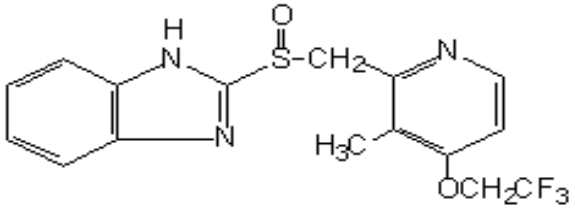
(Nos. 1541, 3046, 7309, 7311)
TAP DN038-V2- Rev. Month, Year

PREVACID®
(lansoprazole)
Delayed-Release Capsules

PREVACID®
(lansoprazole)
For Delayed-Release Oral Suspension

DESCRIPTION

The active ingredient in PREVACID (lansoprazole) Delayed-Release Capsules and PREVACID (lansoprazole) for Delayed-Release Oral Suspension 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 rate of degradation of the compound in aqueous solution increases with decreasing pH. The degradation half-life of the drug substance in aqueous solution at 25°C 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 and in a packet for delayed-release oral suspension.

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 for Delayed-Release Oral Suspension is composed of the active ingredient, lansoprazole, in the form of enteric-coated granules and also contains inactive granules. The packets contain lansoprazole granules which are identical to those contained in PREVACID Delayed-Release Capsules and are available in 15 mg and 30 mg strengths. Inactive granules are composed of the following

ingredients: confectioner's sugar, mannitol, docusate sodium, ferric oxide, colloidal silicon dioxide, xanthan gum, crospovidone, citric acid, sodium citrate, magnesium stearate, and artificial strawberry flavor. The lansoprazole granules and inactive granules, present in unit dose packets, are constituted with water to form a suspension and consumed orally.

* PREVACID 15-mg capsules only.

CLINICAL PHARMACOLOGY

Pharmacokinetics and Metabolism

PREVACID Delayed-Release Capsules and PREVACID for Delayed-Release Oral Suspension 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 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 were studied in pediatric patients with GERD aged 1 to 11 years, with lansoprazole doses of 15 mg q.d. for subjects weighing ≤ 30 kg and 30 mg q.d. for subjects weighing > 30 kg. Lansoprazole pharmacokinetics in these pediatric patients were similar to that observed in healthy adult subjects. The mean C_{max} and AUC values were similar between the two dose groups and were not affected by weight or age within each weight- adjusted dose group used in this study.

Gender

In a study comparing 12 male and 6 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 that included lansoprazole 15 and 30 mg for five days, the following effects on intragastric pH were noted:

Mean Antisecretory Effects After Single and Multiple Daily Dosing

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

NOTE: An intragastric pH of >4 reflects a reduction in gastric acid by 99%.
[*](p<0.05) versus baseline and lansoprazole 15 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 and 2-3 hours with lansoprazole 15 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.

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

Other Gastric Effects in Humans

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

Serum Gastrin Effects

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

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	
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 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 ($1 \times 10^7 - 1 \times 10^8$ 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 µg/mL
H. pylori ATCC 43504	Amoxicillin	0.015-0.12 µg/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
Week	15 mg q.d. (N=68)	30 mg q.d. (N=74)	60 mg q.d. (N=70)	(N=72)
2	42.4%*	35.6%*	39.1%*	11.3%
4	89.4%*	91.7%*	89.9%*	46.1%

* ($p \leq 0.001$) 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
Week	15 mg q.d. (N=80)	30 mg q.d. (N=77)	300 mg h.s. (N=82)	(N=41)
2	35.0%	44.2%	30.5%	34.2%
4	92.3%**	80.3%*	70.5%*	47.5%

* ($p \leq 0.05$) versus placebo.
** ($p \leq 0.05$) 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 that the 10-day triple therapy was equivalent to the 14-day triple therapy in eradicating *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 Analysis#
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* infection at baseline defined as at least two of three positive endoscopic tests from CLOtest®, 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 were 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 above and had a confirmed duodenal ulcer (active or within one year). All dropouts were included as failures of therapy.

† ($p<0.05$) 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) in the 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* infection at baseline defined as at least two of three positive endoscopic tests from CLOtest®, 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 were included in the analysis as failures of therapy.

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

† ($p<0.05$) 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 independent, double-blind, multicenter, controlled trials were conducted in patients with endoscopically confirmed healed duodenal ulcers. Patients remained healed significantly longer and the number of recurrences of duodenal ulcers was significantly less in patients treated with PREVACID than in patients treated with placebo over a 12-month period.

Endoscopic Remission Rates

Trial	Drug	No. of Pts.	Percent in Endoscopic Remission		
			0-3 mo.	0-6 mo.	0-12 mo.
#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
* ($p \leq 0.001$) 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
Week	15 mg q.d. (N=65)	30 mg q.d. (N=63)	60 mg q.d. (N=61)	(N=64)
4	64.6%*	58.1%*	53.3%*	37.5%
8	92.2%*	96.8%*	93.2%*	76.7%

* ($p \leq 0.05$) 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.

Healing of NSAID-Associated Gastric Ulcer

In two U.S. and Canadian multicenter, double-blind, active-controlled studies in patients with endoscopically confirmed NSAID-associated gastric ulcer who continued their NSAID use, the percentage of patients healed after 8 weeks was statistically significantly higher with 30 mg of PREVACID than with the active control. A total of 711 patients were enrolled in the study, and 701 patients were treated. Patients ranged in age from 18 to 88 years (median age 59 years), with 67% female patients and 33% male patients. Race was distributed as follows: 87% Caucasian, 8% Black, 5% other. There was no statistically significant difference between PREVACID 30 mg q.d. and the active control on symptom relief (i.e., abdominal pain).

NSAID-Associated Gastric Ulcer Healing Rates [1]		
Study #1		
	PREVACID 30 mg q.d.	Active Control [2]
Week 4	60% (53/88) [3]	28% (23/83)
Week 8	79% (62/79) [3]	55% (41/74)
Study #2		
	PREVACID 30 mg q.d.	Active Control [2]
Week 4	53% (40/75)	38% (31/82)
Week 8	77% (47/61) [3]	50% (33/66)

[1] Actual observed ulcer(s) healed at time points ± 2 days

[2] Dose for healing of gastric ulcer

[3] ($p \leq 0.05$) versus the active control

Risk Reduction of NSAID-Associated Gastric Ulcer

In one large U.S., multicenter, double-blind, placebo- and misoprostol-controlled (misoprostol blinded only to the endoscopist) study in patients who required chronic use of an NSAID and who had a history of an endoscopically documented gastric ulcer, the proportion of patients remaining free from gastric ulcer at 4, 8, and 12 weeks was significantly higher with 15 or 30 mg of PREVACID than placebo. A total of 537 patients were enrolled in the study, and 535 patients were treated. Patients ranged in age from 23 to 89 years (median age 60 years), with 65% female patients and 35% male patients. Race was distributed as follows: 90% Caucasian, 6% Black, 4% other. The 30 mg dose of PREVACID demonstrated no additional benefit in risk reduction of the NSAID-associated gastric ulcer than the 15 mg dose.

NSAID-Associated Gastric Ulcer Risk Reduction Rates				
% of Patients Remaining Gastric Ulcer-Free [1]				
Week	PREVACID 15 mg q.d. (N=121)	PREVACID 30 mg q.d. (N=116)	Misoprostol 200 µg q.i.d. (N=106)	Placebo (N=112)
4	90%	92%	96%	66%
8	86%	88%	95%	60%
12	80%	82%	93%	51%

[1] % = Life Table Estimate

($p<0.001$) PREVACID 15 mg q.d. versus placebo; PREVACID 30 mg q.d. versus placebo; and misoprostol 200 µg q.i.d. versus placebo.

($p<0.05$) Misoprostol 200 µg q.i.d. versus PREVACID 15 mg q.d.; and misoprostol 200 µg q.i.d. versus PREVACID 30 mg q.d.

Gastroesophageal Reflux Disease (GERD)

Symptomatic GERD

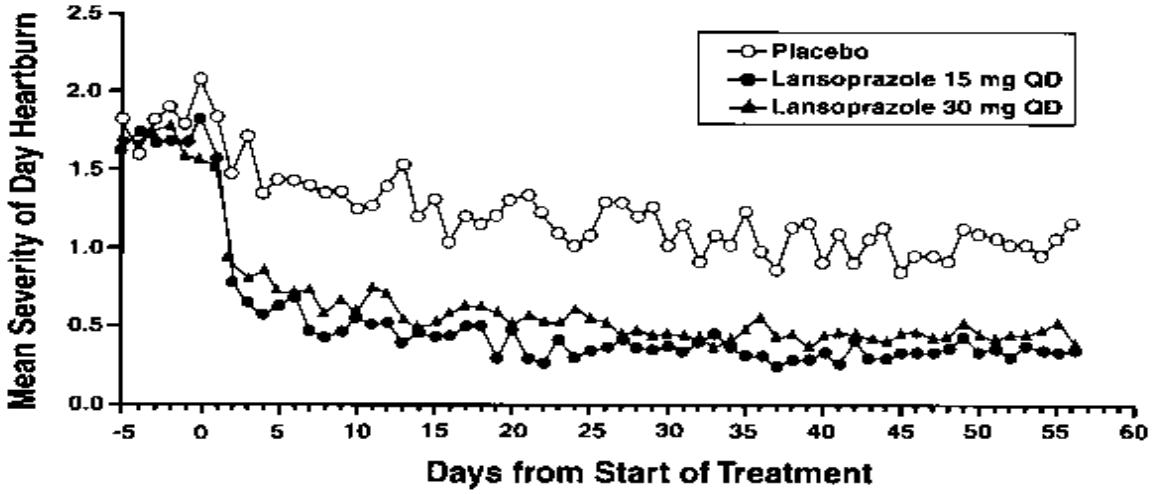
In a U.S. multicenter, double-blind, placebo-controlled study of 214 patients with frequent GERD symptoms, but no esophageal erosions by endoscopy, significantly greater relief of heartburn associated with GERD was observed with the administration of lansoprazole 15 mg once daily up to 8 weeks than with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

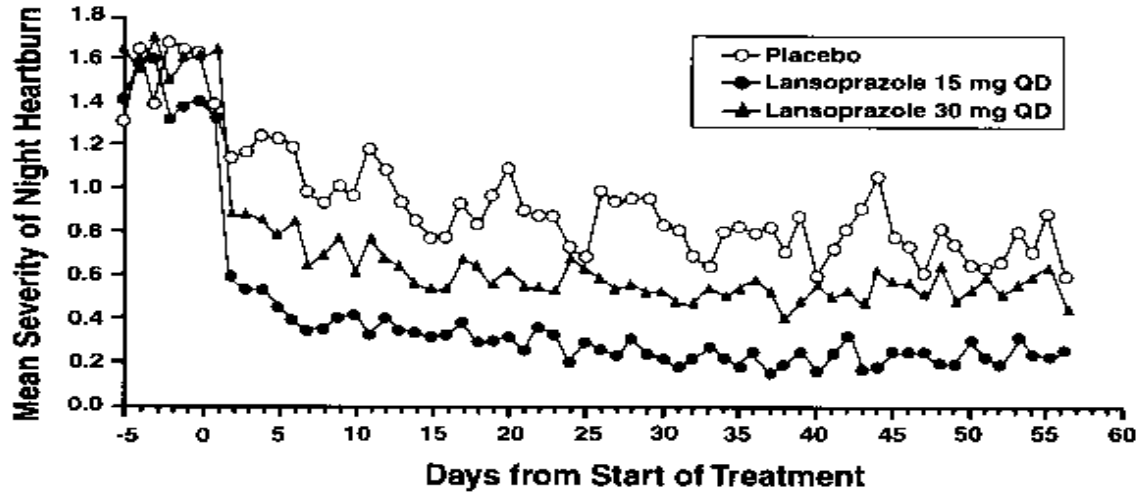
Frequency of Heartburn			
Variable	Placebo (n=43)	PREVACID 15 mg (n=80)	PREVACID 30 mg (n=86)
	Median		
% of Days without Heartburn			
Week 1	0%	71%*	46%*
Week 4	11%	81%*	76%*
Week 8	13%	84%*	82%*
% of Nights without Heartburn			
Week 1	17%	86%*	57%*
Week 4	25%	89%*	73%*
Week 8	36%	92%*	80%*

* ($p<0.01$) 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)



In two U.S., multicenter double-blind, ranitidine-controlled studies of 925 total patients with frequent GERD symptoms, but no esophageal erosions by endoscopy, lansoprazole 15 mg was superior to ranitidine 150 mg (b.i.d.) in decreasing the frequency and severity of day and night heartburn associated with GERD for the 8-week treatment period. No significant additional benefit from lansoprazole 30 mg once daily was observed.

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:

Erosive Esophagitis Healing Rates

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

* ($p \leq 0.001$) versus placebo.
** ($p \leq 0.05$) 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%

* ($p \leq 0.001$) 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%

* ($p \leq 0.001$) 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

			Percent in Endoscopic Remission		
Trial	Drug	No. of Pts.	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
* ($p \leq 0.001$) versus placebo.

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

In a U.S., randomized, double-blind, study, PREVACID 15 mg q.d. (n = 100) was compared with ranitidine 150 mg b.i.d (n = 106), at the recommended dosage, in patients with endoscopically-proven healed erosive esophagitis over a 12-month period. Treatment with PREVACID resulted in patients remaining healed (Grade 0 lesions) of erosive esophagitis for significantly longer periods of time than those treated with ranitidine ($p<0.001$). In addition, PREVACID was significantly more effective than ranitidine in providing complete relief of both daytime and nighttime heartburn. Patients treated with PREVACID remained asymptomatic for a significantly longer period of time than patients treated with ranitidine.

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

PREVACID Delayed-Release Capsules and PREVACID for Delayed-Release Oral Suspension are indicated for:

Short-Term Treatment of Active Duodenal Ulcer

PREVACID is 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 in combination with amoxicillin plus clarithromycin as triple therapy, is 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 in combination with amoxicillin as dual therapy, is 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 is indicated to maintain healing of duodenal ulcers. Controlled studies do not extend beyond 12 months.

Short-Term Treatment of Active Benign Gastric Ulcer

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

Healing of NSAID-Associated Gastric Ulcer

PREVACID IS INDICATED FOR THE TREATMENT OF NSAID-ASSOCIATED GASTRIC ULCER IN PATIENTS WHO CONTINUE NSAID USE. CONTROLLED STUDIES DID NOT EXTEND BEYOND 8 WEEKS.

Risk Reduction of NSAID-Associated Gastric Ulcer

PREVACID is indicated for reducing the risk of NSAID-associated gastric ulcers in patients with a history of a documented gastric ulcer who require the use of an NSAID. Controlled studies did not extend beyond 12 weeks.

Gastroesophageal Reflux Disease (GERD)

Short-Term Treatment of Symptomatic GERD

PREVACID is indicated for the treatment of heartburn and other symptoms associated with GERD.

Short-Term Treatment of Erosive Esophagitis

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

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

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

Maintenance of Healing of Erosive Esophagitis

PREVACID is indicated to maintain healing of erosive esophagitis. Controlled studies did not extend beyond 12 months.

Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome

PREVACID is indicated for the long-term treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome.

CONTRAINDICATIONS

PREVACID Delayed-Release Capsules and PREVACID for Delayed-Release Oral Suspension are contraindicated in patients with known hypersensitivity to any component of the formulations.

Amoxicillin is contraindicated in patients with a known hypersensitivity to any penicillin. (Please refer to full prescribing information for amoxicillin before prescribing.)

Clarithromycin is contraindicated in patients with a known hypersensitivity to any macrolide antibiotic, and in patients receiving terfenadine therapy who have preexisting cardiac abnormalities or electrolyte disturbances. (Please refer to full prescribing information for clarithromycin before prescribing.)

WARNINGS

CLARITHROMYCIN SHOULD NOT BE USED IN PREGNANT WOMEN EXCEPT IN CLINICAL CIRCUMSTANCES WHERE NO ALTERNATIVE THERAPY IS APPROPRIATE. IF PREGNANCY OCCURS WHILE TAKING CLARITHROMYCIN, THE PATIENT SHOULD BE APPRISED OF THE POTENTIAL HAZARD TO THE FETUS. (SEE **WARNINGS** IN PRESCRIBING INFORMATION FOR CLARITHROMYCIN.)

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including clarithromycin and amoxicillin, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy. These reactions are more apt to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens.

There have been well-documented reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before initiating therapy with any penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, amoxicillin should be discontinued and the appropriate 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 and PREVACID for Delayed-Release Oral Suspension should be taken before eating.

Alternative Administration Options

PREVACID Delayed-Release Capsules

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 either applesauce, ENSURE® pudding, cottage cheese, yogurt, or strained pears and swallowed immediately. The granules should not be chewed or crushed. Alternatively, PREVACID Delayed-Release Capsules may be emptied into a small volume of either orange juice or tomato juice (60 mL – approximately 2 ounces), mixed briefly and swallowed immediately. To insure complete delivery of the dose, the glass should be rinsed with two or more volumes of juice and the contents swallowed immediately. USE IN OTHER FOODS AND LIQUIDS HAS NOT BEEN STUDIED CLINICALLY AND IS THEREFORE NOT RECOMMENDED.

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.

PREVACID for Delayed-Release Oral Suspension
In addition, for patients who have difficulty swallowing capsules, PREVACID for Delayed-Release Oral Suspension is available in strengths of 15 mg and 30 mg. Directions for use: Empty packet contents into a container containing 2 tablespoons of **WATER.** DO NOT USE OTHER LIQUIDS OR FOODS. Stir well, and drink immediately. DO NOT CRUSH OR CHEW THE GRANULES. If any material remains after drinking, add more water, stir, and drink immediately.

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, or clarithromycin 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.

In a study of healthy subjects neither the pharmacokinetics of warfarin enantiomers nor prothrombin time were affected following single or multiple 60mg doses of lansoprazole. However, there have been reports of increased INR and prothrombin time in patients receiving proton pump inhibitors, including lansoprazole, and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with proton pump inhibitors and warfarin may need to be monitored for increases in INR and prothrombin time.

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

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

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

Carcinogenesis, Mutagenesis, 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.

Pregnancy Category C

Clarithromycin

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

The safety and effectiveness of PREVACID have been established in the age group 1 year to 11 years for short-term treatment of symptomatic GERD and erosive esophagitis. Safety and effectiveness have not been established in patients < 1 year or 12-17 years of age.

Use of PREVACID in the age group 1 year to 11 years is supported by evidence from adequate and well controlled studies of PREVACID in adults with additional clinical, pharmacokinetic, pharmacodynamic, and safety studies performed in pediatric patients.

In an uncontrolled, open label, U.S. multicenter study, 66 pediatric patients (1 to 11 years of age) with GERD were assigned, based on body weight, to receive an initial dose of either PREVACID 15 mg q.d. if ≤ 30 kg or PREVACID 30 mg q.d. if > 30 kg administered for 8 to 12 weeks. The PREVACID dose was increased (up to 30 mg b.i.d.) in 24 of 66 pediatric patients after 2 or more weeks of treatment if they remained symptomatic. At baseline 85% of patients had mild to moderate overall GERD symptoms (assessed by investigator interview), 58% had non-erosive GERD and 42% had erosive esophagitis (assessed by endoscopy).

After 8 to 12 weeks of PREVACID treatment, the intent-to-treat analysis demonstrated an approximate 50% reduction in frequency and severity of GERD symptoms.

Twenty-one of 27 erosive esophagitis patients were healed at 8 weeks and 100% of patients were healed at 12 weeks by endoscopy.

GERD	**Final Visit**[a] % (n/N)
Symptomatic GERD Improvement in Overall GERD Symptoms[b]	76% (47/62 [c])
Erosive Esophagitis Improvement in Overall GERD Symptoms[b] Healing Rate	81% (22/27) 100% (27/27)

[a] At Week 8 or Week 12
[b] Symptoms assessed by patients diary kept by caregiver.
[c] No data were available for 4 pediatric patients

In a study of 66 pediatric patients in the age group 1 year to 11 years old after treatment with PREVACID given orally in doses of 15mg q.d. to 30mg b.i.d., increases in serum gastrin levels were similar to those observed in adult studies. Median fasting serum gastrin levels increased 89% from 51 pg/ml at baseline to 97 pg/ml [interquartile range (25^{th}-75^{th} percentile) of 71-130 pg/ml] at the final visit.

The pediatric safety of PREVACID Delayed-Release Capsules has been assessed in 66 pediatric patients aged 1 to 11 years of age. Of the 66 patients with GERD 85% (56/66) took lansoprazole for 8 weeks and 15% (10/66) took it for 12 weeks.

The adverse event profile in these pediatric patients resembled that of adults taking lansoprazole. The most frequently reported (2 or more patients) treatment-related adverse events in patients 1 to 11 years of age (N=66) were constipation (5%) and headache (3%). There were no adverse events reported in this U.S. clinical study that were not previously observed in adults.

Use in Women

Over 4,000 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

Clinical

Worldwide, over 10,000 patients have been treated with lansoprazole in Phase 2-3 clinical trials involving various dosages and durations of treatment. The adverse reaction profiles for PREVACID Delayed-Release Capsules and PREVACID for Delayed-Release Oral Suspension are similar. 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= 2768) %	Placebo (N= 1023) %
Body as a Whole		
Abdominal Pain	2.1	1.2
Digestive System		
Constipation	1.0	0.4
Diarrhea	3.8	2.3
Nausea	1.3	1.2

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.

In the risk reduction study of PREVACID for NSAID-associated gastric ulcers, the incidence of diarrhea for patients treated with PREVACID was 5%, misoprostol 22%, and placebo 3%.

Additional adverse experiences occurring in <1% of patients or subjects in domestic trials are shown below. Refer to **Postmarketing** for adverse reactions occurring since the drug was marketed.

Body as a Whole – abdomen enlarged, allergic reaction, asthenia, back pain, candidiasis, carcinoma, chest pain (not otherwise specified), chills, edema, fever, flu syndrome, halitosis, infection (not otherwise specified), malaise, neck pain, neck rigidity, pain, pelvic pain; *Cardiovascular System* - angina, arrhythmia, bradycardia, cerebrovascular accident/cerebral infarction, hypertension/hypotension, migraine, myocardial infarction, palpitations, shock (circulatory failure), syncope, tachycardia, vasodilation; *Digestive System* – abnormal stools, anorexia, bezoar, cardiospasm, cholelithiasis, colitis, dry mouth, dyspepsia, dysphagia, enteritis, eructation, esophageal stenosis, esophageal ulcer, esophagitis, fecal discoloration, flatulence, gastric nodules/fundic gland polyps, gastritis, gastroenteritis, gastrointestinal anomaly, gastrointestinal disorder, gastrointestinal hemorrhage, glossitis, gum hemorrhage, hematemesis, increased appetite, increased salivation, melena, mouth ulceration, nausea and vomiting, nausea and vomiting and diarrhea, oral moniliasis, rectal disorder, rectal hemorrhage, stomatitis, tenesmus, thirst, tongue disorder, ulcerative colitis, ulcerative stomatitis; *Endocrine System* - diabetes mellitus, goiter, hypothyroidism; *Hemic and Lymphatic System* - anemia, hemolysis, lymphadenopathy; *Metabolic and Nutritional Disorders* - gout, dehydration, hyperglycemia/hypoglycemia, peripheral edema, weight gain/loss; *Musculoskeletal System* - arthralgia, arthritis, bone disorder, joint disorder, leg cramps, musculoskeletal pain, myalgia, myasthenia, synovitis; *Nervous System* – abnormal dreams, agitation, amnesia, anxiety, apathy, confusion, convulsion, depersonalization, depression, diplopia, dizziness, emotional lability, hallucinations, hemiplegia, hostility aggravated, hyperkinesia, hypertonia, hypesthesia, insomnia, libido decreased/increased, nervousness, neurosis, paresthesia, sleep disorder, somnolence, thinking abnormality, tremor, vertigo; *Respiratory System* - asthma, bronchitis, cough increased, dyspnea, epistaxis, hemoptysis, hiccup, laryngeal neoplasia, pharyngitis, pleural disorder, pneumonia, respiratory disorder, upper respiratory inflammation/infection, rhinitis, sinusitis, stridor; *Skin and Appendages* - acne, alopecia, contact dermatitis, dry skin, fixed eruption, hair disorder, maculopapular rash, nail disorder, pruritus, rash, skin carcinoma, skin disorder, sweating, urticaria; *Special Senses* – abnormal vision, blurred vision, conjunctivitis, deafness, dry eyes, ear disorder, eye pain, otitis media, parosmia, photophobia, retinal degeneration, taste loss, taste perversion, tinnitus, visual field defect; *Urogenital System* - abnormal menses, breast enlargement, breast pain, breast tenderness, dysmenorrhea, dysuria, gynecomastia, impotence, kidney calculus, kidney pain, leukorrhea, menorrhagia, menstrual disorder, penis disorder, polyuria, testis disorder, urethral pain, urinary frequency, urinary tract infection, urinary urgency, urination impaired, vaginitis.

Postmarketing

On-going Safety Surveillance: Additional adverse experiences have been reported since lansoprazole has been marketed. The majority of these cases are foreign-sourced and a relationship to lansoprazole has not been established. Because these events were reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events are listed below by COSTART body system.

Body as a Whole - anaphylactoid-like reaction; *Digestive System* - hepatotoxicity, vomiting; *Hemic and Lymphatic System* - agranulocytosis, aplastic anemia, hemolytic anemia, leukopenia, neutropenia, pancytopenia, thrombocytopenia, and thrombotic thrombocytopenic purpura; *Special Senses* - speech disorder; *Urogenital System* - urinary retention.

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.

Triple Therapy: PREVACID/amoxicillin/clarithromycin

The most frequently reported adverse events for patients who received triple therapy for 14 days were diarrhea (7%), headache (6%), and taste perversion (5%). There were no statistically significant differences in the frequency of reported adverse events between the 10- and 14-day triple therapy regimens. No treatment-emergent adverse events were observed at significantly higher rates with triple therapy than with any dual therapy regimen.

Dual Therapy: PREVACID/amoxicillin

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

For more information on adverse reactions with amoxicillin or clarithromycin, refer to their package inserts, **ADVERSE REACTIONS** sections.

Laboratory Values

The following changes in laboratory parameters for lansoprazole were reported as adverse events:
Abnormal liver function tests, increased SGOT (AST), increased SGPT (ALT), increased creatinine, increased alkaline phosphatase, increased globulins, increased GGTP, increased/decreased/abnormal WBC, abnormal AG ratio, abnormal RBC, bilirubinemia, eosinophilia, hyperlipemia, increased/decreased electrolytes, increased/decreased cholesterol, increased glucocorticoids, increased LDH, increased/decreased/abnormal platelets, and increased gastrin levels. Urine abnormalities such as albuminuria, glycosuria, and hematuria were also reported. Additional isolated laboratory abnormalities were reported.

In the placebo controlled studies, when SGOT (AST) and SGPT (ALT) were evaluated, 0.4% (4/978) placebo patients and 0.4% (11/2677) lansoprazole patients had enzyme elevations greater than three times the upper limit of normal range at the final treatment visit. None of these lansoprazole patients reported jaundice at any time during the study.

In clinical trials using combination therapy with PREVACID plus amoxicillin and clarithromycin, and PREVACID plus amoxicillin, no increased laboratory abnormalities particular to these drug combinations were observed.

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

OVERDOSAGE

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

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

DOSAGE AND ADMINISTRATION

Indication	Dose	Frequency
Duodenal Ulcers		
Short-Term Treatment	15 mg	Once daily for 4 weeks
Maintenance of Healed	15 mg	Once daily
***H. pylori* Eradication to Reduce the Risk of Duodenal Ulcer Recurrence**		
Triple Therapy:		
PREVACID	30 mg	Twice daily (q12h) for 10 or 14 days
Amoxicillin	1 gram	Twice daily (q12h) for 10 or 14 days
Clarithromycin	500 mg	Twice daily (q12h) for 10 or 14 days
Dual Therapy:		
PREVACID	30 mg	Three times daily (q8h) for 14 days
Amoxicillin	1 gram	Three times daily (q8h) for 14 days
Benign Gastric Ulcer		
Short-Term Treatment	30 mg	Once daily for up to 8 weeks
NSAID-associated Gastric Ulcer		
Healing	30 mg	Once daily for up to 8 weeks*
Risk Reduction	15 mg	Once daily for up to 12 weeks*
Gastroesophageal Reflux Disease (GERD)		
Short-Term Treatment of Symptomatic GERD	15 mg	Once daily for up to 8 weeks
Short –Term Treatment of Erosive Esophagitis	30 mg	Once daily for up to 8 weeks**
Pediatric (short-term treatment of symptomatic GERD, short-term treatment of erosive esophagitis)(1 – 11 years of age)		Once daily for up to 12 weeks+
≤ 30 kg	15 mg	
> 30 kg	30 mg	
Maintenance of Healing of Erosive Esophagitis	15 mg	Once daily
Zollinger-Ellison Syndrome (and other Pathological hypersecretory condition)	60 mg	Once daily***

NOTE: Additional information is available in CLINICAL STUDIES and/or INDICATIONS AND USAGE.

* Controlled studies did not extend beyond indicated duration.

** For patients who do not heal with PREVACID for 8 weeks (5–10%), it may be helpful to give an additional 8 weeks of treatment. If there is a recurrence of erosive esophagitis an additional 8 week course of PREVACID may be considered.

*** Dosages up to 90 mg b.i.d. have been administered. Daily dosage of greater than 120 mg should be administered in divided doses.

+ The PREVACID dose was increased (up to 30 mg B.I.D.) in some pediatric patients after 2 or more weeks of treatment if they remained symptomatic. For pediatric patients unable to swallow an intact capsule please see **Alternative Administration Options**.

Alternative Administration Options

PREVACID Delayed-Release Capsules

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 either applesauce, ENSURE® pudding, cottage cheese, yogurt, or strained pears and swallowed immediately. The granules should not be chewed or crushed. Alternatively, PREVACID Delayed-Release Capsules may be emptied into a small volume of either orange juice or tomato juice (60 mL – approximately 2 ounces), mixed briefly and swallowed immediately. To insure complete delivery of the dose, the glass should be rinsed with two or more volumes of juice and the contents swallowed immediately. USE IN OTHER FOODS AND LIQUIDS HAS NOT BEEN STUDIED CLINICALLY AND IS THEREFORE NOT RECOMMENDED.

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.

PREVACID for Delayed-Release Oral Suspension

In addition, for patients who have difficulty swallowing capsules, PREVACID for Delayed-Release Oral Suspension is available in strengths of 15 mg and 30 mg. Directions for use: Empty packet contents into a container containing 2 tablespoons of **WATER.** DO NOT USE OTHER LIQUIDS OR FOODS. Stir well, and drink immediately. DO NOT CRUSH OR CHEW THE GRANULES. If any material remains after drinking, add more water, stir, and drink immediately.

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 capsules 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 0300-1541-19 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

PREVACID for Delayed-Release Oral Suspension contains white to pale brownish lansoprazole granules and inactive pink granules in a unit dose packet. They are available as follows:

NDC 0300-7309-30 Unit dose carton of 30: 15-mg packets

NDC 0300-7311-30 Unit dose carton of 30: 30-mg packets

Storage: Store between 15°C and 30°C (59°F and 86°F). Store in a tight container protected from moisture.

R_x only

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TAP Pharmaceuticals Inc.
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Osaka, Japan 541

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/s/

Victor Raczkowski
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