

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER: 20-406/ S030 & 027**

**APPROVAL LETTER**

NDA 20-406/S-027

JAN 14 1999

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

Dear Dr. Magistrelli:

Please refer to your supplemental new drug application dated February 5, 1998, received February 6, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prevacid (lansoprazole) Delayed-Release Capsules.

We acknowledge receipt of your submission dated November 13, 1998.

This supplemental new drug application provides for revisions to the PRECAUTIONS and DOSAGE AND ADMINISTRATION sections of the package insert to allow administration of the intact granules on pudding, cottage cheese, or yogurt.

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 February 4, 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 recently approved labeling 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-027." Approval of this submission by FDA is not required before the labeling is used.

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

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

If a letter communicating important information about this drug product (i.e., a "Dear Health Care 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., Regulatory Project Manager, at (301) 443-8017.

Sincerely,

/s/ 1-14-99

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

APPEARS THIS WAY  
ON ORIGINAL

NDA 20-406/S-030

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

FEB 22 1999

Dear Dr. Magistrelli:

Please refer to your supplemental new drug application dated June 5, 1998, received June 8, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prevacid (lansoprazole) Delayed-Release Capsules.

We acknowledge receipt of your submission dated February 17, 1999, containing final printed labeling in response to our December 16, 1998 approvable letter.

This supplemental new drug application provides for revisions to the PRECAUTIONS and DOSAGE AND ADMINISTRATION section of the package insert to add statements about sprinkling the granules on strained pears and mixing the granules in orange or tomato juice.

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 submitted final printed labeling (package insert submitted February 16, 1999). Accordingly, the supplemental application is approved effective on the date of this letter.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care 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., Regulatory Project Manager, at (301) 443-8017.

NDA 20-406/S-030

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Sincerely,

/S/ 2-22-99

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-030

HFD-180/Div. Files

HFD-180/PM/M. Walsh

HFD-180/H. Gallo-Torres

HF-2/Med Watch (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 2/22/99

filename: \_\_\_\_\_

APPROVAL (AP)

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ON ORIGINAL

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER: 20-406/ S030 & 027**

**APPROVABLE LETTER**

NDA 20-406/S-030

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

DEC 16 1998

Dear Dr. Magistrelli:

Please refer to your supplemental new drug application dated June 5, 1998, received June 8, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prevacid (lansoprazole) Delayed-Release Capsules.

This supplement proposes the following change(s): Revisions to the PRECAUTIONS and DOSAGE AND ADMINISTRATION section of the package insert to add statements about sprinkling the granules on strained pears and mixing the granules in orange or tomato juice.

We have completed the review of this application and it is approvable. Before this application may be approved, however, it will be necessary for you to submit final printed labeling revised as follows:

Under DOSAGE AND ADMINISTRATION:

1. The following text should be moved to the end of this section. We believe that information regarding the administration of the intact capsules should precede information regarding alternative oral administration.

---

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 or strained pears and swallowed immediately. The granules should not be crushed or chewed. Alternatively, PREVACID Delayed-Release Capsules may be emptied into a small volume of either orange juice or tomato juice (60 mL), 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.

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.

2. A subheader, such as "Alternative \_\_\_\_\_" may be added to this section to separate the information regarding the administration of the intact capsules from that of the granules. The subheader should precede the sentence beginning, "For patients who have difficulty swallowing capsules..."

In addition, all previous revisions as reflected in the most-recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

Please submit 20 copies of the final printed labeling ten of which are individually mounted on heavy weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

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

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

- Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these change prior to approval of this supplemental application.

If you have any questions, contact Maria R. Walsh, M.S., Regulatory Project Manager, at (301) 443-8017.

**APPEARS THIS WAY  
ON ORIGINAL**

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Sincerely,

*/S/ 12-15-98*

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-030

HFD-180/Div. Files

HFD-180/PM/M. Walsh

HFD-95/DDMS

DISTRICT OFFICE

Drafted by: M. Walsh 12/9/98

Initialed by: L. Talarico 12/15/98

Revised: M. Walsh 12/15/98

final: M. Walsh 12/15/98

filename: \_\_\_\_\_

APPROVABLE (AE)

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ON ORIGINAL**

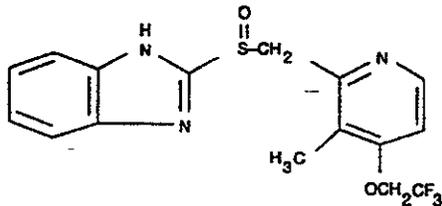
**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER: 20-406/ S030 & 027**

**FINAL PRINTED LABELING**

## DESCRIPTION

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



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

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

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

\* PREVACID 15-mg capsules only.

## CLINICAL PHARMACOLOGY

### Pharmacokinetics and Metabolism

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

### Absorption

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

### Distribution

Lansoprazole is 97% bound to plasma proteins. Plasma protein binding is constant over the concentration range of 0.05 to 5.0  $\mu$ g/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 canalculus, 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.

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### ***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  $^{14}\text{C}$ -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  $C_{\text{max}}$  and  $T_{\text{max}}$  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 I studies (N=513) were compared to the mean pharmacokinetic parameters from two Asian studies (N=20). The mean AUCs of lansoprazole in Asian subjects were approximately twice those seen in pooled U.S. data; however, the inter-individual variability was high. The  $C_{\text{max}}$  values were comparable.

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## PHARMACODYNAMICS

### Mechanism of action

Lansoprazole belongs to a class of antisecretory compounds, the substituted benzimidazoles, that do not exhibit anticholinergic or histamine H<sub>2</sub>-receptor antagonist properties, but that suppress gastric acid secretion by specific inhibition of the (H<sup>+</sup>,K<sup>+</sup>)-ATPase enzyme system at the secretory surface of the gastric parietal cell. Because this enzyme system is regarded as the acid (proton) pump within the parietal cell, lansoprazole has been characterized as a gastric acid-pump inhibitor, in that it blocks the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated gastric acid secretion irrespective of the stimulus.

### Antisecretory activity

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

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

Mean Antisecretory Effects after Single and Multiple Daily Dosing

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

NOTE: An intragastric pH of >4 reflects a reduction in gastric acid by 99%.

<sup>\*</sup>(p<0.05) versus baseline, lansoprazole 15 mg and omeprazole 20 mg.

<sup>+</sup>(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

Parameter	PREVACID			
	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 <sup>+</sup>	77 <sup>*</sup>
% Time Gastric pH>6	20	23	28	45 <sup>*</sup>

<sup>\*</sup>(p<0.05) versus PREVACID 30 mg q.d.

<sup>+</sup>(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

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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<sub>3</sub>), thyroxine (T<sub>4</sub>), and somatotrophic hormone (STH). Lansoprazole in oral doses of 15 to 60 mg for up to one year had no clinically significant effect on sexual function. In addition, lansoprazole in oral doses of 15 to 60 mg for two to eight weeks had no clinically significant effect on thyroid function.

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

**Other effects**

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

**CLINICAL 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 ( $\geq 2.0 \mu\text{g/mL}$ ) 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 ( $\leq 0.25 \mu\text{g/mL}$ ) 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  $> 0.25 \mu\text{g/mL}$ . One patient on the 14 day triple therapy regimen had an unconfirmed pretreatment amoxicillin minimum inhibitory concentration (MIC) of  $> 256 \mu\text{g/mL}$  by E-test and the patient was eradicated of *H. pylori*.

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Clarithromycin Susceptibility Test Results and Clinical/Bacteriological Outcomes<sup>a</sup>

Clarithromycin Pretreatment Results	Clarithromycin Post-treatment Results				
	<i>H. pylori</i> negative-eradicated	<i>H. pylori</i> positive-not eradicated			
		Post-treatment susceptibility results			
		S <sup>b</sup>	I <sup>b</sup>	R <sup>b</sup>	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 <sup>b</sup>	112	105			7
Intermediate <sup>b</sup>	3	3			
Resistant <sup>b</sup>	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 <sup>b</sup>	42	40	1		1
Intermediate <sup>b</sup>					
Resistant <sup>b</sup>	4	1			3

<sup>a</sup> Includes only patients with pretreatment clarithromycin susceptibility test results

<sup>b</sup> Susceptible (S) MIC  $\leq 0.25 \mu\text{g/mL}$ , Intermediate (I) MIC 0.5 - 1.0  $\mu\text{g/mL}$ , Resistant (R) MIC  $\geq 2 \mu\text{g/mL}$

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 pre-treatment amoxicillin susceptible MICs ( $\leq 0.25$   $\mu\text{g/mL}$ ) were eradicated of *H. pylori*. Of those with pretreatment amoxicillin MICs of  $> 0.25$   $\mu\text{g/mL}$ , 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.<sup>1</sup> 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 ( $\geq 2$  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 ( $\mu\text{g/mL}$ ) <sup>a</sup>	Interpretation
$\leq 0.25$	Susceptible (S)
0.5-1.0	Intermediate (I)
$\geq 2.0$	Resistant (R)

Amoxicillin MIC ( $\mu\text{g/mL}$ ) <sup>b</sup>	Interpretation
$\leq 0.25$	Susceptible (S)

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

<sup>b</sup> There were not enough organisms with MICs  $> 0.25$   $\mu\text{g/mL}$  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 ( $\mu\text{g/mL}$ ) <sup>c</sup>
<i>H. pylori</i> ATCC 43504	Clarithromycin	0.015-0.12 mcg/mL
<i>H. pylori</i> ATCC 43504	Amoxicillin	0.015-0.12 mcg/mL

<sup>c</sup> 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

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

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## 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

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

\*(p<0.001) versus placebo.

PREVACID 15 mg was significantly more effective than placebo in relieving day and night-time 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

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

\*(p<0.05) versus placebo.

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

### *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

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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 <sup>†</sup> [80.0-97.7] (N=48)	86 <sup>†</sup> [73.3-93.5] (N=55)
M95-392	14 days	86 <sup>‡</sup> [75.7-93.6] (N=66)	83 <sup>‡</sup> [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® (Delta West Ltd., Bentley, 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 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 <sup>†</sup> [62.5-87.2] (N=51)	70 <sup>†</sup> [56.8-81.2] (N=60)
M93-125	66 <sup>‡</sup> [51.9-77.5] (N=58)	61 <sup>‡</sup> [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.

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### 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%

\*Fisher Table Estimate

\*(p<0.001) versus placebo.

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

### Gastric Ulcer

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

#### Gastric Ulcer Healing Rates

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

\*(p<0.05) versus placebo.

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

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

### 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)
<b>% of Days without Heartburn</b>			
Week 1	0%	71%*	46%*
Week 4	11%	81%*	76%*
Week 8	13%	84%*	82%*
<b>% of Nights without Heartburn</b>			
Week 1	17%	86%*	57%*
Week 4	25%	89%*	73%*
Week 8	36%	92%*	80%*

\*(p<0.01) versus placebo.

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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.

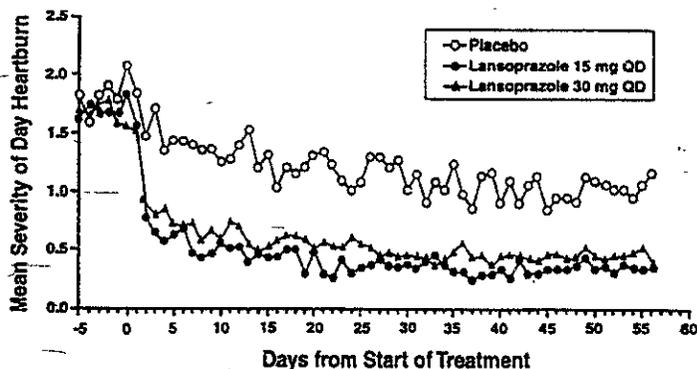
The intent-to-treat analyses demonstrated significant reduction in frequency and severity of day and night heartburn. Data for frequency and severity for the 8-week treatment period were as follows:

**Frequency of Heartburn**

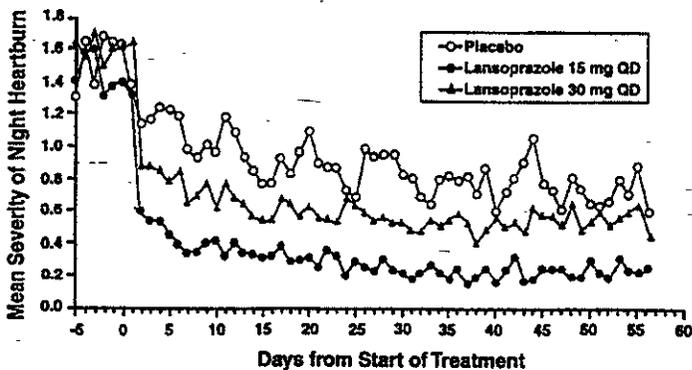
Variable	Placebo (n=43)	Median	
		PREVACID 15 mg (n=80)	PREVACID 30 mg (n=86)
<b>% of Days without Heartburn</b>			
Week 1	0%	71%*	46%*
Week 4	11%	81%*	76%*
Week 8	13%	84%*	82%*
<b>% of Nights without Heartburn</b>			
Week 1	17%	86%*	57%*
Week 4	25%	89%*	73%*
Week 8	36%	92%*	80%*

\*(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)**



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**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:

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**Erosive Esophagitis Healing Rates**

Week	PREVACID			Placebo (N=63)
	15 mg q.d. (N=69)	30 mg q.d. (N=65)	60 mg q.d. (N=72)	
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	Ranitidine
	30 mg q.d. (N=115)	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<sub>2</sub>-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<sub>2</sub>-receptor antagonists with PREVACID, as all patients had demonstrated unresponsiveness to the histamine H<sub>2</sub>-receptor antagonist mode of treatment. It does indicate, however, that PREVACID may be useful in patients failing on a histamine H<sub>2</sub>-receptor antagonist.

**Reflux Esophagitis Healing Rates in Patients Poorly Responsive to Histamine H<sub>2</sub>-Receptor Antagonist Therapy**

Week	PREVACID	Ranitidine
	30 mg q.d. (N=100)	150 mg b.i.d. (N=51)
4	74.7%*	42.6%
8	83.7%*	32.0%

\* (p<0.001) versus ranitidine.

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### 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.

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**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**

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

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

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

**Maintenance of Healing of Erosive Esophagitis**

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

**Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome**

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

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**CONTRAINDICATIONS**

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

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 appropri-

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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.

### Alternative Administration Options

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<sup>®</sup> 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. The granules have also been shown *in vitro* to remain intact when exposed to apple, cranberry, grape, orange, pineapple, prune, tomato, and V-8<sup>®</sup> 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<sub>450</sub> 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<sub>450</sub> 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<sub>450</sub> 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).

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### 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<sup>2</sup>) basis, of a 50-kg person of average height (1.46 m<sup>2</sup> body surface area) given the recommended human dose of 30 mg/day (22.2 mg/m<sup>2</sup>). 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.

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**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:

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**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, hypoglycemia/hypoglycemia; *Hematologic and Lymphatic System\** - agranulocytosis, aplastic anemia, hemolysis, hemolytic anemia, leukopenia, neutropenia, pancytopenia, thrombocytopenia, and thrombotic thrombocytopenic purpura; *Metabolic and Nutrition 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 unclear.

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### 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. Additional isolated laboratory abnormalities were reported.

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

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.

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## DOSAGE AND ADMINISTRATION

### Short-Term Treatment of Duodenal Ulcer

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

### *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.

#### Alternative Administration Options

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 peas and equal

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### 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.

#### Alternative Administration Options

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. 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).

Rx 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

ENSURE® is a registered trademark of Abbott Laboratories.

V-8® is a registered trademark of the Campbell Soup Company.

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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER: 20-406/ S030 & 027**

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

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20-406

SUBMISSION DATE: 02/05/98

LANSOPRAZOLE DELAYED-RELEASE CAPSULES  
PREVACID®

JAN - 8 1999

TAP HOLDINGS, INC.  
2355 WAUKEGAN ROAD  
DEERFIELD, IL 60015

REVIEWER: David G. Udo, Ph.D.

TYPE OF SUBMISSION: LABELING SUPPLEMENT (S-027)

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## SYNOPSIS/BACKGROUND

Supplement 027 was submitted to NDA 20-406 for lansoprazole delayed-release capsules (Prevacid®) by the sponsor on February 5, 1998. Prevacid® is an FDA approved, orally administered drug indicated for (i) short term treatment (for up to four weeks) for the healing and symptom relief of active duodenal ulcer (the package recommended adult dose is 15 mg once daily), (ii) *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence (in combination with amoxicilin and 500 mg of clarithromycin: the package insert recommended adult dose is 30 mg of Prevacid® with 1 g of amoxicilin and 500 mg of clarithromycin given twice daily for 14 days or 30 mg of Prevacid® with 1 g of amoxicilin given three times daily for 14 days), (iii) maintenance of healed duodenal ulcers (the package insert recommended adult dose is 15 mg once daily), (iv) treatment of gastric ulcers (the package insert recommended adult dose is 30 mg once daily for up to eight weeks), (v) treatment of erosive esophagitis (the package insert recommended adult dose is 30 mg once daily for up to 8 weeks), maintenance of healing of erosive esophagitis (the package insert recommended adult dose is 15 mg once daily) and pathological hypersecretory conditions including Zollinger-Ellison syndrome (the package insert recommended, starting, adult dose is 60 mg once daily). In the Clinical Pharmacology section of the approved package insert, under the sub-section of Metabolism, it is stated that lansoprazole is "thought to be transformed into two active species which inhibit acid secretion by (H<sup>+</sup>,K<sup>+</sup>)-ATPase within the parietal cell canaliculus". It is further stated that these active species are "not present in the systemic circulation". In the amendment submitted to Supplement 027 of this NDA on 11/13/98, it is stated that

The elimination half-life of lansoprazole is approximately 1.5 h but a single dose inhibits acid secretion for more than 24 h. These data suggest that in the half-lives of the active species at the site of drug action canaliculus are significantly longer than the plasma half-life of the parent drug.

In the approved package insert, it is stated that "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 teaspoon of applesauce".

In this supplement, the sponsor seeks approval of two labeling changes to the approved Prevacid® labeling. The first of the requested changes is to modify the Precautions and Dosage and Administration sections of the labeling to include Ensure® pudding, cottage cheese and yogurt as food items to which intact lansoprazole granules from Prevacid® capsule can be added for oral administration to patients who have difficulty swallowing capsules with water. To this end, the sponsor submits a study report (Study #M97-673) comparing the bioavailability of lansoprazole from the 30 mg Prevacid® capsule administered orally by adding intact granules from the capsule to yogurt (Regimen A: test), Ensure® pudding (Regimen B: test) and cottage cheese (Regimen C: test) to that of the intact 30 mg Prevacid® capsule administered orally

with water (Regimen D: reference). The second is to add the following statement at the end of the approved drug product labeling: "*Ensure*<sup>®</sup> is a registered trade mark of Abbott Laboratories".

The bioavailability of lansoprazole for each of the test regimens and the reference regimen specified in the preceding paragraph was compared using the Two One-sided Tests Procedure for the 90% confidence intervals. Based on the results of these tests, bioequivalence of lansoprazole administered orally as the intact *Prevacid*<sup>®</sup> capsule with water or as intact granules from the capsule sprinkled on one tablespoon of yogurt or cottage cheese has been demonstrated.

For the *Ensure*<sup>®</sup> pudding regimen, however, the ratio (test/reference) of the mean log transformed  $C_{max}$  was in the range of 78-103.1% versus 80-125% that is required for bioequivalence. On January 5, 1999, the 2% difference in these confidence intervals was discussed with the HFD-180 medical team leader, Dr. John Senior who stated that the observed difference would not have any detectable effect on the clinical benefit of the drug (see page 5, last paragraph in item #2).

Based on the facts summarized in the two preceding paragraphs, the **Precautions and Dosage and Administration** sections of the approved drug product labeling may be modified to include yogurt, cottage cheese and *Ensure*<sup>®</sup> pudding as media for oral administration with lansoprazole granules from *Prevacid*<sup>®</sup> capsule to patients who cannot swallow the intact *Prevacid*<sup>®</sup> capsule with water. It is further considered that this modification may also be applied to the **Information for Patients** sections of the approved drug product labeling.

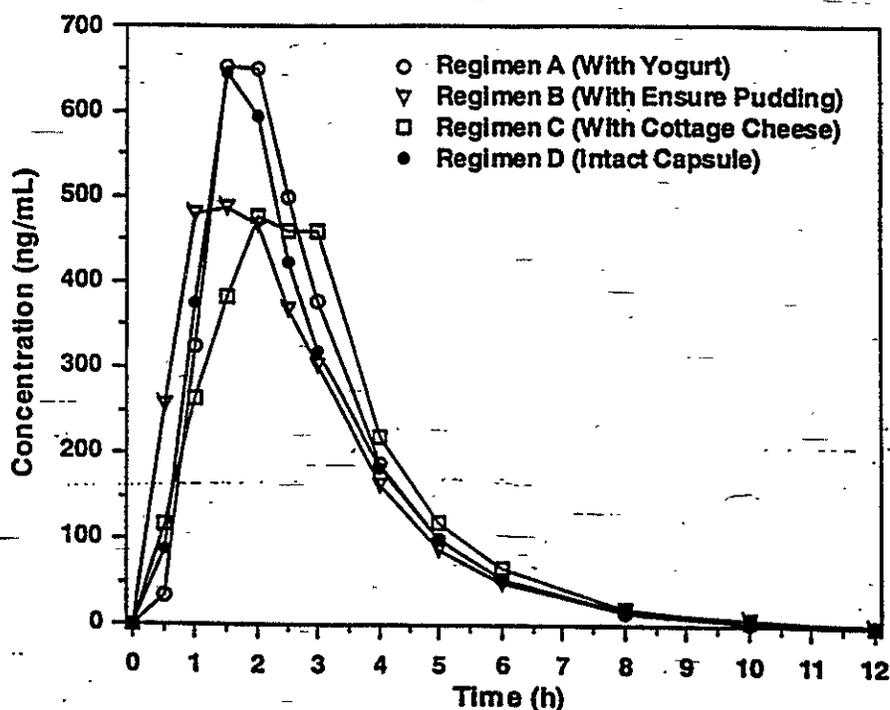
The statement, that "*Ensure*<sup>®</sup> is a registered trade mark of Abbott Laboratories", may be added to the drug product labeling as requested.

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## II. SUMMARY OF INFORMATION ON PHARMACOKINETICS AND BIOEQUIVALENCE

1. **PHARMACOKINETICS:** The kinetics of lansoprazole from the 30 mg Prevacid® capsule was evaluated in 24 normal volunteers (19 men and five women) each receiving four treatment regimens (Regimens A, B, C and D) in a crossover study (Study #/M97-673). The plot of the untransformed, mean concentration of lansoprazole versus time for each treatment regimen is presented in Fig. 1. The mean ( $\pm$ SD) pharmacokinetic parameters of lansoprazole for each treatment regimen are presented in Table 1. The treatment regimens are identified in Fig. 1 and Table 1. Individual subject pharmacokinetic data are presented in Appendix II (pages 10-13).

**Figure 1. Mean Lansoprazole Plasma Concentrations-time Profiles after Oral Administration of the Contents of a 30 mg Lansoprazole Capsule and an Intact 30 mg Lansoprazole Capsule**



Based on the results of analysis of variance (ANOVA), the mean value of each of the pharmacokinetic parameters of lansoprazole for each test regimen (Regimen A, B or C) was similar to that of the reference regimen (Regimen D) except that for Regimen C, the mean  $t_{max}$  was significantly longer. The mean  $t_{max}$  for Regimen C was 2.1 h versus 1.5-1.7 h for Regimens A, B and D. Individual subject  $t_{max}$  values ranged from \_\_\_\_\_ for Regimen A, \_\_\_\_\_ h for Regimen D and \_\_\_\_\_ for Regimens B and C. In this supplement, the sponsor provides a mean harmonic mean half-life of 1.0 h, without any measure of deviation from the mean, for each treatment regimen. In an Amendment to this NDA dated November 13, 1998, the

sponsor states (i) that rate constants are symmetrically distributed, (ii) that half-lives are reciprocally related to rate constants and, therefore, cannot be symmetrically distributed and (iii) that since half-lives are not symmetrically distributed, its harmonic mean is a more appropriate measure of its central tendency than its arithmetic mean. The arithmetic mean values ( $\pm$ SD), calculated in the review process ( $1.1 \pm 0.3$  h for Regimens A, B and C and  $1.1 \pm 0.4$  h for Regimen D), appear to be similar to the harmonic mean values provided by the sponsor. Subsequently, further comments in this regard are not necessary.

Table 1. Pharmacokinetic Parameters of Lansoprazole Following Administration of Regimens A, B, C and D.

Pharmacokinetic Parameters (N=23) of Lansoprazole Following Administration of Regimens A, B, C, and D						
Regimen	$T_{max}$ (hour)	$C_{max}$ (ng/mL)	$t_{1/2}$ (hour)	$\beta$ (1/hour)	$AUC_{0-t}$ (ng•h/mL)	$AUC_{0-\infty}$ (ng•h/mL)
A	1.7 (0.4)	814 (293)	1.0	0.7132 (0.2095)	1760 (781)	1790 (783)
B	1.5 (0.7)	711 (212)	1.0	0.6834 (0.2047)	1619 (586)	1652 (590)
C	2.1 (0.9) <sup>†</sup>	765 (358)	1.0	0.7280 (0.2332)	1673 (765)	1701 (770)
D	1.5 (0.7)	797 (272)	1.0	0.6872 (0.2139)	1699 (746)	1735 (744)

\* Harmonic mean  
<sup>†</sup> Statistically significantly different from reference.  
 Regimen A: Lansoprazole granules from one 30 mg capsule with yogurt (test).  
 Regimen B: Lansoprazole granules from one 30 mg capsule with Ensure<sup>®</sup> pudding (test).  
 Regimen C: Lansoprazole granules from one 30 mg capsule with small curd cottage cheese (test).  
 Regimen D: One 30 mg lansoprazole capsule (reference).

2. BIOEQUIVALENCE OF TEST REGIMENS AND REFERENCE REGIMEN: The results of the Two One-sided Tests Procedure, for the 90% confidence-intervals, for the ratio of the mean values of log transformed  $C_{max}$  and  $AUC_{(0-\infty)}$  for each of the test regimens (Regimens A, B and C) to those of the reference regimen (Regimen D), are presented in Table 2.

Table 2. Point Estimates and 90% Confidence Intervals for the Ratios of Lansoprazole  $AUC_{(0-\infty)}$  and  $C_{max}$  Central Values between Test Regimens A, B, and C and Reference Regimen D.

Point Estimates and 90% Confidence Intervals for the Ratios of Lansoprazole $C_{max}$ and $AUC_{0-\infty}$ Central Values between Test Regimens A, B and C and Reference Regimen D				
Parameter	Regimen		Relative Bioavailability	
	Test	Reference	Point Estimate	90% Confidence Interval
$C_{max}$	A	D	1.013	0.881 - 1.164
	B	D	0.897	0.780 - 1.031
	C	D	0.924	0.804 - 1.062
$AUC_{0-\infty}$	A	D	1.032	0.923 - 1.153
	B	D	0.973	0.871 - 1.088
	C	D	0.982	0.879 - 1.098

For the 90% confidence intervals, the ratios of the mean value of log transformed  $AUC_{(0-\infty)}$  of each test regimen (Regimen A, B or C) and the mean log transformed  $C_{max}$  of test regimens A and C, to those of the reference regimen (Regimen D), were within the range of 80-125% that is required for bioequivalence. Based on these results, bioequivalence has been demonstrated for lansoprazole administered orally as the intact Prevacid® capsule with water or as intact granules from the capsule sprinkled on one tablespoonful of yogurt or cottage cheese. Accordingly, lansoprazole granules from Prevacid® capsule may be sprinkled on one tablespoonful of yogurt or cottage cheese for oral administration to patients who cannot swallow the intact Prevacid® capsule with water.

The ratio of the mean log transformed  $C_{max}$  for the Ensure® pudding regimen (test Regimen B) to that of the Reference regimen (Regimen D) was only within the range of 78-103.1%. On January 5, 1999, the issue of whether or not the difference between the lower confidence limit of the mean  $C_{max}$  (test/reference) ratio (78%) for this test regimen and the statistical lower confidence limit acceptable for bioequivalence (80%) would be of clinical significance was discussed with the HFD-160 medical team leader, Dr. John Senior. Dr. Senior stated that for this drug, "the clinical range of therapeutic benefit is very broad and flat over a [dose] range of 10 to 40 mg/day of drug" and, subsequently, "a 2% lowering" of  $C_{max}$  would have "no detectable clinical effect on healing of lesions". On this premise, it is considered that lansoprazole granules from Prevacid® capsule may also be sprinkled on one tablespoonful of Ensure® pudding for oral administration to patients who cannot swallow the intact Prevacid® capsule with water.

3. SAMPLE ANALYSIS: See Appendix I (page 8).

4. PHARMACOKINETIC ANALYSIS: See Appendix I (pages 8-9).

13. FORMULATION: The approved commercial Prevacid® formulation was used in this study. Batch information is provided in Appendix I (page 7).

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III. RECOMMENDATION

Supplement 027 submitted to NDA 20-406 for lansoprazole delayed release capsule (Prevacid®) by the sponsor on February 5, 1998 has been reviewed by the Division of Pharmaceutical Evaluation II of the Office of Clinical Pharmacology and Biopharmaceutics. Based on the information provided in the supplement, bioequivalence of lansoprazole administered orally as the intact Prevacid® capsule with water or as intact granules from the capsule sprinkled on one tablespoonful of yogurt or cottage cheese has been demonstrated. Regarding the Ensure® pudding regimen, the findings of the bioequivalence study suggest a slightly lower rate of systemic availability of lansoprazole as compared to oral administration of the intact capsule with water. However, it is felt that the observed slight reduction in systemic availability of lansoprazole observed for this regimen might not significantly affect its clinical benefit. Accordingly, the Precautions and Dosage and Administration sections of the approved drug product labeling may be modified to include the administration of intact lansoprazole granules from Prevacid® capsule with one tablespoonful of yogurt, cottage cheese or Ensure® pudding to patients who cannot swallow the intact Prevacid® capsule with water. It is further considered appropriate to also apply this modification to the Information for Patients section of the approved drug product labeling.

The statement, that "Ensure® is a registered trade mark of Abbot Laboratories", may be added to the drug product labeling as requested.

Please convey this Recommendation, as appropriate, to the sponsor.

Appendices I and II are retained in the Office of Clinical Pharmacology and Biopharmaceutics and may be obtained upon request.

/S/ 01/08/99

David G. Udo, Ph.D.  
Division of Pharmaceutical Evaluation II

RD Initialed by John Hunt 12/30/98

FT Initialed by John Hunt /S/ 1/8/99

cc: NDA 20-406, HFD-180, HFD-100 (Walsh), HFD-850 (Huang), HFD-870 (M. Chen, Hunt, Lee and Udo), CD R (Attn: Barbara Murphy).

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**IV. APPENDIX I: SUMMARY OF BIOEQUIVALENCE STUDY**

**A. STUDY NUMBER:** M97-673

**B. TITLE:** Bioavailability of Lansoprazole from Alternative Methods of Administration of Lansoprazole Granules.

**C. PRINCIPAL INVESTIGATOR AND CLINICAL STUDY SITE:** \_\_\_\_\_

**D. ANALYTICAL INVESTIGATOR AND SITE:** \_\_\_\_\_

**E. OBJECTIVES:** The objective of the study was to compare the bioavailability of lansoprazole after administration of granules from the capsule with soft foods with that after the administration of an intact lansoprazole capsule.

**F. DOSAGE FORM:** Lansoprazole 30 mg (Bulk Lot # 0163) was used for the study. The batch size was \_\_\_\_\_ capsules (commercial batch size).

**G. DESIGN:** 1. TYPE OF DESIGN: This was a single dose, open-label, crossover, four-period study conducted at a single center.

2. STUDY POPULATION: The study population consisted of 24 healthy volunteers (18 men ranging in age from 19 years to 52 years and weighing 143.3-202.8 pounds [65.1-92.2 kg] and six women also ranging in age from 19 years to 52 years and weighing 143.3-178.6 pounds [65.1-81.2 kg]). The ethnic composition of the study population was 21 Caucasians, two Hispanics and one Black. A complete summary of information on subject demography is provided in Appendix II (pages 14-15).

3. INCLUSION AND EXCLUSION CRITERIA: See Appendix II (pages 16-18).

4. SUBJECT GROUPING AND DOSE ADMINISTRATION: The subjects were randomly assigned to four groups (Groups I, II, III and IV). Each group received orally all of the following dose regimens in a crossover fashion: Regimen A (test): lansoprazole granules from one 30 mg capsule administered with one tablespoonful of yogurt, Regimen B (test): lansoprazole granules from one 30 mg capsule administered with one tablespoonful of Ensure® chocolate pudding, Regimen C: (test): lansoprazole granules from one 30 mg capsule administered with one tablespoonful of small curd cottage cheese and Regimen D: (reference): one, intact 30 mg lansoprazole capsule administered with 180 mL water. Each dose in Regimens A, B and C was followed by 180 mL of water. Successive regimens were separated by a washout period of seven days. For each regimen, each dose was administered following a fast of at least eight hours.

5. **FEEDING OF SUBJECTS:** Pre-dose dinner was served at 7.00 p.m. of Day -1 (day immediately preceding dosing). On the day of dosing (Day 1), the study drug was administered at approximately 8.00 a.m. and breakfast, lunch and dinner were, respectively, served at 3, 5 and 10 h postdose.

6. **BLOOD SAMPLE COLLECTION:** Blood samples for pharmacokinetic analysis were obtained pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12 h postdose. Each blood sample was centrifuged to obtain the plasma which was then stored at -10 degrees or lower pending analysis.

4. **SPECIFICITY:** The assay method was developed to measure lasoprazole in human plasma.

I. **PHARMACOKINETIC ANALYSIS:** For each lasoprazole dose regimen, the pharmacokinetic analysis of lasoprazole was performed using \_\_\_\_\_ methods. The maximum

concentration ( $C_{max}$ ), time to reach the maximum concentration  $t_{max}$ , terminal elimination rate constant, elimination half-life ( $t_{1/2}$ ), area under the plasma concentration versus time curve to the time of last quantifiable drug concentration ( $AUC_{[0-t]}$ ) and total area under the plasma concentration versus time curve ( $AUC_{[0-infinity]}$ ) were determined.  $T_{max}$ ,  $t_{1/2}$ , elimination rate constant,  $C_{max}$ , and AUC for all dose regimens were compared using ANOVA.

J. **BIOEQUIVALENCE:** To assess the bioequivalence of each test regimen to the reference regimen, its log transformed  $AUC_{(0-infinity)}$  and  $C_{max}$  were compared to those of the reference regimen using the Two One-sided Tests Procedure for the 90% confidence intervals. Bioequivalence was declared where the ratios the mean values of log transformed  $AUC_{(0-infinity)}$  and  $C_{max}$  of the test regimen to those of the reference regimen were within the range of 80-125%.

K. **RESULTS:** The results of this study are presented on pages 3-5.

**APPEARS THIS WAY  
ON ORIGINAL**

**Table 6. Individual Lansoprazole Pharmacokinetic Parameters and Summary Statistics for Regimen A**

Subject	Period	T <sub>max</sub> (h)	C <sub>max</sub> (ng/mL)	AUC <sub>0-t</sub> ----- (ng·h/mL) -----	AUC <sub>0-∞</sub>	t <sub>1/2</sub> (h)	β (1/h)
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
13							
14							
15							
16							
17							
18							
19							
20							
21							
22							
23							
24							
N		23	23	23	23	23	23
Mean		1.7	813.670	1760.14	1789.93	1.00	0.7132
Median		1.5	854.700	1668.35	1708.42	1.1	0.6338
SD		0.4	293.236	781.15	783.29	0.3	0.2095
CV%		26.1	36.0	44.4	43.8	27.3	29.4
Min							
Max							

Regimen A (test): Lansoprazole granules from one 30 mg capsule administered with yogurt  
 ① Harmonic mean

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**Table 7. Individual Lansoprazole Pharmacokinetic Parameters and Summary Statistics for Regimen B**

Subject	Period	T <sub>max</sub> (h)	C <sub>max</sub> (ng/mL)	AUC <sub>0-t</sub> ----- (ng·h/mL) -----	AUC <sub>0-∞</sub>	t <sub>1/2</sub> (h)	β (1/h)
*1							
2							
3							
4							
5							
6							
7							
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10							
11							
12							
13							
14							
15							
16							
17							
18							
19							
20							
21							
22							
23							
24							
N		23	23	23	23	23	23
Mean		1.5	710.904	1618.82	1652.19	1.08	0.6834
Median		1.5	721.300	1688.98	1719.25	1.1	0.6418
SD		0.7	211.930	585.89	589.86	0.3	0.2047
CV%		49.5	29.8	36.2	35.7	26.4	30.0
Min							
Max							

Regimen B (test): Lansoprazole granules from one 30 mg capsule administered with Ensure pudding

\* Subject 1 excluded due to premature termination

⊖ Harmonic mean

**Table 8. Individual Lansoprazole Pharmacokinetic Parameters and Summary Statistics for Regimen C**

Subject	Period	$T_{max}$ (h)	$C_{max}$ (ng/mL)	$AUC_{0-t}$ ----- (ng·h/mL) -----	$AUC_{0-\infty}$	$t_{1/2}$ (h)	$\beta$ (1/h)
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
13							
14							
15							
16							
17							
18							
19							
20							
21							
22							
23							
24							
0.6143							
N		23	23	23	23	23	23
Mean		2.1	764.643	1672.77	1701.25	1.00	0.7280
Median		2.0	628.100	1603.15	1625.30	1.1	0.6249
SD		0.9	358.338	764.59	769.52	0.3	0.2332
CV%		44.0	46.9	45.7	45.2	27.6	32.0
Min							
Max							

Regimen C (test): Lansoprazole granules from one 30 mg capsule administered with small curd cottage cheese  
 @ Harmonic mean

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Drug Metabolism. — 65006:56. — 97/595

**Table 9. Individual Lansoprazole Pharmacokinetic Parameters and Summary Statistics for Regimen D**

Subject	Period	T <sub>max</sub> (h)	C <sub>max</sub> (ng/mL)	AUC <sub>0-t</sub> (ng·h/mL)	AUC <sub>0-∞</sub>	t <sub>1/2</sub> (h)	β (1/h)
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
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13							
14							
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16							
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18							
19							
20							
21							
22							
23							
24							
N		23	23	23	23	23	23
Mean		1.5	797.448	1698.58	1735.40	1.00	0.6872
Median		1.5	778.500	1748.35	1780.84	1.1	0.6456
SD		0.7	271.585	745.97	743.77	0.4	0.2139
CV%		43.6	34.1	43.9	42.9	38.9	31.1
Min							
Max							

Regimen D (reference): One 30 mg lansoprazole capsule administered with water  
 @ Harmonic mean

19JAN98 15:06

Drug Metabolism. — 65006:56. — 97/595

15JAN98 15:45  
 LANSOPRAZOLE (65006)  
 STUDY M97-671  
 97/797 - CLINICAL/STATISTICAL

APPENDIX PAGE 1

APPENDIX B.1  
 DEMOGRAPHICS

SUBJECT NUMBER	INITIALS	DATE OF BIRTH	AGE (YEARS)	SEX	RACE	HEIGHT (IN)	WEIGHT (LBS)	FRAME	REGIMEN SEQUENCE*
INV:									
1#			40	FEMALE	CAUCASIAN	67.7	167.5	MEDIUM	BCDA
2			41	MALE	CAUCASIAN	70.1	160.9	MEDIUM	CABD
3			52	FEMALE	CAUCASIAN	64.6	165.3	LARGE	DBAC
4			49	FEMALE	CAUCASIAN	69.7	178.6	LARGE	ADCB
5			35	MALE	HISPANIC	66.9	178.6	LARGE	DBAC
6			35	MALE	BLACK	69.7	160.9	SMALL	ADCB
7			23	MALE	CAUCASIAN	68.5	174.4	MEDIUM	BCDA
8			44	MALE	CAUCASIAN	70.5	198.4	LARGE	CABD
9			29	MALE	CAUCASIAN	70.1	178.6	LARGE	ADCB
10			21	MALE	CAUCASIAN	66.5	154.3	MEDIUM	BCDA
11			20	MALE	CAUCASIAN	69.3	200.4	LARGE	DBAC
12			52	MALE	HISPANIC	67.7	178.6	LARGE	CABD
13			31	FEMALE	CAUCASIAN	66.1	149.9	MEDIUM	DBAC
14			23	MALE	CAUCASIAN	69.3	179.7	LARGE	CABD
15			47	MALE	CAUCASIAN	70.9	202.8	MEDIUM	BCDA
16			19	FEMALE	CAUCASIAN	64.6	154.3	MEDIUM	ADCB
17			46	MALE	CAUCASIAN	68.1	156.5	MEDIUM	DBAC
18			22	MALE	CAUCASIAN	72.4	178.6	MEDIUM	CABD
19			32	MALE	CAUCASIAN	71.7	176.4	MEDIUM	ADCB

APPEARS THIS WAY  
 ON ORIGINAL

\* A) LANSOPRAZOLE GRANULES FROM ONE 30 MG CAPSULE ADMINISTERED WITH YOGURT.  
 B) LANSOPRAZOLE GRANULES FROM ONE 30 MG CAPSULE ADMINISTERED WITH ENSURE PUDDING.  
 C) LANSOPRAZOLE GRANULES FROM ONE 30 MG CAPSULE ADMINISTERED WITH SMALL CURD COTTAGE CHEESE.  
 D) ONE 30 MG LANSOPRAZOLE CAPSULE ADMINISTERED WITH WATER.  
 # SUBJECT PREMATURELY TERMINATED.

15JAN98 15:45  
LANSOPRAZOLE -65006)  
STUDY M97-673  
-/97/797 - CLINICAL/STATISTICAL

APPENDIX B.1  
DEMOGRAPHICS.

APPENDIX PAGE 2  
LAST APPENDIX PAGE

SUBJECT NUMBER	INITIALS	DATE OF BIRTH	AGE (YEARS)	SEX	RACE	HEIGHT (IN)	WEIGHT (LBS)	FRAME	REGIMEN SEQUENCE*
INV:									
20			46	MALE	CAUCASIAN	72.0	189.6	LARGE	BCDA
21			19	FEMALE	CAUCASIAN	67.3	143.3	MEDIUM	BCDA
22			32	MALE	CAUCASIAN	65.7	143.3	MEDIUM	CABD
23			19	MALE	CAUCASIAN	69.7	143.3	SMALL	ADCB
24			29	MALE	CAUCASIAN	73.2	169.8	MEDIUM	DBAC

APPEARS THIS WAY  
ON ORIGINAL

- \* A) LANSOPRAZOLE GRANULES FROM ONE 30 MG CAPSULE ADMINISTERED WITH YOGURT.
- B) LANSOPRAZOLE GRANULES FROM ONE 30 MG CAPSULE ADMINISTERED WITH ENSURE PUDDING.
- C) LANSOPRAZOLE GRANULES FROM ONE 30 MG CAPSULE ADMINISTERED WITH SMALL CURD COTTAGE CHEESE.
- D) ONE 30 MG LANSOPRAZOLE CAPSULE ADMINISTERED WITH WATER.

### 3.1 Dosage

A single, 30 mg dose of lansoprazole will be administered in each period. All doses will be administered orally under fasting conditions. The test Regimens A, B and C will be administered with one tablespoon of vanilla yogurt, Ensure chocolate pudding, and small curd cottage cheese, respectively, and will be followed by administration of 180 mL of water. The reference Regimen D will be administered as the intact capsule with 180 mL of water.

## 4.0 Subject Selection

### 4.1 Study Population

Twenty-four (24) healthy adult males and females are to participate in the study. In addition, they must meet all selection criteria as specified in Sections 4.2 and 4.3 of this protocol.

### 4.2 Inclusion Criteria

Subjects will be selected for study participation if they meet the following criteria:

- 4.2.1 Age is between 18 and 55 years, inclusive.
- 4.2.2 If female, must be postmenopausal for a minimum of one year, surgically sterile (bilateral tubal ligation or hysterectomy), or if of child-bearing potential, not nursing, and practicing a reliable method of birth control.

Examples of methods of birth control in order to prevent pregnancy are:

- condoms, sponge, IUD, foams, jellies, cervical cap.
- oral contraceptives or hormone replacement therapy for a period of three months prior to study start.
- total abstinence.

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ON ORIGINAL

A urine pregnancy test will be performed at screening on a specimen obtained within four weeks prior to study drug administration and the result must be negative. A serum pregnancy test will be performed on Study Day -1 and the result must be negative.

- 4.2.3 Body weight is within  $\pm 10\%$  of the ranges based on height, sex, and body frame set forth in Appendix A, and is a minimum of 54.4 kg for women and 61.2 kg for men.
- 4.2.4 Judged to be in general good health based upon the results of a medical history, vital signs (as described in Section 6.6.1), physical examination, laboratory profile (as described in Section 6.6.4), and 12-lead electrocardiogram (ECG).
- 4.2.5 No medications (including over-the-counter medication, and excluding oral contraceptives or hormonal replacement therapy, for females only) or alcohol are to be taken during the course of the study.
- 4.2.6 All medications (including over-the-counter medication, and excluding oral contraceptives or hormonal replacement therapy, for females only) must be discontinued starting at least two weeks before study drug administration.
- 4.2.7 Non-nicotine user, defined as an individual who has abstained from nicotine for a minimum of the six-month period preceding study drug administration.
- 4.2.8 Prior to any study-specific procedure, an informed consent, approved by an Institutional-Review Board (IRB), must be voluntarily signed and dated.

### 4.3 Exclusion Criteria

Admittance of a subject into the study when the subject has acknowledged taking any medication (including over-the-counter medication, and excluding oral contraceptives or hormonal replacement therapy, for females only), within two weeks prior to study drug administration, will be at the discretion of the investigator with the concurrence of the study monitor. The medication, dosage information, date(s) of administration, and indication(s) will be recorded on the appropriate case report form.

Subjects will be excluded from the study if they meet any of the following criteria:

- 4.3.1 History of significant drug sensitivity or a significant allergic reaction to any drug.
- 4.3.2 Requires any medication, excluding oral contraceptives or hormonal replacement therapy, for females only, on a regular basis.
- 4.3.3 Recent history of drug and/or alcohol abuse.
- 4.3.4 Positive result for hepatitis B and/or C test.
- 4.3.5 Positive result for urine drug and/or alcohol screen.
- 4.3.6 Has been administered an injectable drug within 30 days prior to study drug administration.
- 4.3.7 Has donated or lost 450 mL or more blood volume (including plasmapheresis) or had a transfusion of any blood product within six weeks prior to study drug administration.
- 4.3.8 Has received any investigational drug within six weeks prior to study drug administration.
- 4.3.9 Considered by the investigator, for any reason, to be an unsuitable candidate for receiving lansoprazole.

## 5.0— Materials and Supplies

### 5.1 Test Preparations

Lansoprazole will be supplied as capsules containing 30 mg lansoprazole (TAP Holdings Inc.). Finishing Lot No. 28-316-S2 ( — 8615).

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ON ORIGINAL

**ANNOTATED LABELING**

35

PAGE(S) REDACTED

Draft Labeling

**PROPOSED TEXT OF LABELING  
(CLEAN COPY)**

20 PAGE(S) REDACTED

Draft

Labeling

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER: 20-406/S030 & 027**

**ADMINISTRATIVE DOCUMENTS**

**Division of Gastrointestinal & Coagulation Drug Products**

**REGULATORY PROJECT MANAGER REVIEW**

**Application Number:** NDA 20-406/SLR-027

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

JAN 14 1999

**Sponsor:** TAP Holdings, Inc.

**Material Reviewed**

**Submission Date(s):** February 5, 1998

**Receipt Date(s):** February 6, 1998

**Background and Summary Description:** Supplement 027, submitted February 5, 1998, provides for revisions to the PRECAUTIONS and DOSAGE AND ADMINISTRATION sections of the package insert to allow administration of the intact granules on pudding, cottage cheese, or yogurt.

**Review**

The submitted draft labeling, dated February 4, 1998, was compared to the currently approved labeling identified as "03-4891-R11-Rev. June, 1998," submitted July 14, 1998 as the final printed labeling (FPL) for supplement 024 (approved June 23, 1998) and acknowledged and retained on July 23, 1998. The following differences were noted.

1. Under **PRECAUTIONS/Information for Patients and DOSAGE AND ADMINISTRATION:**

The first sentence of the second paragraph in the **PRECAUTIONS/Information for Patients** section and the third sentence of the last paragraph in the **DOSAGE AND ADMINISTRATION** section was revised to add "ENSURE® pudding, cottage cheese or yogurt" as follows:—

"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 or yogurt and swallowed immediately."

2. At the end of the package insert, the following sentence was added:

"ENSURE® is a registered trademark of Abbott Laboratories."

**The biopharmaceutics review recommends approval of the above revisions (see review dated January 8, 1999).**

3. The draft labeling does not contain the revisions approved in the following supplement:
  - A. Supplement 016 - approved March 12, 1998. Provides for a new indication: short-term treatment of symptomatic gastroesophageal reflux disease (GERD). Provides for the addition of "speech disorder" and "urinary retention" to the ADVERSE REACTIONS section of the package insert.
  - B. Supplement 021 - approved July 20, 1998. Provides for a 10-day dosing regimen for triple therapy (lansoprazole/amoxicillin/clarithromycin) for the eradication of *H. pylori*.
  - C. Supplement 022 - approved July 20, 1998. Provides for revisions to the PRECAUTIONS/Information for Patients and DOSAGE AND ADMINISTRATION sections of the package insert to add statements regarding the *in vitro* stability of the granules in various fruit and vegetable juices.
  - D. Supplement 024 - approved June 23, 1998. Provides for revisions to the ADVERSE REACTIONS section of the package insert to add "anaphylactoid-like reaction" and substitute "blurred vision" for \_\_\_\_\_

#### Conclusions

1. The medical officer should consider the approval recommendation made in the biopharmaceutics review, dated January 8, 1999.
2. The FPL must contain the revisions approved in supplements 016, 021, 022, and 024.

          / S /                1/14/99  
Maria R. Walsh, M.S.  
Regulatory Project Manager

          / S / - 1-14-99

APPEARS THIS WAY  
ON ORIGINAL

**Division of Gastrointestinal & Coagulation Drug Products**

**REGULATORY PROJECT MANAGER REVIEW**

**Application Number:** NDA 20-406/SLR-027 and SLR-030

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

FEB 22 1999

**Sponsor:** TAP Holdings, Inc.

**Material Reviewed**

**Submission Date(s):** February 17, 1999

**Receipt Date(s):** February 18, 1999

**Background and Summary Description:** Supplement 027, submitted February 5, 1998, provides for revisions to the PRECAUTIONS and DOSAGE AND ADMINISTRATION sections of the package insert to allow administration of the intact granules on pudding, cottage cheese, or yogurt. This supplement was approved with draft labeling on January 14, 1999.

Supplement 030, submitted June 5, 1998, provides for revisions to the PRECAUTIONS and DOSAGE AND ADMINISTRATION sections of the package insert to add statements about sprinkling the intact granules on strained pears and mixing the intact granules in orange juice or tomato juice. This supplement was approvable on December 16, 1998 pending final printed labeling (FPL).

The sponsor has submitted FPL in response to our action letters of December 16, 1998 and January 14, 1999.

**Review**

The submitted FPL, identified as "03-4939-R12-Rev. Jan., 1999," was compared to the currently approved labeling, identified as "03-4891-R11-Rev. June, 1998," approved in supplement 024 on June 23, 1998, to the draft labeling submitted with supplements 027 and 030, and to the recommendations in the December 16, 1998 approvable letter for S-030 (attached). The following differences were noted.

1. Under **INFORMATION FOR PATIENTS** and **DOSAGE AND ADMINISTRATION**, the subheader, *Alternative Administration Options*, was added.

Per the December 16, 1998 approvable letter and the January 6, 1999 telephone conversation between Maria R. Walsh, Project Manager, of this Division and Gary Magistrelli, Ph.D., Regulatory Affairs, of TAP Holdings, Inc. (memorandum of telecon attached), this subheading is acceptable.

2. Under **INFORMATION FOR PATIENTS** and **DOSAGE AND ADMINISTRATION**, the phrase "approximately 2 ounces" has been added to the following sentence:

"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."

Per the January 6, 1999 telephone conversation referenced above, this addition is acceptable.

3. The following sentence was added at the end of the package insert:

"V-8® is a registered trademark of the Campbell Soup Company."

This revision is acceptable.

#### Conclusions

1. The submitted final printed labeling is acceptable and will be acknowledged and retained for supplement 027.
2. Supplement 030 may be approved.

MS

2/22/99

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

cc:

Original NDA 20-406/S-027

/S-030

HFD-180/Div. Files

HFD-180/H.Gallo-Torres

L.Talarico

Final: M. Walsh 2/22/99

filename: \_\_\_\_\_

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ON ORIGINAL**

PM REVIEW

NDA 20-406/S-027

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

FEB 22 1999

Dear Dr. Magistrelli:

We acknowledge the receipt of your February 17, 1999 submission containing final printed labeling in response to our January 14, 1999 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 January 14, 1999 letter, and we find it acceptable.

If you have any questions, contact Maria R. Walsh, M.S., Regulatory Project Manager, at (301) 443-8017.

Sincerely,

/S/ 2-22-99

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

APPEARS THIS WAY  
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-406/ S030 & 027

CORRESPONDENCE



**TAP HOLDINGS INC.**  
parent of TAP Pharmaceuticals Inc.

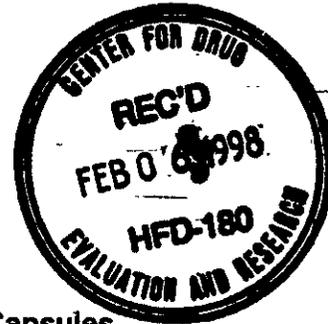
Bannockburn Lake Office Plaza  
2355 Waukegan Rd.  
Deerfield, IL 60015

SLR-027

February 5, 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  
5600 Fishers Lane  
Rockville, MD 20857

Attn: Lilia Talarico  
Director



**RE: PREVACID® (lansoprazole) Delayed-Release Capsules  
NDA 20-406, S-027  
Labeling Supplement**

Dear Dr. Talarico:

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

This supplement requests approval for a labeling change for PREVACID (lansoprazole) Delayed-Release Capsules, NDA 20-406 which was approved on May 10, 1995. Namely, under the PRECAUTIONS section and under the DOSAGE AND ADMINISTRATION section of the package insert (PI), we wish to add text describing three additional soft foods upon which intact granules of PREVACID can be sprinkled prior to being swallowed. This additional text is supported by data obtained from the bioavailability study report enclosed in this submission (Report No. 97/797; volumes 2 and 3).

Specifically, the old statement in the PRECAUTIONS section, under Information for Patients, second paragraph, first sentence, and the old statement in the DOSAGE AND ADMINISTRATION section, last paragraph, third sentence, reads, "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". This sentence has been changed in both the

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TAP Holdings Inc.  
NDA 20-406, S-027  
February 5, 1998  
Page 2

PRECAUTIONS and the DOSAGE AND ADMINISTRATION sections to, "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 or yogurt* and swallowed immediately". The only other change to the PI is the addition of the following sentence at the end of the PI, "*ENSURE® is a registered trademark of Abbott-Laboratories*". (New text is shown in italics).

The change to the PRECAUTIONS section is annotated in volume 1, page 028 of the Annotated Labeling section of this submission; the change to the DOSAGE AND ADMINISTRATION section is annotated in volume 1, page 039 of the Annotated Labeling section of this submission; and the addition of the ENSURE registered trademark statement is highlighted in volume 1, page 040 of the Annotated Labeling section of this submission. A clean copy of the PI with the complete proposed text for labeling is located in volume 1, pages 041-062 of this submission.

The objective of the bioavailability study entitled, "Bioavailability of Lansoprazole From Alternative Methods of Administration of Lansoprazole Granules", was to compare the bioavailability of lansoprazole after administration of granules from the capsule with soft foods with that after administration of an intact lansoprazole capsule. The study design was a single-dose, open-label, crossover, four-period, randomized, single-center study. Subjects were randomly assigned to four groups of equal size with the groups receiving the four study regimens in different sequences. The four regimens included: 30 mg of lansoprazole granules administered with 1) yogurt, 2) ENSURE® pudding, 3) cottage cheese, and 4) an intact lansoprazole capsule administered with water. All doses were administered under fasting conditions.

Pharmacokinetic parameters measured/calculated in this study included  $C_{max}$ ,  $T_{max}$ ,  $\beta$ ,  $C_t$ ,  $t_{1/2}$ ,  $AUC_{0-\infty}$ , and  $AUC_{0-t}$ . Briefly, the 90% confidence intervals for all three test regimens (the three, new soft foods with lansoprazole granules compared to the lansoprazole capsule alone) for  $C_{max}$  were within the 0.80-1.25 range, except for the lower limit of the 90% confidence interval for the ENSURE® pudding regimen, which was 0.78. The 90%

**TAP Holdings Inc.**  
**NDA 20-406, S-027**  
**February 5, 1998**  
**Page 3**

confidence intervals for the principal bioavailability parameter,  $AUC_{0-\infty}$  for the three test regimens were within the 0.80-1.25 criterion for bioequivalence. These results demonstrate that lansoprazole capsules may be administered by adding the capsule contents to small amounts of yogurt, pudding or cottage cheese for ingestion.

If you have any questions or if you require additional information please contact me at the number listed below or Ms. Judy Wargel at (847) 317-5781.

Sincerely,



Gary C. Magistrelli, Ph.D.  
Associate Director, Regulatory Affairs

(847) 267-4961  
(847) 317-5795 FAX

**APPEARS THIS WAY  
ON ORIGINAL**

741  
NDA 20-406/S-027

FEB 10 1998

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

Dear Dr. Magistrelli:

We acknowledge receipt of your supplemental application for the following:

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

NDA Number: NDA 20-406

Supplement Number: S-027

Therapeutic Classification: Standard

Date of Supplement: February 5, 1998

Date of Receipt: February 6, 1998

This supplement provides for revisions to the PRECAUTIONS and DOSAGE AND ADMINISTRATION sections of the package insert to allow administration of the intact granules on pudding, cottage cheese, or yogurt.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on April 7, 1998 in accordance with 21 CFR 314.101(a).

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

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

NDA 20-406/S-027

Page 2

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

Sincerely yours,

/S/ 2/10/98

Maria R. Walsh, M.S.  
Project Manager  
Division of Gastrointestinal and  
Coagulation Drug Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

cc:

Original NDA 20-406/S-027

HFD-180/Div. Files

HFD-180/M. Walsh

HFD-180/J. Hunt

DISTRICT OFFICE

Final: M. Walsh 2/10/98

filename: \_\_\_\_\_

~~SUPPLEMENT ACKNOWLEDGEMENT (AC)~~

APPEARS THIS WAY  
ON ORIGINAL

NDA 20-406/S-027

74.1  
SEP 28 1998

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

Dear Dr. Magistrelli:

Please refer to your pending February 5, 1998 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prevacid (lansoprazole) Delayed-Release Capsules.

We are reviewing the Biopharmaceutics section(s) of your submission and have the following information requests regarding Study #M97-673 entitled, "Bioavailability of Lansoprazole From Alternative Methods of Administration of Lansoprazole Granules:"

1. Please provide the drug product batch size for the study.
2. Please provide the drug product commercial batch size.
3. Please provide the precision and accuracy data for the  $\mu\text{g/mL}$  concentration (limit of quantitation) during the assay validation process.
4. Please explain the discrepancies in the precision and accuracy data provided under Methods (Volume 3, page 94) and under Results (Volume 3, page 107).
5. Please provide the reason(s) for providing the harmonic mean for the elimination half-life of lansoprazole and the arithmetic mean for the other pharmacokinetic parameters.
6. Please provide the minimum effective plasma concentration of lansoprazole for each of the approved package insert indications.

We would appreciate your prompt written response so we can continue our evaluation of your supplemental application.

APPEARS THIS WAY  
ON ORIGINAL

NDA 20-406/S-027

Page 2

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

Sincerely,

*/S/ 9/28/98*

Kati Johnson  
Supervisory Consumer Safety Officer  
Division of Gastrointestinal and Coagulation Drug Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

cc:

Archival NDA 20-406/S-027

HFD-180/Div. Files

HFD-180/PM/M.Walsh

HFD-870/D.Udo

D.Lee

DISTRICT OFFICE

Drafted by: M.Walsh 9/17/98

Initiated by: D.Lee 9/17/98

K.Johnson 9/22/98

final: M.Walsh 9/23/98

filename: \_\_\_\_\_

INFORMATION REQUEST (IR)

**APPEARS THIS WAY  
ON ORIGINAL**

## MEMORANDUM OF TELECON

DATE: January 6, 1999

APPLICATION NUMBER: NDA 20-406/S-030; Prevacid (lansoprazole) Delayed-Release Capsules

**BETWEEN:**

Name: Gary Magistrelli, Ph.D., Regulatory Affairs  
Phone: (847) 267-4961  
Representing: TAP Holdings, Inc.

**AND**

Name: Maria R. Walsh, M.S., Regulatory Project Manager  
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

**SUBJECT:** Approvable Labeling

**BACKGROUND:** Supplement 030, submitted June 5, 1998 provides for revisions to the PRECAUTIONS and DOSAGE AND ADMINISTRATION section of the package insert to add statements about sprinkling the granules on strained pears and mixing the granules in orange or tomato juice. The supplement was approvable on December 16, 1998 with some labeling revisions, i.e. the entire text regarding administration of the granules should be placed at the end of the DOSAGE AND ADMINISTRATION section as per the currently approved labeling and a subheader, such as "Alternative Media for Dose Administration" may be added to this section to separate the information regarding the intact capsules from that of the granules.

**TODAY'S CALL:** Dr. Magistrelli called and proposed the following alternative subheader: "Alternative Administration Options." He proposed that this subheader also precede the identical information contained in the PRECAUTIONS, Information for Patients subsection. In addition, Dr. Magistrelli proposed that in the text regarding the administration of the granules in a small volume of juice, an equivalent amount in \_\_\_\_\_ be inserted after "60 ml."

I told Dr. Magistrelli that I would consult with Dr. Hugo Gallo-Torres, Medical Team Leader, and inform him of the Agency's recommendation as soon as possible. The call was then concluded.

After consulting with Dr. Gallo-Torres, I called Dr. Magistrelli and left a voice mail message that the sponsor's proposals as described above are acceptable and the final printed labeling should reflect these revisions.

/S/

1/6/99

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

APPEARS THIS WAY  
ON ORIGINAL