CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-406/S018

Trade Name: Prevacid Delayed Release Capsules

Generic Name: (lansoprazole)

Sponsor: TAP Holdings Inc

Approval Date: June 23, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-406/S018

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-406/S018

APPROVAL LETTER

NDA 20-406/S-018

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

JUN 23 1997

Dear Ms. Wargel:

Please refer to your supplemental new drug application dated February 11, 1997, received February 12, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prevacid (lansoprazole) Delayed-Release Capsules.

The User Fee goal date for this application is August 12, 1997.

The supplemental application provides for revisions to the ADVERSE EVENTS section of the labeling to add hematological adverse events.

We have completed the review of this supplemental application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling in the submission dated February 12, 1997. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical in content to the draft labeling submitted on February 12, 1997. In addition, all previous revisions as reflected in the most recently approved package inserts 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 "FINAL PRINTED LABELING" for approved supplemental NDA 20-406/S-018. Approval of this submission by FDA is not required before the labeling is used.

Please provide, if possible, the annual reports of the Japanese six-year cohort surveys as referenced in the November 21, 1996 Agency report (page 5) attached to our January 7, 1997 letter. We also suggest that you consider more carefully the differences in reporting systems between Japan and the United States, beyond simple differences in cut-off levels for blood platelet counts, to explain possible ascertainment bias that may be operating.

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

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

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

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

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

Sincerely yours,

LT 6-23-97

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

cc:
Original NDA 20-406/S-018
HFD-180/Div. files
HFD-180/CSO/M.Walsh
HFD-180/J.Senior
DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-92/DDM-DIAB (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-735/DPE (with labeling) - for all NDAs and supplements for adverse reaction changes.
HFI-20/Press Office (with labeling)

Drafted by: M.Walsh 6/23/97
Initialed by: L.Talarico 6/23/97 6-23-97
final: M.Walsh 6/23/97
filename: 20406S18.AP

APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-406/S018

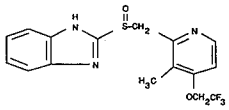
LABELING

(Nos. 1541, 3046)
03-4816-R8-Rev. August, 1997

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

CRIPTION

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



nsoprazole is a white to brownish-white odorless crystalline powder which melts
lecomposition at approximately 166°C. Lansoprazole is freely soluble in dimethyl-
mide; soluble in methanol; sparingly soluble in ethanol; slightly soluble in ethyl
e, dichloromethane and acetonitrile; very slightly soluble in ether; and practically
uble in hexane and water.

nsoprazole is stable when exposed to light for up to two months. The compound
des in aqueous solution, the rate of degradation increasing with decreasing pH. At
the $t_{1/2}$ is approximately 0.5 hour at pH 5.0 and approximately 18 hours at pH 7.0.
EVACID is supplied in delayed-release capsules for oral administration. The
ed-release capsules contain the active ingredient, lansoprazole, in the form of
c-coated granules and are available in two dosage strengths: 15 mg and 30 mg of
razole per capsule. Each delayed-release capsule contains enteric-coated granules
sting of lansoprazole, hydroxypropyl cellulose, low substituted hydroxypropyl cel-
, colloidal silicon dioxide, magnesium carbonate, methacrylic acid copolymer,
, talc, sugar sphere, sucrose, polyethylene glycol, polysorbate 80, and titanium
le. Components of the gelatin capsule include gelatin, titanium dioxide, D&C Red
8, FD&C Blue No. 1, FD&C Green No. 3*, and FD&C Red No. 40.

*ACID 15-mg capsules only.

IICAL PHARMACOLOGY

nacokinetics and Metabolism

*ACID Delayed-Release Capsules contain an enteric-coated granule formulation of
razole. Absorption of lansoprazole begins only after the granules leave the stom-
bsorption is rapid, with mean peak plasma levels of lansoprazole occurring after
ximately 1.7 hours. Peak plasma concentrations of lansoprazole (C_{max}) and the
nder the plasma concentration curve (AUC) of lansoprazole are approximately pro-
nal in doses from 15 mg to 60 mg after single-oral administration. Lansoprazole
ot accumulate and its pharmacokinetics are unaltered by multiple dosing.

ption

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

bution

prazole is 97% bound to plasma proteins. Plasma protein binding is constant over
ncentration range of 0.05 to 5.0 µg/mL.

olism

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

nation

ving single-dose oral administration of lansoprazole, virtually no unchanged lan-
zole was excreted in the urine. In one study, after a single oral dose of
nsoprazole, approximately one-third of the administered radiation was excreted in
ine and two-thirds was recovered in the feces. This implies a significant biliary
ion of the metabolites of lansoprazole.

al Populations

riatric

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

ric

harmacokinetics of lansoprazole has not been investigated in patients <18 years of

er

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

Insufficiency

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

ic Insufficiency

ients with various degrees of chronic hepatic disease, the mean plasma half-life of
ug was prolonged from 1.5 hours to 3.2-7.2 hours. An increase in mean AUC of up
)% was observed at steady state in hepatically-impaired patients compared to
y subjects. Dose reduction in patients with severe hepatic disease should be con-
d.

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

RMACODYNAMICS

anism of action

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

cretory activity

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

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

Mean Antisecretory Effects after Single and Multiple Daily Dosing

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

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

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

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

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

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

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

Enterochromaffin-like (ECL) cell effects

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

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

Other gastric effects in humans

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

Serum gastrin effects

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

Endocrine effects

Human studies for up to one year have not detected any clinically significant effects on the endocrine system. Hormones studied include testosterone, luteinizing hormone (LH), follicle stimulating hormone (FSH), sex hormone binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEA-S), prolactin, cortisol, estradiol, insulin, aldosterone, parathormone, glucagon, thyroid stimulating hormone (TSH), triiodothyronine (T_3), thyroxine (T_4), and somatotropic hormone (STH). Lansoprazole in oral doses of 15 to 60 mg for up to one year had no clinically significant effect on sexual function. In addition, lansoprazole in oral doses of 15 to 60 mg for two to eight weeks had no clinically significant effect on thyroid function.

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

Other effects

No systemic effects of lansoprazole on the central nervous system, lymphoid, hematopoietic, renal, hepatic, cardiovascular or respiratory systems have been found in humans. No visual toxicity was observed among 26 patients who had extensive baseline eye evaluations, were treated with up to 180 mg/day of lansoprazole and were observed for up to 58 months. Other rat-specific findings after lifetime exposure included focal pancreatic atrophy, diffuse lymphoid hyperplasia in the thymus, and spontaneous retinal atrophy.

Microbiology

Susceptibility Testing for Helicobacter pylori

In vitro susceptibility testing methods and diagnostic products currently available for determining minimum inhibitory concentrations (MICs) and zone sizes have not been standardized, validated, or approved for testing *H. pylori* microorganisms.

Culture and susceptibility testing should be obtained in patients who fail triple therapy. If clarithromycin resistance is found, a non-clarithromycin-containing regimen should be used.

CLINICAL STUDIES

Duodenal Ulcer

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

Duodenal Ulcer Healing Rates

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

*(p≤0.001) versus placebo.

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

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

Duodenal Ulcer Healing Rates

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

*(p≤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.

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

Study	Triple Therapy Evaluable Analysis*	Triple Therapy Intent-to-Treat Analysis#
M93-131	92† [80.0-97.7] (N=48)	86† [73.3-93.5] (N=55)
M95-392	86† [75.7-93.6] (N=66)	83† [72.0-90.8] (N=70)

*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 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.

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

Study	Dual Therapy Evaluable Analysis*	Dual Therapy Intent-to-Treat Analysis#
M93-131	77† [62.5-87.2] (N=51)	70† [56.8-81.2] (N=60)
M95-125	66‡ [51.9-77.5] (N=58)	61‡ [48.5-72.9] (N=67)

*Based on evaluable patients with confirmed duodenal ulcer (active or within one year) and *H. pylori* infection at baseline defined as at least two of three positive endoscopic tests from CLOtest®, histology and/or culture. Patients were included in the analysis if they completed the study. Additionally, if patients dropped out of the study due to an adverse event related to the study drug, they were included in the analysis as failures of therapy.
#Patients were included in the analysis if they had documented *H. pylori* infection at baseline as defined above and had a confirmed duodenal ulcer (active or within one year). All dropouts were included as failures of therapy.
†(p<0.05) versus PREVACID alone.
‡(p<0.05) versus PREVACID alone or amoxicillin alone.

Long-Term Maintenance Treatment of Duodenal Ulcers

PREVACID has been shown to prevent the recurrence of duodenal ulcers. Two indepe
dent, double-blind, multicenter, controlled trials were conducted in patients with end
scopically confirmed healed duodenal ulcers. Patients remained healed significant
longer and the number of recurrences of duodenal ulcers was significantly less in patier
treated with PREVACID than in patients treated with placebo over a 12-month period

Endoscopic Remission Rates

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

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

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

Gastric Ulcer

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

Gastric Ulcer Healing Rates

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

*(p≤0.05) versus placebo.

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

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

Erosive Esophagitis

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

Erosive Esophagitis Healing Rates

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

*(p≤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 ar
less day and night abdominal pain along with fewer days of antacid use and fewer antaci
tablets taken per day than the placebo group.

Although all doses were effective, the earlier healing in the higher two doses sugges
30 mg q.d. as the recommended dose.

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

Erosive Esophagitis Healing Rates

	PREVACID 30 mg q.d. (N=115)	Ranitidine 150 mg b.i.d. (N=127)
Week		
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 heartbu
and took less antacid tablets for fewer days than patients taking ranitidine 150 mg b.i.

Although this study demonstrates effectiveness of PREVACID in healing erosi
esophagitis, it does not represent an adequate comparison with ranitidine because the re
ommended ranitidine dose for esophagitis is 150 mg q.i.d., twice the dose used in th
study.

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

In a U.S. multicenter, double-blind, active-controlled study, 30 mg of PREVACID wa
compared with ranitidine 150 mg b.i.d. in 151 patients with erosive reflux esophagit
that was poorly responsive to a minimum of 12 weeks of treatment with at least o
H_2-receptor antagonist given at the dose indicated for symptom relief or greater, namel
cimetidine 800 mg/day, ranitidine 300 mg/day, famotidine 40 mg/day or nizatidi
300 mg/day. PREVACID 30 mg was more effective than ranitidine 150 mg b.i.d. in hea
ing reflux esophagitis, and the percentage of patients with healing were as follows. Th
study does not constitute a comparison of the effectiveness of histamine H_2-recepto
antagonists with PREVACID, as all patients had demonstrated unresponsiveness to th
histamine H_2-receptor antagonist mode of treatment. It does indicate, however, th
PREVACID may be useful in patients failing on a histamine H_2-receptor antagonist.

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

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

*(p≤0.001) versus ranitidine.

Long-Term Maintenance Treatment of Erosive Esophagitis

Two independent, double-blind, multicenter, controlled trials were conducted in patient
with endoscopically confirmed healed esophagitis. Patients remained in remission sig
nificantly longer and the number of recurrences of erosive esophagitis was significantl
less in patients treated with PREVACID than in patients treated with placebo over
12-month period.

Endoscopic Remission Rates

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

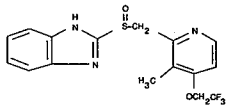
%=Life Table Estimate

(Nos. 1541, 3046)
03-4816-R9-Rev. August, 1997

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

ESCRIPTION

e active ingredient in PREVACID (lansoprazole) Delayed-Release Capsules is a sub-tuted benzimidazole, 2-[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl] methyl] finyl] benzimidazole, a compound that inhibits gastric acid secretion. Its empirical for-da 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 th decomposition at approximately 166°C. Lansoprazole is freely soluble in dimethyl-rmamide; soluble in methanol; sparingly soluble in ethanol; slightly soluble in ethyl etate, dichloromethane and acetonitrile; very slightly soluble in ether; and practically soluble in hexane and water.

Lansoprazole is stable when exposed to light for up to two months. The compound grades in aqueous solution, the rate of degradation increasing with decreasing pH. At °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 layed-release capsules contain the active ingredient, lansoprazole, in the form of teric-coated granules and are available in two dosage strengths: 15 mg and 30 mg of ısoprazole per capsule. Each delayed-release capsule contains enteric-coated granules nsisting of lansoprazole, hydroxypropyl cellulose, low substituted hydroxypropyl cel-ose, colloidal silicon dioxide, magnesium carbonate, methacrylic acid copolymer, urch, talc, sugar sphere, sucrose, polyethylene glycol, polysorbate 80, and titanium xide. Components of the gelatin capsule include gelatin, titanium dioxide, D&C Red), 28, FD&C Blue No. 1, FD&C Green No. 3*, and FD&C Red No. 40.

REVACID 15-mg capsules only.

LINICAL PHARMACOLOGY

harmacokinetics and Metabolism

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

sorption

e absorption of lansoprazole is rapid, with mean C_{max} occurring approximately 7 hours after oral dosing, and relatively complete with absolute bioavailability over %. In healthy subjects, the mean (± SD) plasma half-life was 1.5 (± 1.0) hours. Both ax and AUC are diminished by about 50% if the drug is given 30 minutes after food opposed to the fasting condition. There is no significant food effect if the drug is given fore meals.

stribution

nsoprazole is 97% bound to plasma proteins. Plasma protein binding is constant over : concentration range of 0.05 to 5.0 μg/mL.

etabolism

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

imination

llowing single-dose oral administration of lansoprazole, virtually no unchanged lan-prazole was excreted in the urine. In one study, after a single oral dose of C-lansoprazole, approximately one-third of the administered radiation was excreted in : urine and two-thirds was recovered in the feces. This implies a significant biliary cretion of the metabolites of lansoprazole.

ecial Populations

riatric

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

diatric

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

nder

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

nal Insufficiency

patients with severe renal insufficiency, plasma protein binding decreased by 1.0%-9% after administration of 60 mg of lansoprazole. Patients with renal insufficiency had hortened elimination half-life and decreased total AUC (free and bound). AUC for free ısoprazole in plasma, however, was not related to the degree of renal impairment, and T_{max} were not different from subjects with healthy kidneys.

patic Insufficiency

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

ce

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

HARMACODYNAMICS

echanism of action

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

tisecretory activity

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

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

Mean Antisecretory Effects after Single and Multiple Daily Dosing

		PREVACID				Omeprazole	
	Baseline	15 mg		30 mg		20 mg	
rameter	Value	Day 1	Day 5	Day 1	Day 5	Day 1	Day 5
ean 24-Hour pH	2.1	2.7*	4.0*	3.6*	4.9*	2.5	4.2*
ean 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*

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

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

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

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

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

Enterochromaffin-like (ECL) cell effects

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

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

Other gastric effects in humans

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

Serum gastrin effects

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

Endocrine effects

Human studies for up to one year have not detected any clinically significant effects on the endocrine system. Hormones studied include testosterone, luteinizing hormone (LH), follicle stimulating hormone (FSH), sex hormone binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEA-S), prolactin, cortisol, estradiol, insulin, aldosterone, parathormone, glucagon, thyroid stimulating hormone (TSH), triiodothyronine (T_3), thyroxine (T_4), and somatotropic hormone (STH). Lansoprazole in oral doses of 15 to 60 mg for up to one year had no clinically significant effect on sexual function. In addition, lansoprazole in oral doses of 15 to 60 mg for two to eight weeks had no clinically significant effect on thyroid function.

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

Other effects

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

Microbiology

Susceptibility Testing for Helicobacter pylori

In vitro susceptibility testing methods and diagnostic products currently available for determining minimum inhibitory concentrations (MICs) and zone sizes have not been standardized, validated, or approved for testing *H. pylori* microorganisms.

Culture and susceptibility testing should be obtained in patients who fail triple therapy. If clarithromycin resistance is found, a non-clarithromycin-containing regimen should be used.

CLINICAL STUDIES

Duodenal Ulcer

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

Duodenal Ulcer Healing Rates

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

*(p≤0.001) versus placebo.

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

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

Duodenal Ulcer Healing Rates

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

*(p≤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.

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

Study	Triple Therapy Evaluable Analysis*	Triple Therapy Intent-to-Treat Analysis#
M93-131	92† [80.0-97.7] (N=48)	86† [73.3-93.5] (N=55)
M95-392	86† [75.7-93.6]	83† [72.0-90.8]

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

Study	Dual Therapy Evaluable Analysis*	Dual Therapy Intent-to-Treat Analysis#
M93-131	77† [62.5-87.2] (N=51)	70† [56.8-81.2] (N=60)
M95-125	66‡ [51.9-77.5] (N=58)	61‡ [48.5-72.9] (N=67)

*Based on evaluable patients with confirmed duodenal ulcer (active or within one year) and *H. pylori* infec 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 study due to an adverse event related to the study drug, they were included in the analysis as failures of th
#Patients were included in the analysis if they had documented *H. pylori* infection at baseline as defined ab and had a confirmed duodenal ulcer (active or within one year). All dropouts were included as failures of the
†(p<0.05) versus PREVACID alone.
‡(p<0.05) versus PREVACID alone or amoxicillin alone.

Long-Term Maintenance Treatment of Duodenal Ulcers

PREVACID has been shown to prevent the recurrence of duodenal ulcers. Two ind dent, double-blind, multicenter, controlled trials were conducted in patients with scopically confirmed healed duodenal ulcers. Patients remained healed signific longer and the number of recurrences of duodenal ulcers was significantly less in pa treated with PREVACID than in patients treated with placebo over a 12-month per

Endoscopic Remission Rates

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

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

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

Gastric Ulcer

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

Gastric Ulcer Healing Rates

	PREVACID			Placebo
Week	15 mg q.d. (N=65)	30 mg q.d. (N=63)	60 mg q.d. (N=61)	(N=64)
4	64.6%*	58.1%*	53.3%*	31.5%
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 abdominal pain along with fewer days of antacid use and fewer antacid tablets use day than the placebo group.

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

Erosive Esophagitis

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

Erosive Esophagitis Healing Rates

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

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

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

Although all doses were effective, the earlier healing in the higher two doses sug 30 mg q.d. as the recommended dose.

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

Erosive Esophagitis Healing Rates

	PREVACID 30 mg q.d. (N=115)	Ranitidine 150 mg b.i.d. (N=127)
Week		
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 hea and took less antacid tablets for fewer days than patients taking ranitidine 150 mg

Although this study demonstrates effectiveness of PREVACID in healing er esophagitis, it does not represent an adequate comparison with ranitidine because th ommended ranitidine dose for esophagitis is 150 mg q.i.d., twice the dose used i study.

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

In a U.S. multicenter, double-blind, active-controlled study, 30 mg of PREVACI compared with ranitidine 150 mg b.i.d. in 151 patients with erosive reflux esoph that was poorly responsive to a minimum of 12 weeks of treatment with at leas H_2-receptor antagonist given at the dose indicated for symptom relief or greater, na cimetidine 800 mg/day, ranitidine 300 mg/day, famotidine 40 mg/day or nizat 300 mg/day. PREVACID 30 mg was more effective than ranitidine 150 mg b.i.d. in ing reflux esophagitis, and the percentage of patients with healing were as follows. study does not constitute a comparison of the effectiveness of histamine H_2-rec antagonists with PREVACID, as all patients had demonstrated unresponsiveness histamine H_2-receptor antagonist mode of treatment. It does indicate, however PREVACID may be useful in patients failing on a histamine H_2-receptor antagonis

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

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

*(p≤0.001) versus ranitidine.

Long-Term Maintenance Treatment of Erosive Esophagitis

Two independent, double-blind, multicenter, controlled trials were conducted in pa with endoscopically confirmed healed esophagitis. Patients remained in remissio nificantly longer and the number of recurrences of erosive esophagitis was signific less in patients treated with PREVACID than in patients treated with placebo o 12-month period.

Endoscopic Remission Rates

			Percent in Endoscopic Remission		
Trial	Drug	No. of Pts.	0-3 mo.	0-6 mo.	0-12 mo.
#1	PREVACID 15 mg q.d.	59	83%*	81%*	79%*
	PREVACID 30 mg q.d.	56	93%*	93%*	90%*

PREVACID significantly inhibited gastric acid secretion and controlled associated symptoms of diarrhea, anorexia and pain. Doses ranging from 15 mg every other day to 80 mg per day maintained basal acid secretion below 10 mEq/hr in patients without prior gastric surgery and below 5 mEq/hr in patients with prior gastric surgery.

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

INDICATIONS AND USAGE

Short-Term Treatment of Active Duodenal Ulcer

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

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

Triple Therapy (PREVACID/amoxicillin/clarithromycin)

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

Dual Therapy (PREVACID/amoxicillin)

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

Maintenance of Healed Duodenal Ulcers

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

Short-Term Treatment of Active Benign Gastric Ulcer

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

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.

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 appropriate therapy instituted.

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

PRECAUTIONS

General

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

Information for Patients

PREVACID Delayed-Release Capsules should be taken before eating.

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

Drug Interactions

Lansoprazole is metabolized through the cytochrome P_{450} system, specifically through the CYP3A and CYP2C19 isozymes. Studies have shown that lansoprazole does not have clinically significant interactions with other drugs metabolized by the cytochrome P_{450} system, such as warfarin, antipyrine, indomethacin, ibuprofen, phenytoin, propranolol, prednisone, diazepam, clarithromycin, or terfenadine in healthy subjects. These compounds are metabolized through various cytochrome P_{450} isozymes including CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A. When lansoprazole was administered concomitantly with theophylline (CYP1A2, CYP3A), a minor increase (10%) in the clearance of theophylline was seen. Because of the small magnitude and the direction of the effect on theophylline clearance, this interaction is unlikely to be of clinical concern. Nonetheless, individual patients may require additional titration of their theophylline dosage when lansoprazole is started or stopped to ensure clinically effective blood levels.

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

In a single-dose crossover study examining lansoprazole 30 mg and omeprazole 40 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.

gastric enterochromaffin-like (ECL) cell hyperplasia and ECL cell carcinoids in both male and female rats. It also increased the incidence of intestinal metaplasia of the gastric epithelium in both sexes. In male rats, lansoprazole produced a dose-related increase of testicular interstitial cell adenomas. The incidence of these adenomas in rats receiving doses of 15 to 150 mg/kg/day (4 to 40 times the recommended human dose based on body surface area) exceeded the low background incidence (range = 1.4 to 10%) for this strain of rat. Testicular interstitial cell adenoma also occurred in 1 of 30 rats treated with 50 mg/kg/day (13 times the recommended human dose based on body surface area) in a 1-year toxicity study.

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

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

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

Pregnancy: Teratogenic Effects. Pregnancy Category B

Lansoprazole

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

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

Clarithromycin

Pregnancy Category C

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

Nursing Mothers

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

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Use in Women

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

Use in Geriatric Patients

Ulcer healing rates in elderly patients are similar to those in a younger age group. The incidence rates of adverse events and laboratory test abnormalities are also similar to those seen in younger patients. For elderly patients, dosage and administration of lansoprazole need not be altered for a particular indication.

ADVERSE REACTIONS

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

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

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

Body System/Adverse Event	PREVACID (N=1457) %	Placebo (N=467) %
Body as a Whole		
Abdominal Pain	1.8	1.3
Digestive System		
Diarrhea	3.6	2.6
Nausea	1.4	1.3

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

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

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

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

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

Combination Therapy with Amoxicillin and Clarithromycin

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

Triple Therapy: PREVACID/amoxicillin/clarithromycin

The most frequently reported adverse events for patients who received triple therapy were diarrhea (7%), headache (6%), and taste perversion (5%). 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:

visit. None of these patients reported jaundice at any time during the study.

In clinical trials using combination therapy with PREVACID plus amoxicillin, clarithromycin, and PREVACID plus amoxicillin, no increased laboratory abnormalities in 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 report of overdose, the patient consumed 600 mg of lansoprazole with no adverse reaction.

DOSAGE AND ADMINISTRATION

Treatment of Duodenal Ulcer

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

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 14 days. (See INDICATIONS AND USAGE.)

Dual Therapy: PREVACID/amoxicillin

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

Please refer to amoxicillin and clarithromycin full prescribing information for TRAINDICATIONS 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.)

Treatment of Gastric Ulcer

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

Treatment of Erosive Esophagitis

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

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

Maintenance of Healing of Erosive Esophagitis

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

Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome

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

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

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

HOW SUPPLIED

PREVACID Delayed-Release Capsules, 15 mg, are opaque, hard gelatin, colored and green. The 30 mg are opaque, hard gelatin, pink and black colored capsules 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).

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-406/S018

MEDICAL REVIEW(S)

59.1

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

NDA:	20-406 JUN 20 1997 SLR-018
SPONSOR:	TAP Holdings Inc. 2355 Waukegan Road, Deerfield, IL 60015
DATE OF SUBMISSION:	11 February 1997
DATE OF RECEIPT:	12 February 1997
ASSIGNED FOR REVIEW:	12 February 1997
DRUG:	Lansoprazole (PREVACID®) delayed-release capsules; [gastric parietal cell proton pump inhibitor]
ROUTE OF ADMINISTRATION:	Oral, 15 or 30 mg once daily before eating
PROPOSED LABEL CHANGE:	Inclusion of language to reflect reported serious adverse hematological events.
MATERIAL REVIEWED:	Supplemental application; proposed change in labeling, one volume; post-marketing safety report from HFD-735 of 21 November 1996 and letter from HFD-180 of 7 January 1997.
REVIEWER:	John R. Senior, M.D./ 19 June 1997

I. Background

Lansoprazole (PREVACID®, pre'-va-sid, AG-1749, TAP Holdings Inc.), was approved on 10 May 1995 for short-term, up to 4 weeks, treatment by oral dosage of 15 mg once daily before eating for healing of active duodenal ulcer; for doses of 30 mg once daily before eating for up to 8 weeks for healing of erosive esophagitis (plus an additional 8 weeks if not healed or recurrent); and for 60 or more mg/day indefinitely for the Zollinger-Ellison syndrome or other pathological hypersecretory conditions (divided doses are recommended for over 120 mg/day).It has subsequently been approved for maintenance of erosive esophagitis, 8 April 1996, and for maintenance of healing of duodenal ulcer, 17 April 1997. The drug is now approved in over 60 countries around the world, and is very heavily prescribed by thousands of physicians. As the total patient-years of exposure mounts into the hundreds of thousands and millions, it may be anticipated that rare or unusual adverse events may be reported. Surveillance had shown in 1996 that several serious but unlabeled hematologic adverse events had been reported, often with scant information about the surrounding circumstances. However, 13 cases of serious hematologic events had been discovered in patients in whom the lansoprazole ingestion was not confounded by other drugs known to cause such changes, and in whom the lansoprazole was administered in the period immediately before the event. These included: 3 patients with agranulocytosis, 2 patients with aplastic anemia, and 1 patient each with leukopenia, pancytopenia,

thrombocytopenia, leukopenia and thrombocytopenia together, agranulocytosis and thrombocytopenia together, thrombotic thrombocytopenic purpura, hemolytic anemia, and iron deficiency anemia. The cases were all in adults, from 30 to 82 years of age; 4 men and 9 women; median time to event after starting lansoprazole 31 days, and median dose 30 mg/day. Of theses 2 patients died, 4 were hospitalized, and the events were considered life-threatening in 6. Most of the cases (8) were reported from Japan, 1 from the U.K., and the other 4 from the U.S. These findings, as expressed in copy of the report from the Division of Pharmacovigilence and Epidemiology (HFD-730), were relayed to the sponsor on 7 January 1997, with a request the data be evaluated to suggest possible labeling changes.

II. Response of the Sponsor

The sponsor reported on 11 February 1997 by letter that the HFD-730 report had been reviewed, along with all other hematologic adverse event reports known to them. It was noted the rather high proportion of cases of thrombocytopenia from Japan might have been the result of the custom in Japan of defining thrombocytopenia more conservatively than in the U.S. (Although only 4 of the 13 patients had specifically mentioned thrombocytopenia). They did agree that their labeling would be revised at the next reprinting opportunity, probably at about this time (a labeling change to accommodate the use of anti-Helicobacter therapy was just discussed with the sponsor earlier this week). The sponsor agreed to restructure the ADVERSE REACTIONS section of the labeling to include the language:

"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.

ADVERSE EVENTS: Hematologic and Lymphatic System* - agranulocytosis, aplastic anemia, hemolytic anemia, leukopenia, pancytopenia, thrombocytopenia, neutropenia, and thrombotic thrombocytopenic purpura.

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

The request of the HFD-735 reviewer that the sponsor explain differences in reporting systems between Japan and the United States, and account for the apparent greater incidence of reports in the latter, was not entirely answered in the submission of 11 February 1997. It was mentioned by the HFD-735 reviewer that according to Harmonisation guidelines stated that Japanese regulatory authorities require a survey of a cohort of several thousand patients over a period of 6 years after approval, to provide precise denominator data, be submitted annually there. Such reports could well indicate a higher incidence of adverse events than spontaneous reporting.

III. Regulatory Recommendations

It is recommended that the sponsor's proposed changes to the labeling, to reflect the reported relatively small number of serious hematologic adverse events, be accepted and incorporated into the reprinted labeling at the next opportunity. It is further suggested that this could be done at this time, in conjunction with the labeling changes discussed earlier this week concerning the Helicobacter pylori eradication therapy utilizing lansoprazole and antibiotics. The labeling changes reasonably reflect the state of current knowledge concerning the hematologic safety of lansoprazole, but further vigilance is appropriate. It is suggested that the sponsor consider more carefully the differences in reporting systems between Japan and the United States, beyond simple differences in cut-off levels for blood platelet counts, to explain possible ascertainment bias that may be operating.

John R. Senior MD 20 Jun '97

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

cc:
NDA 20-406, SLR-018
HFD-180
HFD-180/LTALARICO LT 6-20-97
HFD-180/JSenior
HFD-180/JChoudary
HFD-180/EDuffy
HFD-180/FHarrison
HFD-181/CSO
f/t 6/20/97 jgw
MED/N/20406706.0JS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-406/S018

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

NDA 20-406/S-018

OCT - 8 1997

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

Dear Dr. Magistrelli:

We acknowledge the receipt of your September 5, 1997 submission containing final printed labeling in response to our June 23, 1997 letter approving your supplemental new drug application for Prevacid (lansoprazole) Delayed-Release Capsules.

Supplement 018 provides for revisions to the ADVERSE EVENTS section of the labeling to add hematological adverse events.

We have reviewed the labeling that you have submitted in accordance with our June 23, 1997 letter, and we find it acceptable.

Sincerely yours,

LT 10-7-97

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

cc:

Original NDA 20-406/SLR-018
HFD-180/Div. Files
HF-2/Medwatch (with labeling)
HFD-103/Office Director (with labeling)
HFD-180/CSO/M.Walsh
HFD-40/DDMAC (with labeling)
HFD-92/DDM-DIAB (with labeling)
HFD-613/OGD (with labeling)
HFD-735/DPE (with labeling)

final: M.Walsh 10/6/97
filename: 20406S18.A&R

ACKNOWLEDGE AND RETAIN (AR)

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: NDA 20-406/SLR-018

OCT - 6 1997

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

Sponsor: TAP Holdings, Inc.

Material Reviewed

Submission Date(s): September 5, 1997

Receipt Date(s): September 8, 1997

Background and Summary Description: The sponsor submitted final printed labeling (FPL) for supplement 018, approved on draft on June 23, 1997. This supplement provides for revisions to the ADVERSE EVENTS section of the labeling to add hematological adverse events.

Review

The submitted FPL, identified as "03-4816-R9-Rev.August, 1997," was compared to the approved draft labeling and the currently approved labeling, identified as "03-4807-R8-Rev.June, 1997," approved in supplements 013 and 015 on June 17, 1997. All approved revisions to the labeling were incorporated into the submitted FPL and no other differences were noted.

Conclusions

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

Maria R. Walsh 10/6/97

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

cc:
Original NDA 20-406/S-018
HFD-180/Div. Files
HFD-180/M.Walsh
HFD-180/L.Talarico 10-2-97

final: M.Walsh 10/6/97
filename: 20406S18.rev

CSO REVIEW

59.1

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: NDA 20-406/SLR-018

MAR 18 1997

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

Sponsor: TAP Holdings, Inc.

Material Reviewed

Submission Date(s): February 11, 1997

Receipt Date(s): February 12, 1997

Background and Summary Description: The sponsor submitted supplement 018 on February 11, 1997 with draft labeling. The supplement provides for revisions to the ADVERSE REACTIONS section of the package insert to include additional hematologic adverse events as recommended in our January 7, 1997 letter.

Review

The submitted draft labeling was compared to the currently approved labeling, identified as "03-4742-R5-Rev. December, 1996" approved December 24, 1996 in supplement 012. The following differences were noted.

1. PRECAUTIONS, Pediatric Use

   This section was revised

   from: "Safety and effectiveness in children have not been established."

   to: "Safety and effectiveness in pediatric patients have not been established."

   ACCEPTABLE. This revision conforms to the final rule published in the Federal Register on December 13, 1994, which revised the labeling requirements for the "Pediatric Use" subsection of the labeling for prescription drugs.

2. ADVERSE REACTIONS

   A. The header, "Incidence in Clinical Trials" was deleted.

B. Under *Hematologic and Lymphatic System*

1) the following terms were added following this title: agranulocytosis, aplastic anemia, hemolytic anemia, leukopenia, neutropenia, pancytopenia, thrombocytopenia, and thrombotic thrombocytopenia purpura.

2) an asterisk was added to the end of this title with an accompanying footnote stating, "The majority of hematologic cases received were foreign-sourced and their relationship to lansoprazole was unclear."

THESE REVISIONS MUST BE REVIEWED BY THE MEDICAL OFFICER.

Conclusions

The medical officer must review the proposed revisions to the ADVERSE REACTIONS section of the labeling.

Maria R. Walsh 3/17/97
Maria R. Walsh, Project Manager

cc:
Original NDA 20-406/SLR-018
HFD-180/Div. Files
HFD-180/M.Walsh
HFD-180/S.Fredd
J.Senior

3/17/97

final: M.Walsh 3/17/97
C:\wpfiles\cso\n\20406S018.R01

CSO REVIEW

NDA 20-406/S-018

59.1

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

FEB 14 1997

Dear Ms. Wargel:

We acknowledge receipt of your supplemental application for the following:

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

NDA Number: NDA 20-406

Supplement Number: S-018

Therapeutic Classification: Standard

Date of Supplement: February 11, 1997

Date of Receipt: February 12, 1997

This supplement provides for revisions to the ADVERSE EVENTS section of the labeling to add hematological adverse events.

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 11, 1997 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

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

Sincerely yours,

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

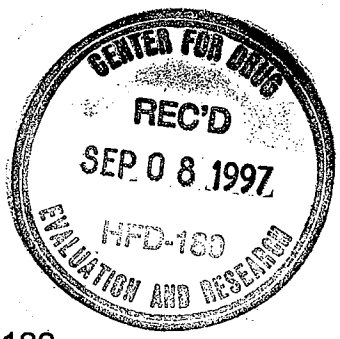
cc:
Original NDA 20-406/S-018
HFD-180/Div. Files
HFD-180/CSO/M.Walsh MRW 2/13/97
HFD-180/J.Senior
DISTRICT OFFICE

Final: M.Walsh 2/13/97

SUPPLEMENT ACKNOWLEDGEMENT (AC)

TAP HOLDINGS INC.
parent of TAP Pharmaceuticals Inc.

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



September 5, 1997

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

SLR/FA 018

Attn: Lilia Talarico, M.D.

RE: PREVACID®(lansoprazole) Delayed-Release Capsules
NDA 20-406; S-018
Final Printed Labeling

Dear Dr. Talarico:

Per your letter of June 23, 1997, enclosed are 20 copies of Final Printed Labeling, ten of which are individually mounted on heavy weight paper. The wording cleared by the Agency on adverse reactions is incorporated into the enclosed package insert. This wording is identical to that which was submitted to the Agency in SNDA 018 on February 11, 1997. However, since that time, five SNDAs have been cleared by the Agency which have impacted the labeling. The enclosed insert incorporates the revised adverse reaction information into the most recently approved package insert which reflects all previous revisions.

Sincerely,

Mary C. Mazzatelli for

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

JDW/mea

CONFIDENTIAL INFORMATION

Contains trade secret and/or confidential information which is the property of TAP HOLDINGS INC. As provided by 21 CFR § 20.61, DO NOT DISCLOSE to the public.

21 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

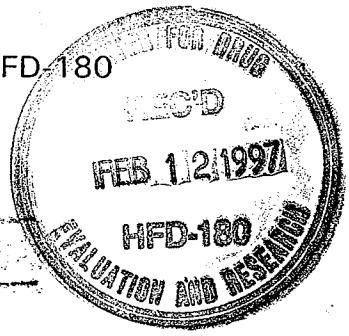
Withheld Track Number: Administrative- 20-406
SOI8

TAP HOLDINGS INC.
parent of TAP Pharmaceuticals Inc.

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

ORIGINAL

February 11, 1997



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

NDA NO 20406 SUPPL NO 018
NDA SUPPL TYPE SLR

Attn: Stephen B. Fredd, M.D.

RE: PREVACID® (Lansoprazole) Delayed-Release Capsules
NDA: 20-406
Supplemental Application for Labeling Change SNDA 018

Dear Dr. Fredd:

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

Reference is made to your letter dated January 7, 1997, regarding Carol Pamer's review of reports of hematologic adverse events coincident with lansoprazole therapy. TAP thoroughly reviewed all of the reports we have received. It was noted that most of these originated ex-USA. Unfortunately, few details were provided to TAP for many of these cases including laboratory values in some instances. Also, it was noted that the definition of thrombocytopenia, for instance, differed in Japan from that commonly used in the United States resulting in reports of thrombocytopenia from physicians in Japan which do not meet the commonly accepted U.S. criterion. Some of these hematologic adverse events are currently covered in the labeling under Laboratory Values. However, we agree it is prudent to advise the prescribing physician of these reports in the Adverse Events section of the labeling. Therefore, we proposed to add the following to the package insert under "ADVERSE EVENTS": *Hematologic and Lymphatic System** - agranulocytosis, aplastic anemia, hemolytic anemia, leukopenia, pancytopenia, thrombocytopenia, neutropenia, and thrombotic thrombocytopenic purpura.

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

2/20/97

To accommodate this additional information, we propose to restructure the ADVERSE REACTIONS section of the package insert. Namely, the header **Incidence in Clinical Trials** was removed.

The verbiage introducing adverse events reported in <1% of patients was changed from:

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

to:

> 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.

This restructuring facilitates the addition of the postmarketing hematologic events into the current listing. It will also allow for the inclusion of additional adverse events should it be deemed necessary. Finally, this structure more closely parallels the adverse event section of the Prilosec® (omeprazole) package insert.

We propose to make this change at the next revision/reprinting of the package insert which we believe will occur within the next six months. At that time, we will also make the change regarding the use of PREVACID in children. This was discussed with Ms. Maria Walsh on January 14, 1997. The new wording will be: "Safety and effectiveness in pediatric patients..."

Please advise if the wording and structure of the attached labeling is acceptable to the Agency as well as our timeline.

Should you have any questions or require additional information, do not hesitate to contact me.

Sincerely,

Judy Decker Wargel

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

JDW/pjp

59.1

USER FEE DATA ENTRY/VALIDATION FORM

Ver.2(9/1/93)

NDA #20-406 DOCUMENT ID/LETTER DATE SLR018 2-11-97 - 2-12-97

APPLICANT NAME TAP Holdings Inc

PRODUCT NAME Prevacid DR Capsules

FORM MUST BE COMPLETED BY (10 DAYS FROM DOCUMENT RECEIPT): _____

1. YES (NO) **CLINICAL DATA?**
[Check YES if contains study reports or literature reports of what are explicitly or implicitly represented by the applicant to be adequate and well-controlled trials. "Clinical data" do not include data used to modify the labelling to add a restriction that would improve the safe use of the drug (e.g., to add an adverse reaction, contraindication or warning to the labeling).]

REF **IF NO CLINICAL DATA IN SUBMISSION, INDICATE IF CLINICAL DATA ARE CROSS REFERENCED IN ANOTHER SUBMISSION?**

IF SUPPLEMENT and NO CLINICAL DATA INCLUDED, SKIP TO ITEM 11!

2. YES NO **505(b)(2) NDA?** An application in which one or more of the pivotal studies (rather than all) was not conducted or sponsored by the applicant and the applicant does not have a right of reference to that study. In addition, the firm must have made a patent certification under section 505(b)(2)(A) and (B) of the Act and must have cited a reference listed drug on which it is basing its application.

YES NO **If 505(b)(2) NDA - FEE APPLIES?**
[Check YES if application is for a new chemical entity or Indication. Check NO if application is for a previously approved drug substance or indication.]

3. YES NO **LARGE VOLUME PARENTERAL APPROVED BEFORE 9/1/92?** [Check YES only if a supplement with clinical data submitted to an LVP application first approved before 9/1/92.]

YES NO **505(j) NDA?** Abbreviated Application **IF YES, SKIP TO ITEM 11!**

5. YES NO **506 NDA?** Insulin Product **IF YES, SKIP TO ITEM 11!**

6. YES NO **NDA BEING SPLIT FOR ADMINISTRATIVE CONVENIENCE (OTHER THAN BUNDLING)?** IF YES, list ALL NDA numbers, review divisions & indicate those for which application fees apply.

NDA #	DIVISION		
N_____	_____	FEE	NO FEE
N_____	_____	FEE	NO FEE

7. YES NO **BUNDLING POLICY APPLIED CORRECTLY?** NO DATA ENTRY REQUIRED FOR ELEMENT
[Check YES if application is properly designated as one application or is properly submitted as a supplement instead of an original application. Check NO if application should be split into more than one application or submitted as an original instead of a supplement. IF NO, list resulting NDA numbers, and review divisions.]

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8. YES NO **SMALL BUSINESS EXCEPTION GRANTED?** [Check YES only if the NDA contains a copy of a written notice from the FDA Waiver Officer that a exception has been granted.]

9. YES NO **WAIVER GRANTED?** [Check YES only if the NDA contains a copy of a written notice from the FDA Waiver Officer that a waiver has been granted.]

10. YES NO **PRIORITY SUBMISSION?** [Check YES if Priority. Check NO if Standard.]

Maria R Walsh 2/13/97
CSO SIGNATURE/DATE

R Johnson 2/13/97
SCSO CONCURRENCE SIGNATURE/DATE

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Maria R Walsh 2/13/97
11. CSO SIGNATURE/DATE

K Johnson 2/13/97
SCSO CONCURRENCE SIGNATURE/DATE

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