly very difficult to ascertain when only spontaneous reports are available. Pancreatitis was not noted in the preclinical

studies in animals (see pharmacology/toxicology review of NDA 20-406 by Dr. Y. Chopra, 9 January 1995, and medical review by Dr. H. Gallo-Torres, 15 September 1994)

With respect to the question of amblyopia vs blurred vision, it may be more likely that patients as well as physicians understand the latter term better than the rather pedantic, Greek-derived term "ambly-opia" that means dullness-vision/eye defect. The sponsor's suggestion to substitute the more common term is acceptable. However, it must be noted that a recent case of ***blindness*** *was reported to MedWatch by the sponsor initially on 2 April 1998. This occurred in a 64-year-old male* [redacted] *who experienced loss of vision in his left eye after a first dose of PREVACID 15 mg on 23 March, and then in the right eye after a second dose the following day. A follow-up report was received on 18 May, in which the sponsor reported that after the patient had been hospitalized 25-31 March for treatment with intravenous cortisone and subsequent oral cortisone 20 mg t.i.d., there was later improvement in vision but residual peripheral field loss. We shall initiate a search of the spontaneous adverse event reporting system to investigate all effects on visual function, minor or major, in patients taking lansoprazole. The question of proton-pump inhibitors on rare occasions causing vision problems has been raised before with respect to omeprazole in the German literature, although contested (see Leber Magen Darm 1995; 25:6-8, 39, 152-5).*

b(6)

III. Regulatory Recommendations

It is recommended that the labeling changes proposed by the sponsor be implemented at the next opportunity for printing and distribution of revised labeling. It is further recommended that the sponsor be asked to provide followup on the case of blindness initially reported in April of this year, and that a consultation request be forwarded to the Division of Pharmacovigilance and Epidemiology for a search of the adverse event reporting system database for all cases of visual disturbance in patients taking lansoprazole, as well as for cases of pancreatitis.

John R. Senior, M.D., Medical Officer date
Division of Gastrointestinal & Coagulation Drug Products

cc:
NDA 20-406, SLR-024
HFD-180
HFD-180/LTalarico
HFD-180/HGallo-Torres
HFD-180/JSenior
HFD-180/JChoudary
HFD-180/EDuffy
HFD-181/CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-406/S024

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Division of Gastrointestinal & Coagulation Drug Products

REGULATORY PROJECT MANAGER REVIEW

Application Number: NDA 20-406/SLR-024

Name of Drug: Prevacid (lansoprazole) Delayed-Release Capsules JUL 22 1998

Sponsor: TAP Holdings, Inc.

Material Reviewed

Submission Date(s): July 14, 1998

Receipt Date(s): July 15, 1998

Background and Summary Description: Supplement 024 provides for the following changes to the ADVERSE REACTIONS section of the package insert: addition of "anaphylactoid-like reaction" under the subheading *Body as a Whole*, and the substitution of "blurred vision" for "amblyopia" in the subheading, *Special Senses*.

This supplement was approved on June 23, 1998 with draft labeling (as submitted in the original supplement dated January 12, 1998). The sponsor has submitted final printed labeling (FPL) in response to the approval letter.

Review

The submitted FPL, identified as "03-4891-R11-Rev.June, 1998," was compared to the original draft labeling and is acceptable. The FPL also contains the changes approved in supplement 021 on July 20, 1998.

Conclusions

The FPL is acceptable and should be acknowledged and retained.

Maria Walsh 7/22/98

Maria R. Walsh, M.S.
Regulatory Project Manager

cc:
Original NDA 20-406/S-024
HFD-180/Div. Files
HFD-180/PM/M.Walsh
HFD-180/L.Talarico

final: M.Walsh 7/22/98
filename: 20406S24807.rev2.doc

PM REVIEW

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: NDA 20-406/SLR-024

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

Sponsor: TAP Holdings, Inc.

Material Reviewed

Submission Date(s): January 9, 1998

Receipt Date(s): January 12, 1998

Background and Summary Description: Supplement 024 provides for the following changes to the ADVERSE REACTIONS section of the package insert: Addition of "anaphylactoid-like reaction" under the subheading, *Body as a Whole* and the substitution of "blurred vision" for "amblyopia" under the subheading, *Special Senses*.

Review

The submitted draft labeling was compared to the currently approved labeling identified as "03-4837-R10-Rev. March, 1998" (approved March 12, 1998 in supplement 016). The following differences were noted.

1. ADVERSE REACTIONS:

   A. The term "anaphylactoid-like reaction" was added under the subheading, *Body as a Whole.*

   B. The term "blurred vision" was substituted for the term "amblyopia" under the subheading, *Special Senses.*

These revisions are recommended for approval per the Medical Officer's review dated June 19, 1998.

2. In addition, the revisions approved on March 12, 1998 in supplement 016 do not appear in the draft labeling. These revisions include addition of the term "speech disorder" under the subheading, *Special Senses*, and the term "urinary retention" under the subheading, *Urogenital System* under the ADVERSE REACTIONS section; and revisions to the CLINICAL STUDIES, INDICATIONS, and DOSAGE AND ADMINISTRATION which reflect the addition of a new indication for symptomatic gastroesophageal reflux disease (GERD).

These revisions were approved on March 12, 1998 in supplement 016 and must appear in the final printed labeling (FPL) to be submitted for this supplement.

Conclusions

1. The labeling revisions proposed in this supplement have been recommended for approval by the Medical Officer (see Medical Officer review dated June 19, 1998).

2. The labeling revisions approved on March 12, 1998 in supplement 016 must be included in the FPL to be submitted for this supplement.

Maria R. Walsh, M.S.
Regulatory Project Manager

cc:
Original NDA 20-406/S-024
HFD-180/Div. Files
HFD-180/M.Walsh

final: M.Walsh 6/23/98
filename: 20406S24-rev806.doc

CSO REVIEW

87.1

NDA 20-406/S-024

JUL 23 1998

TAP Holdings, Inc.
Attention: Gary C. Magistrelli, Ph.D.
2355 Waukegan Road
Deerfield, IL 60015

Dear Dr. Magistrelli:

We acknowledge the receipt of your July 14, 1998 submission containing final printed labeling in response to our June 23, 1998 letter approving your supplemental new drug application for Prevacid (lansoprazole) Delayed-Release Capsules.

We have reviewed the labeling that you submitted in accordance with our June 23, 1998 letter, and we find it acceptable.

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

Sincerely,

LT 7-22-98

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

cc:
Archival NDA 20-406/S-024
HFD-180/Div. Files
HFD-180/M.Walsh
HF-2/Medwatch (with labeling)
HFD-103/ADRA (with labeling)
HFD-40/DDMAC (with labeling)
HFD-95/DDMS (with labeling)
HFD-613/OGD (with labeling)
HFD-735/OPDRA (with labeling)
DISTRICT OFFICE

final: M.Walsh 7/22/98
filename: 20406S24807.A&R.doc

ACKNOWLEDGE AND RETAIN (AR)

TAP HOLDINGS INC.
parent of TAP Pharmaceuticals Inc.

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

ORIGINAL

July 14, 1998

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

Attn: Lilia Talarico, M.D.
Director

RE: PREVACID® (lansoprazole) Delayed-Release Capsules
Addition/Substitution to the ADVERSE REACTIONS Section
FPL for Approved Supplement NDA 20-406/S-024

Dear Dr. Talarico:

TAP Holdings submits this Final Printed Labeling (FPL) to the supplemental new drug application for PREVACID.

Reference is made to the Agency's letter dated June 23, 1998, which stated that this supplemental application was approved. Enclosed are 20 copies of the final printed labeling, ten of which are individually mounted on heavy-weight paper.

Please do not hesitate to contact me at the number listed below should additional information be needed.

Sincerely,

Gary C. Magistrelli, Ph.D.
Associate Director, Regulatory Affairs
Phone: (847) 267-4961
Fax: (847) 317-5795