

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-406/S004

Trade Name: Prevacid Delayed Release Capsules

Generic Name: (lansoprazole)

Sponsor: TAP Holdings Inc

Approval Date: October 18, 1995

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-406/S004

CONTENTS

Reviews / Information Included in this NDA Review.

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

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 20-406/S004

APPROVAL LETTER

NDA 20-406/S-004

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

OCT 18 1995

Dear Ms. Wargel:

We acknowledge your September 25, 1995 supplemental new drug application, submitted as "Special Supplement-Changes Being Effected", received on September 26, 1995 under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prevacid (lansoprazole) Delayed-Release Capsules.

The supplemental application provides for the following changes to the package insert:

1. DOSAGE AND ADMINISTRATION section

A. Treatment of Duodenal Ulcer

from: "The recommended adult oral dose is 15 mg daily before eating for 4 weeks."

to: "The recommended adult oral dose is 15 mg once daily before eating for 4 weeks."

B. Treatment of Erosive Esophagitis

from: "The recommended adult oral dosage is 30 mg daily before eating for up to 8 weeks."

to: "The recommended adult oral dosage is 30 mg once daily before eating for up to 8 weeks."

These revisions were requested by the Agency on August 31, 1995.

2. Minor editorial revisions to the DESCRIPTION and ADVERSE REACTIONS sections.

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the final printed labeling submitted on September 25, 1995. Accordingly, the supplemental application is approved effective on the date of this letter.

NDA 20-406

Page 2

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

If you have any questions, please contact:

Maria Walsh
Consumer Safety Officer
(301) 443-0487

Sincerely yours,

Stephen B. Fredd, M.D.
Director

Division of Gastrointestinal
and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and
Research

cc:

Original NDA 20-406/S-004

HFD-180/Div. files

HFD-180/CSO/M.Walsh

HFD-100

DISTRICT OFFICE

HF-2/medwatch (with labeling)

HFD-80 (with labeling)

HFD-240/S.Sherman (with labeling)

HFD-500/L.Ripper (with labeling)

HFD-613 (with labeling - Only for applications with labeling.)

Drafted: MRW 10/6/95

R/D init: S.Fredd 10/12/95

Final: MRW 10/13/95

MRW/10/13/95/C:\wpfiles\cso\n\20406510.A04

APPROVAL

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 20-406/S004

LABELING

(1)

Labeling: Drug Street
NDA No: 20-406 Rc'd. 9-26-95
Reviewed by: M Walsh 10/6/95

APPROVED

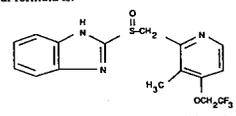
(Nos. 1541, 3046)
03-4623-R2-Rev. September, 1995

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

OCT 18 1995

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]sulfanyl] benzimidazole, a compound that inhibits gastric acid secretion. Its empirical formula is C₁₆H₁₄F₃N₃O₂S 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

* PREVACID 15 mg capsules only.

CLINICAL PHARMACOLOGY

Pharmacokinetics and Metabolism

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

Absorption

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

Distribution

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

Metabolism

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

Elimination

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

Special Populations

Geriatric

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

Pediatric

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

Gender

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

Renal Insufficiency

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

Hepatic Insufficiency

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

PHARMACODYNAMICS

Mechanism of action

Lansoprazole belongs to a class of antisecretory compounds; the substituted benzimidazoles, that do not exhibit anticholinergic or histamine H_2 -receptor antagonist properties, but that suppress gastric acid secretion by specific inhibition of the (H^+,K^+)-ATPase enzyme system at the secretory surface of the gastric parietal cell. Because this enzyme system is regarded as the acid (proton) pump within the parietal cell, lansoprazole has been characterized as a gastric acid-pump inhibitor, in that it blocks the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated gastric acid secretion irrespective of the stimulus.

Antisecretory activity

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

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

Mean Antisecretory Effects after Single and Multiple Daily Dosing

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*	4.0*	3.6*	4.9*	2.5	4.2*
Mean Nighttime pH	1.9	2.4	3.0*	2.6	3.8*	2.2	3.0*
% Time Gastric pH >3	18	33*	59*	51*	72*	30*	61*
% Time Gastric pH >4	12	22*	49*	41*	66*	19	51*

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

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

(3)

Mean Antisecretory Effects after Single and Multiple Daily Dosing

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

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

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

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

Enterochromaffin-like (ECL) cell effects

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

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

Other gastric effects in humans

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

Serum gastrin effects

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

Endocrine effects

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

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

Other effects

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

CLINICAL STUDIES

Duodenal Ulcer

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

Duodenal Ulcer Healing Rates

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

* (p<0.001) versus placebo.

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

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

Duodenal Ulcer Healing Rates

Week	PREVACID		Ranitidine	Placebo (N=41)
	15 mg qd (N=80)	30 mg qd (N=77)	300 mg hs (N=52)	
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.

(4)

(LH), follicle stimulating hormone (FSH), sex hormone binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEA-S), prolactin, cortisol, estradiol, insulin, aldosterone, parathormone, glucagon, thyroid stimulating hormone (TSH), triiodothyronine (T₃), thyroxine (T₄), and somatotrophic hormone (STH). Lansoprazole in oral doses of 15 to 60 mg for up to one year, had no clinically significant effect on sexual function. In addition, lansoprazole in oral doses of 15 to 60 mg for two to eight weeks had no clinically significant effect on thyroid function.

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

Other effects

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

CLINICAL STUDIES

Duodenal Ulcer

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

Duodenal Ulcer Healing Rates

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

* (p<0.001) versus placebo.

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

In a second U.S. multicenter study, also double-blind, placebo-, 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
	15 mg qd (N=80)	30 mg qd (N=77)	300 mg bid (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.

Erosive Esophagitis

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

Erosive Esophagitis Healing Rates

Week	PREVACID			Placebo
	15 mg qd (N=69)	30 mg qd (N=65)	60 mg qd (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 suggest 30 mg qd as the recommended dose.

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

Erosive Esophagitis Healing Rates

Week	PREVACID	Ranitidine
	30 mg qd (N=115)	150 mg bid (N=127)
2	62.7%*	38.7%
4	82.5%*	52.0%
6	93.0%*	67.8%
8	92.1%*	69.9%

* (p<0.001) versus ranitidine.

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

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

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

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

(3)

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

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

**p* < 0.001 versus ranitidine.

Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome

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

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

INDICATIONS AND USAGE

Short-Term Treatment of Active Duodenal Ulcer

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

PREVACID SHOULD NOT BE USED AS MAINTENANCE THERAPY FOR TREATMENT OF PATIENTS WITH DUODENAL ULCER DISEASE.

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.

PREVACID SHOULD NOT BE USED AS MAINTENANCE THERAPY.

Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome

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

CONTRAINDICATIONS

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

PRECAUTIONS

General

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

Information for Patients

PREVACID Delayed-Release Capsules should be taken before eating.

Patients should be cautioned that PREVACID Delayed-Release Capsules should not be opened, chewed or crushed. Capsules should be swallowed whole.

Drug Interactions

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

Coadministration of lansoprazole with sucralfate delayed absorption and reduced lansoprazole bioavailability by approximately 30%. Therefore, lansoprazole should be taken at least 30 minutes prior to sucralfate. In clinical trials, antacids were administered concomitantly with PREVACID Delayed-Release Capsules; this did not interfere with its effect.

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

Carcinogenesis, Mutagenesis, and Fertility

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

In a 24-month carcinogenicity study, CD-1 mice were treated orally with doses of 15 to 600 mg/kg/day, 2 to 80 times the recommended human dose based on body surface area. Lansoprazole produced a dose related increase in 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

(6)

Carcinogenesis, Mutagenesis, and Fertility

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

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

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

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

Pregnancy

Teratogenic Effects. Pregnancy Category B

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

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

Nursing Mothers

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

Pediatric Use

Safety and effectiveness in children have not been established.

Use in Women

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

Use in Elderly Patients

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

ADVERSE REACTIONS

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

Incidence in Clinical Trials

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

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 is similar between placebo and lansoprazole 15 mg and 30 mg patients, but higher in the lansoprazole 60 mg patients (2.9%, 1.4%, 4.2%, and 7.4%, respectively).

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

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

Body as a Whole - asthenia, candidiasis, chest pain (not otherwise specified), edema, fever, flu syndrome, halitosis, infection (not otherwise specified), malaise; **Cardiovascular System** - angina, cerebrovascular accident, hypertension/hypotension, myocardial infarction, palpitations, shock (circulatory failure), vasodilation; **Digestive System** - melena, anorexia, bezoar, cardiospasm, cholelithiasis, constipation, dry mouth/thirst, dyspepsia, dysphagia, eructation, esophageal stenosis, esophageal ulcer, esophagitis, fecal discoloration, flatulence, gastric nodules/fundic gland polyps, gastroenteritis, gastrointestinal hemorrhage, hematemesis, increased appetite, increased salivation, rectal hemorrhage, stomatitis, tenesmus, ulcerative colitis; **Endocrine System** - diabetes mellitus, goiter, hyperglycemia/hypoglycemia; **Hematologic and Lymphatic System** - anemia, hemolysis; **Metabolic and Nutritional Disorders** - gout, weight gain/loss; **Musculoskeletal System** - arthritis/arthralgia, musculoskeletal pain, myalgia;

(7)

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

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

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

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

Laboratory Values

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

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

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

OVERDOSAGE

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

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

DOSAGE AND ADMINISTRATION

Treatment of Duodenal Ulcer

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

Treatment of Erosive Esophagitis

The recommended adult oral dose is 30 mg once daily before eating 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.

Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome

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

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

HOW SUPPLIED

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

NDC 0300-1541-30

Unit of use bottles of 30: 15 mg capsules

NDC 0300-1541-13

Bottles of 100: 15 mg capsules

NDC 0300-1541-11

Unit dose package of 100: 15 mg capsules

NDC 0300-3046-30

Unit of use bottles of 30: 30 mg capsules

NDC 0300-3046-13

Bottles of 100: 30 mg capsules

NDC 0300-3046-11

Unit dose package of 100: 30 mg capsules

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

Store between 59°F and 86°F.

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

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

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

(8)

and 0.3% (2/795) lansoprazole patients had enzyme elevations greater than three times the upper limit of normal range at the final treatment visit. None of these patients reported jaundice at any time during the study.

OVERDOSAGE

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

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

DOSAGE AND ADMINISTRATION

Treatment of Duodenal Ulcer

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

Treatment of Erosive Esophagitis

The recommended adult oral dose is 30 mg once daily before eating 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.

Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome

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

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

HOW SUPPLIED

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

NDC 0300-1541-30

Unit of use bottles of 30: 15 mg capsules

NDC 0300-1541-13

Bottles of 100: 15 mg capsules

NDC 0300-1541-11

Unit dose package of 100: 15 mg capsules

NDC 0300-3046-30

Unit of use bottles of 30: 30 mg capsules

NDC 0300-3046-13

Bottles of 100: 30 mg capsules

NDC 0300-3046-11

Unit dose package of 100: 30 mg capsules

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

Store between 59°F and 86°F.

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

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



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

®—Registered Trademark

(Nos. 1541, 3046)
03-4623-R2-Rev. September, 1995
PREVACID[®]
(pre-va-sid)
(lansoprazole)
Delayed-Release Capsules



034623R2

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 20-406/S004

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS



TAP HOLDINGS INC.
parent of TAP Pharmaceuticals Inc.

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

September 25, 1995

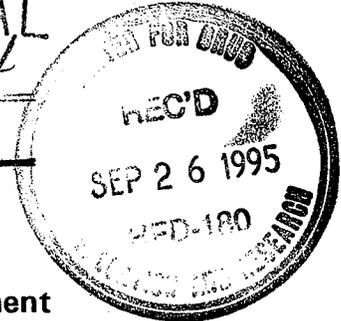
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Document Control Room 6B-24
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

ORIGINAL

NO. 20406 004

ATTN: Stephen B. Fredd, M.D. NDA SUPPL FOR SLR

RE: **Prevacid® (Lansoprazole) Delayed-Release Capsules**
NDA 20-406



Special Supplement
Changes Being Effected

Dear Dr. Fredd:

Per the request of Ms. Maria Walsh, CSO, on August 31, 1995, the Sponsor has revised the package insert under duodenal ulcer to read "....15 mg once daily before eating..." and under erosive esophagitis "....30 mg once daily before eating." Previously, it read "....15 mg daily..." for duodenal ulcer and "....30 mg daily..." for erosive esophagitis. The Sponsor was also given authorization to correct the error under laboratory values where ALT and AST were switched and used incorrectly. Also, under description the spelling of trifluoroethoxy in the chemical name was corrected to trifluoroethoxy.

Included in this submission are 15 copies of the final printed labeling (FPL). Ten copies are on heavy weight paper, and five copies are enclosed in an envelope.

Sincerely,

Judy Decker Wargel

Judy Decker Wargel
Associate Director, Regulatory Affairs
(708) 317-5781

JDW:pjp
Attachments

10/18/95
JP