CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-406/S004

Trade Name: Prevacid Delayed Release Capsules

Generic Name: (lansoprazole)

Sponsor: TAP Holdings Inc

Approval Date: October 18, 1995
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-406/S004

APPROVAL LETTER
Dear Ms. Wargel:

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

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

1. DOSAGE AND ADMINISTRATION section

   A. Treatment of Duodenal Ulcer

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

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

   B. Treatment of Erosive Esophagitis

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

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

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

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

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the final printed labeling submitted on September 25, 1995. Accordingly, the supplemental application is approved effective on the date of this letter.
We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Maria Walsh
Consumer Safety Officer
(301) 443-0487

Sincerely yours,

Stephen B. Fredd, M.D.
Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Original NDA 20-406/S-004
HFD-180/Div. files
HFD-180/CSO/M.Walsh
HFD-100
DISTRICT OFFICE
HF-2/medwatch (with labeling)
HFD-80 (with labeling)
HFD-240/S.Sherman (with labeling)
HFD-500/L.Ripper (with labeling)
HFD-613 (with labeling - Only for applications with labeling.)

Drafted: MRW 10/6/95
R/D init: S.Fredd 10/12/95
Final: MRW 10/13/95
MRW/10/13/95/C:\wpfiles\cs0\n\20406510.A04

APPROVAL
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-406/S004

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

OCT 18 1995

DESCRIPTION
The active ingredient in PREVACID (lansoprazole) Delayed-Release Capsules is a substituted benzimidazole, 2-[[1-{3-methyl-4-(3,2,3-trifluorothienyl)-2-pyridyl}methyl]sulfanyl]benzimidazole, a compound that inhibits gastric acid secretion. Its empirical formula is C_{17}H_{15}F_{3}N_{3}O_{2} with a molecular weight of 369.37. The structural formula is:

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

Lansoprazole is stable when exposed to light for up to two months. The compound degrades in aqueous solution, the rate of degradation increasing with decreasing pH. At 25°C the half-life is approximately 0.5 hour at pH 5.0 and approximately 10 hours at pH 7.5.

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

* PREVACID 15 mg capsules only.

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

Labeling: Drug Summary
NDA No: 20-426 Rev'd. 9/95
Reviewed by: ML Walsh 10/1/95
CLINICAL PHARMACOLOGY
Pharmacokinetics and Metabolism
PREDVACD Delayed-Release Capsules contain an enterico-
crusted granule formulation of lasagralose. Absorption of
laspalose begins only after the granules leave the stom-
ach. Absorption is rapid, with mean peak plasma levels of
laspalose occurring after approximately 1.7 hours. Peak
plasma concentrations of lasagralose (Cmax) and the area
under the plasma concentration curve (AUC) of lasagral-
ose are approximately proportional in doses of 15 mg to
60 mg after single-dose administration. Lasagralose does
not accumulate and its pharmacokinetics are unaffected
by multiple dosing.
Absorption
The absorption of lasagralose is rapid, with mean Cmax
occurring approximately 1.7 hours after oral dosing, and
completely consistent with absolute bioavailability over 88%.
In healthy subjects, the mean (± SD) plasma half-life was
1.6 ± 0.8 hours. Both Cmax and AUC are distributed by
about 50% if the drug is given 30 minutes after food as
opposed to the fasting condition. There is no significant
food effect if the drug is given before meals.
Distribution
Lasagralose is 97% bound to plasma proteins. Plasma
protein binding is constant over the concentration range
of 0.2 to 5.9 mg/mL.
Metabolism
Lasagralose is extensively metabolized in the liver. Two
metabolites have been identified in measurable quantities in
plasma (the hydroxylated analogs and sulfonamide deriva-
tives of lasagralose). These metabolites have very little if no anti-
secretory activity. Lasagralose is thought to be trans-
fected into two active species which inhibit acid secretion
by a K+/Cl−-ATPase within the parietal cell compartment, but
are not present in the systemic circulation. The plasma
elimination half-life of lasagralose does not reflect its
duration of suppression of gastric acid secretion. Thus, the
plasma elimination half-life is less than two hours while the
acid inhibitory effect persists for more than 24 hours.
Elimination
Following single-dose oral administration of lasagralose,
virtually no unchanged lasagralose was excreted in the
urine. In our study, after a single oral dose of 10 mg lasag-
ralose, approximately one-third of the administered radiation
was excreted in the urine and two-thirds was recovered in
the feces. This implies a significant bilirubin excretion of
the metabolites of lasagralose.
Special Populations
Geriatric
The clearance of lasagralose is decreased in the elderly,
with elimination half-life increased approximately 50% to
100%. Because the mean half-life in the elderly remains
between 1.9 to 2.9 hours, repeated once daily dosing does
not result in accumulation of lasagralose. Peak plasma
levels were not increased in the elderly.
Pediatric
The pharmacokinetics of lasagralose has not been investi-
gated in patients <18 years of age.
Gender
In a study comparing 12 male and six female human sub-
jects, no gender differences were found in pharmacokinetics
and pharmacodynamic drug results (also see Use in Women).
Renal Insufficiency
In patients with severe renal insufficiency, plasma protein
binding decreased by 1.0%–1.9% after administration of
60 mg of lasagralose. Patients with renal insufficiency
had a decreased elimination half-life and decreased total
AUC (free and bound). AUC for free lasagralose in plasma,
however, was not related to the degree of renal impairment,
and Cmax and Tmax were not different between subjects with
healthy kidneys.
Hepatic Insufficiency
In patients with various degrees of chronic hepatic disease,
the mean plasma half-life of the drug was prolonged from
1.3 hours to 3.2–7.2 hours. An increase in mean AUC of up
to 500% was observed at steady state in hepatically-impair-
ted patients compared to healthy subjects. Drug evalua-
tion in patients with severe hepatic disease should be
considered.
PHARMACODYNAMICS
Mechanism of action
Laspalose belongs to a class of antisecretory compo-
nents, the substituted benzimidazoles, that do not exhibit
inhibitory effects on histamine H2-receptors or agonist prop-
erties. Also, it does not suppress gastric acid secretion by specif-
ic inhibition of the enzyme H+-K+-ATPase, a proton pump
 resistant to inhibition by gastrin or gastrin-like substances.
Because this pump is regulated in the proton (proton) pump
within the parietal cell, lasagralose has been characterized as
a gastrin acid pump inhibitor, in that it blocks the final step
of acid production. This effect is dose-related, and leads to
inhibition of both basal and stimulated gastric acid secretion
 irrespective of the stimulus.
Antisecretory activity
After oral administration, lasagralose was shown to signif-
ically decrease the basal acid output and significantly increase
the mean gastric pH and percent of time the gastric
pH was >3 and >4. Lasagralose also significantly reduced
non-stimulated gastric acid output and secretion volume,
as well as pentagastrin-stimulated acid output. In patients
with hypersecretion of acid, lasagralose significantly
reduced basal and pentagastrin-stimulated gastric acid
secretion. Lasagralose inhibited the normal increase in
secretion volume, acidity and acid output induced by
insulin.
In a crossover study comparing lasagralose 15 and
30 mg with enprozole 30 mg for five days, the following
effects on intragastric pH were noted.
Mean Antisecretory Effects after Single and Multiple
Dose Regimens

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Basal Acid</th>
<th>Dietary Stimulation</th>
<th>Intestinal Stimulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>2.0</td>
<td>1.0</td>
<td>3.0</td>
</tr>
<tr>
<td>Lasagralose</td>
<td>2.0</td>
<td>0.8</td>
<td>2.5</td>
</tr>
<tr>
<td>Enprozole</td>
<td>1.5</td>
<td>0.5</td>
<td>1.5</td>
</tr>
</tbody>
</table>

NOTE: An intragastric pH of 4 reflects an inhibition of gastric acid by 96%.
* (p<.05) versus baseline, lasagralose 15 mg vs enprozole 30 mg.
** (p<.01) versus baseline only.

After the initial dose in this study, increased gastric pH was
seen within 30 minutes with lasagralose 30 mg,
2-3 hours with lasagralose 15 mg, and 4-6 hours with
enprozole 20 mg. After multiple daily dosing, increased
gastric pH was seen within the first ten minutes with
<table>
<thead>
<tr>
<th>Mean Anticipatory Effects after Single and Multiple Daily Dosing</th>
<th>10 mg</th>
<th>30 mg</th>
<th>Omnopon (120 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response (N=70)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mean Peak Value</strong></td>
<td>1.8</td>
<td>3.7</td>
<td>4.5</td>
</tr>
<tr>
<td><strong>Mean Time to Peak</strong></td>
<td>2 h</td>
<td>3 h</td>
<td>1 h</td>
</tr>
<tr>
<td><strong>Time to Peak (h)</strong></td>
<td>2</td>
<td>3</td>
<td>1.5</td>
</tr>
<tr>
<td><strong>Mean Peak Value</strong></td>
<td>1.8</td>
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<td>2 h</td>
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<td>1 h</td>
</tr>
<tr>
<td><strong>Time to Peak (h)</strong></td>
<td>2</td>
<td>3</td>
<td>1.5</td>
</tr>
</tbody>
</table>

**NOTE**: An average peak of 14 effects of a substance in gauge units by 95%. The effects were taken at baseline, after administration of 15 mg and after reagent 20 mg. After multiple daily doses, increased gastric pH was seen within the first hour following ingestion and increased to 30 mg while within 2 hours following ingestion of 15 mg and before increases observed. The inhibition of gastric acid secretion as measured by intragastric pH measurements gradually increased over 2 to 4 days after multiple doses. There was no indication of reduced gastric acidity.

**Enterochromaffin-like (ECL) cell effects**
During lifetime exposure of rats with up to 150 mg/kg/day of losartan, a dose where the liver was exposed to the substance, a decrease in the number of ECL cells was observed. The decrease in ECL cells was associated with a decrease in gastrin-17 levels in the stomach. In addition, a decrease in gastrin-17 levels was observed in patients with gastrin failure. No significant increase in serum gastrin levels was observed.

**Serum gastrin levels**
In over 1000 patients, median fasting serum gastrin levels increased 50% to 100% from baseline, but remained within normal range after treatment with losartan given orally in doses of 15 mg to 60 mg. These elevations reached a plateau within two months of therapy and remained in the normal range levels within four weeks after discontinuation of therapy.

**Endocrine effects**
Hemodynamic studies for up to eight weeks have not detected any clinically significant effects on the endocrine system. Hormones studied included vasopressin, lactating hormones (LH), follicle stimulating hormones (FSH), sex hormone binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEA-S), prolactin, cortisol, estradiol, insulin, aldosterone, renin, androgen, glucagon, growth hormone stimulating hormone (GSH), insulin-like growth factor (IGF-1), and growth hormone binding globulin (GH-BG). In addition, no increase in total doses of 15 mg to 60 mg for two to eight weeks had any clinically significant effect on thyroid function. In 24-month carcinogenicity studies in Sprague-Dawley rats with daily doses of up to 150 mg/kg, no deviations from the study database were observed. No significant changes in the Leydig cells of the testis, including normal spermatocytes, were observed compared to controls.

**Other effects**
No systemic effects of losartan 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 visual eye examination. No treatment with up to 180 mg/day of losartan and were observed for up to 36 months. Other rat specific findings after lifetime exposure included fetal pancreatic atrophy, diffuse lymphoid hyperplasia in the thymus, and spontaneous renal amyloid.

**CLINICAL STUDIES**

**Budweiser Use**

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 of PREVACID 15 mg than with placebo. Based on the results of this study and the second study described below, the recommended dose of PREVACID in duodenal ulcer is 15 mg once daily.

**Budweiser Ulcer Healing Rates**

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>Weeks 2</th>
<th>Weeks 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>52.4%</td>
<td>39.3%</td>
</tr>
<tr>
<td>30</td>
<td>60.4%</td>
<td>46.3%</td>
</tr>
</tbody>
</table>

* (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, a 282 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 two higher doses of PREVACID 15 mg than with placebo. Although the response with the higher dose of PREVACID was superior to that of a lower dose at 15 mg dose of PREVACID was superior to that of a lower dose at 150 mg dose of PREVACID, the lack of significant difference at 2 weeks and the absence of a difference between 30 mg of PREVACID and placebo leaves the comparative effectiveness of these agents undetermined.

**Budweiser Ulcer Healing Rates**

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>Weeks 2</th>
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</tr>
<tr>
<td>30</td>
<td>60.4%</td>
<td>46.3%</td>
</tr>
</tbody>
</table>

* (p<0.001) versus placebo. 

**p<0.05** versus placebo and washout.
(LH), follicle stimulating hormone (FSH), sex hormone binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEAS), prolactin, cortisol, estradiol, insulin, alanine aminotransferase, alkaline phosphatase, gamma glutamyl transferase (GGT), and serum creatinine (S-Cr).

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 dosage up to 150 mg/kg, proliferative changes in the Leydig cells of the testes, including benign neoplasms, were increased compared to control rats.

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 in 56 patients who had extensive baseline eye evaluations, or treated with up to 180 mg/day of lansoprazole and were observed for up to 58 months. Other re-specific findings after lifetime exposure included focal pancreatic atrophy, diffuse lymphoid hyperplasia in the thymus, and spontaneous retinal detachments.

CLINICAL STUDIES

Duodenal Ulcer

In a U.S. multicenter, double-blinded, placebo-controlled, dose-escalation (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**

<table>
<thead>
<tr>
<th>Dose</th>
<th>PREVACID</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 mg</td>
<td>50% (40/80)</td>
<td>20% (16/80)</td>
</tr>
<tr>
<td>30 mg</td>
<td>75% (60/80)</td>
<td>35% (28/80)</td>
</tr>
<tr>
<td>60 mg</td>
<td>115% (95/82)</td>
<td>60% (49/82)</td>
</tr>
</tbody>
</table>

*P<0.05 versus placebo.

PREVACID 15 mg was significantly more effective than placebo in relieving day and night-time abdominal pain and in decreasing the amount of analgesics per day.

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

**Duodenal Ulcer Healing Rates**

<table>
<thead>
<tr>
<th>Dose</th>
<th>PREVACID</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 mg</td>
<td>75% (60/80)</td>
<td>35% (28/80)</td>
</tr>
<tr>
<td>30 mg</td>
<td>85% (85/80)</td>
<td>55% (44/80)</td>
</tr>
</tbody>
</table>

*P<0.05 versus placebo.

**Erosive Esophagitis**

In a U.S. multicenter, double-blind, placebo-controlled study of 205 patients entering an endoscopic diagnosis of erosive esophagitis with erosional grading of 2 or more and grades 3 and 4 signifying erosive disease, the percentages of patients with healing were as follows:

**Erosive Esophagitis Healing Rates**

<table>
<thead>
<tr>
<th>Dose</th>
<th>PREVACID</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 mg</td>
<td>90% (90/80)</td>
<td>90% (81/90)</td>
</tr>
<tr>
<td>30 mg</td>
<td>100% (100/100)</td>
<td>90% (90/100)</td>
</tr>
</tbody>
</table>

*P<0.05 versus placebo.

In this study, all PREVACID groups reported significantly greater relief of heartburn and heartburn and eight patients in 69 patients taking 30 mg of 15 mg of the recommended dose.

PREVACID was also compared in a U.S. multicenter, double-blind study to a low dose of ranitidine in 242 patients with erosive reflex esophagitis. PREVACID at a dose of 30 mg was significantly more effective than ranitidine 15 mg, but as shown below.

**Erosive Esophagitis Healing Rates**

<table>
<thead>
<tr>
<th>Dose</th>
<th>PREVACID</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 mg</td>
<td>100% (100/100)</td>
<td>90% (90/100)</td>
</tr>
</tbody>
</table>

*P<0.05 versus placebo.

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

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

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

In a U.S. multicenter, double-blind, active-controlled study, 30 mg of PREVACID was compared with ranitidine 150 mg bid in 151 patients with erosive reflex esophagitis that was poorly responsive to a minimum of 12 weeks of treatment with at least 24 mg of ranitidine, and was given as the dose indicated for symptoms of heartburn, primarily chronic erosive 800 mg qid, ranitidine 300 mg, famotidine 40 mg or ranitidine 300 mg. PREVACID 30 mg was more effective than ranitidine 150 mg bid in healing reflux esophagitis and the percentage of patients with heal- ing were as follows. This study does not constitute a com-
### Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome
In open studies of 37 patients with pathological hypersecretory conditions, such as Zollinger-Ellison (ZE) syndrome or without multiple endocrine adenomas, PREVACID significantly inhibited gastric acid secretion and controlled associated symptoms of diarrhea, nausea and pain. Dosage ranging from 15 mg every other day to 180 mg per day maintained basal acid inhibition below 10% in patients without prior gastric surgery, and below 5% 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 patients, serum gastrin levels were not modified by PREVACID. However, in some patients serum gastrin increased to levels greater than those present prior to initiation of lansoprazole therapy.

### INDICATIONS AND USAGE
Short-Term Treatment of Active Duodenal Ulcer
PREVACID Delayed-Release Capsules are indicated for short-term treatment (up to 4 weeks) for healing and symptom relief of active duodenal ulcer.

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

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

For patients who do not heal with PREVACID for 8 weeks (5-10%) it may be helpful to give an additional 8 weeks of treatment. If there is a recurrence of erosive esophagitis as an additional 8-week course of PREVACID may be considered. PREVACID SHOULD NOT BE USED AS MAINTENANCE THERAPY.

### Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome
PREVACID Delayed-Release Capsules are indicated for the long-term treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome.

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

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

Information for Patients
PREVACID Delayed-Release Capsules should be taken before eating. Patients should be cautioned that PREVACID Delayed-Release Capsules should not be opened, chewed or crushed. Capsules should be swallowed whole.

Drug Interactions
Lansoprazole is metabolized through the cytochrome P450 system, specifically through the CYP2C19 and CYP3A4 isoenzymes. Studies have shown that lansoprazole does not have clinically significant interactions with other drugs metabolized by the cytochrome P450 system, such as warfarin, anticonvulsants, indomethacin, theophylline, phenytoin, propranolol, prednisone, or diazepam in healthy volunteers. These compounds are metabolized through various cytochrome P450 isoenzymes including CYP1A2, CYP2C9, CYP2C19, CYP3A4 and CYP2E1. When lansoprazole was administered concomitantly with theophylline (CYP1A2, CYP3A4), a mean increase (10%) in the clearance of theophylline was seen. Because of the small magnitude and the duration of the effect on theophylline clearance, this interaction is unlikely to be of clinical concern. Nonetheless, individual patients may require additional titration of the theophylline dosage when lansoprazole is started or stopped to ensure clinically effective blood levels.

Concomitance of lansoprazole with quinolones delayed absorption and reduced lansoprazole bioavailability by approximately 50%. Therefore, lansoprazole should be taken at least 30 minutes prior to metronidazole. In clinical trials, astacids were administered concomitantly with PREVACID Delayed-Release Capsules, this did not interfere with its effect. Lansoprazole causes a profound and long-lasting inhibition of gastric acid secretion; therefore, it is theoretically possible that lansoprazole may interfere with the absorption of drugs whose gastric pH is an important determinant of bioavailability (e.g., ketocazole, ampicillin esters, iron salts, digoxin).

### Carcinogenesis, Mutagenesis, and Fertility
In two 24-month carcinogenicity studies, Sprague-Dawley rats were treated orally with doses of 5 to 150 mg/kg/day, (dose 1 to 40 times the exposure on a body surface mg/kg/day basis). Duration of study length (8-16 wk body surface area) gives the recommended human dose of 30 mg/kg (22 mg/m²). Lansoprazole produced dose-related gastric cancer in male rats (tubular cell hyperplasia and ECL cell hyperplasia and ECL cell carcinomas in both male and female rats). It also increased the incidence of intestinal metaplasia of the gastric mucosa in both sexes. In male rats, lansoprazole produced a dose-related increase of tubular intestinal cell adenomas. The incidence of these adenomas in rats receiving doses of 15 to 50 mg/kg/day (4 to 10 times the recommended human dose based on body surface area) exceeded the low background incidence (range 1 to 4%) for this strain of rats. Tuberular intestinal cell adenomas also occurred in 1 of 30 rats treated with 50 mg/kg/day (3 times the recommended human dose based on body surface area) in a 52-week toxicity study.

In a 24-month carcinogenicity study, CD-1 mice were treated orally with doses of 15 to 600 mg/kg/day, (20 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 (hepato cell adenomas) in male rats. 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 surfaces area) and female mice treated with 150 to 600 mg/kg/day (20 to 40 times the recommended human dose based on body surface area) were lower than those seen in the rat studies.

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

<table>
<thead>
<tr>
<th>Week</th>
<th>PREVACID 30 mg</th>
<th>Standard 30 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>74.39%</td>
<td>12.5%</td>
</tr>
<tr>
<td>8</td>
<td>77.89%</td>
<td>12.5%</td>
</tr>
</tbody>
</table>

*All data represent mean values.
Carcinogenesis, Mutagenesis, and Fertility

In two 24-month carcinogenicity studies, Sprague-Dawley rats were treated orally with doses of 5 to 105 mg/kg/day, about 1 to 40 times the exposure on a body surface (mg/m²) basis, of a 20 kg person of average height (1.64 m body surface area) given the recommended human dose of 30 mg/day (22.5 mg/m²). Lansoprazole produced dose-related gastric carcinomas like ECL cell hyperplasia and ECL cell carcinomas in both male and female rats. It also increased the incidence of intestinal metaplasia of the gastric epithelium in both sexes. In nude rats, lansoprazole produced a dose-related increase of mucosal intestinal 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. Intestinal metaplasia intestinal cell adenomas also occurred in a 30% strain treated with 30 mg/kg/day (13 times the recommended human dose based on body surface area) at a 1-year time interval.

In a 24-month carcinogenicity study, CD-1 mice were treated orally with doses of 13 to 600 mg/kg/day, 2 in 50 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 adenomas and foci). The main incidence was 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 120 to 600 mg/kg/day (20 to 40 times the recommended human dose based on body surface area) exceeded the ranges of background incidence in historical controls for this strain of mice. Lansoprazole-induced preneoplastic adenomas of skin tumors 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 comet assay, the micronucleus test, the DNA fragmentation assay (DDT test), the in vivo mouse micronucleus test or the rat bone marrow cell chromosomal aberration test. It was positive in vitro human lymphocyte chromosomal aberration assays. Lansoprazole in oral doses up to 130 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

Teraolic Effects. Pregnancy Category B

Teratological studies have been performed in pregnant rats at oral doses up to 150 mg/kg/day (10 times the recommended human dose based on body surface area) and pregnant rabbits at oral doses up to 20 mg/kg/day (36 times the recommended human dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to lansoprazole.

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

Nursing Mothers

Lansoprazole or its metabolites are excreted in the milk of rats. It is not known whether lansoprazole is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when deciding whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in children have not been established.

Use in Women

Over 600 women were treated with lansoprazole. Ulcer healing rates in females are similar to those in males. The incidence rates of adverse events are also similar to those seen in males.

Use in Elderly Patients

Ulcer healing rates in elderly patients are similar to those in a younger age group. The incidence rates of adverse events and laboratory test abnormalities are also similar to those seen in younger patients. The initial dosage regimen need not be altered for elderly patients, but subsequent doses higher than 70 mg per day should not be administered unless additional gain in suppression is necessary.

Adverse Reactions

Worldwide, over 6,000 patients have been treated with lansoprazole in Phase II-III clinical trials involving various dosage and duration of treatment. In general, lansoprazole treatment has been well tolerated in both short-term and long-term trials.

Incidence in Clinical Trials

The following adverse events were reported by the treating physician to have a possible or probable relationship to drug use 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

<table>
<thead>
<tr>
<th>Body System/Adverse Event</th>
<th>Placebo (%)</th>
<th>Lansoprazole (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body as a Whole</td>
<td>14</td>
<td>13</td>
</tr>
<tr>
<td>Abnormalities</td>
<td>16</td>
<td>13</td>
</tr>
<tr>
<td>Digestive System</td>
<td>28</td>
<td>26</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>44</td>
<td>42</td>
</tr>
</tbody>
</table>

A headache was also seen at a greater than 1% incidence but was more common on placebo. The incidence of diarrhea in similar between placebo and lansoprazole 15 mg and 30 mg/day, but higher in the lansoprazole 60 mg patients (25%, 4%, 7%, and 7%, respectively).

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

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

- Body as a Whole: arthralgia, chills, dizziness (not orthostatic specified), edema, fever, the syndrome, hepatitis, infectious (not otherwise specified), influenza, myocardial ischemia, myalgia, nausea, nervous system, rash, syncope, vomiting, vulvodynia, pyrexia, headache, chest pain, hypertension, hyperthyroidism, hypothyroidism, impotence, jaundice, abdominal pain, diarrhea, constipation, bloody stool, headache.

- Gastrointestinal: abdominal pain, constipation, diarrhea, dyspepsia, pain, headache.

- Dermatological: rash, urticaria.

- Neoplasms: malignant melanoma, squamous cell carcinoma, adenoma, skin, acne, seborrheic keratosis, warts.

- Psychiatric: mania, delirium, depression, anxiety, agitation, insomnia, tremor, abnormal dreams, mood changes.

- Ocular: blurring of vision, conjunctivitis, blepharoconjunctivitis, iritis, glaucoma, keratitis, cataract.

- Endocrine: gynecomastia, amenorrhea, galactorrhea, hypothyroidism, hyperthyroidism.

- Metabolic and Nutritional: fluid retention.

- Respiratory, Thoracic and mediastinal: dyspnea, bronchitis, respiratory infection, sinusitis, otitis media.


- Natural Language: pain, weight gain, asthenia, hypertension, anemia, fever, pneumonia, joint pain.
Headache was also seen at greater than 1% incidence but was more common on placebo. The incidence of diarrhea was similar between placebo and lansoprazole 15 mg and 30 mg patients, but higher in the lansoprazole 60 mg patients (15%, 4.5%, and 7.4%, respectively).

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

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

- Body as a Whole: asthenia, malaise, chest pain (not otherwise specified), odynophagia, fever, somnolence, anorexia, anemia, sweating, paresthesia, headache, nasopharyngitis, pharyngitis, influenza-like illness, upper respiratory tract infection, sinusitis, dysphonia, fever, malaise, fatigue, myalgia, arthralgia, and rash.

- Nervous System: altered mental status, somnolence, restlessness, dizziness, paresthesia, tremor, syncope, vertigo, insomnia, anxiety, headache, somnolence, insomnia, asthenia, depression, vertigo, confusion, dizziness, somnolence, drowsiness, fatigue, increased intracranial pressure, and irritability.

- Mental and Behavioral Disorders: akathisia, emotional lability, abnormal thinking, and mood swings.

- Musculoskeletal and Connective Tissue: myalgia, arthralgia, joint pain, and joint swelling.

- Skin and Appendages: acne, alopecia, pruritus, rash, urticaria, pruritus, pruritus ani, dermatitis, and hyperpigmentation.

- Special Sensations: auditory, olfactory, and gustatory disturbances.

- Laboratory Values

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

- Abnormal liver function tests, increased SGOT (AST), increased SGPT (ALT), increased creatinine, increased bilirubin, increased alkaline phosphatase, increased globulin, increased LDH, increased transaminase, increased hemoglobin, increased uric acid, increased alkaline phosphatase, and increased alanine transaminase.

- Increased fasting blood glucose, increased fasting plasma glucose, and increased fasting serum glucose.

- Increased fasting serum cholesterol, increased serum triglycerides, increased serum phosphorus, increased serum potassium, and increased serum sodium.

- Increased serum calcium, increased serum iron, increased serum magnesium, increased serum total protein, and increased serum albumin.

- Increased serum alkaline phosphatase, increased serum alanine transaminase, increased serum aspartate transaminase, increased serum alkaline phosphatase, and increased serum gamma-glutamyl transpeptidase.

- Increased serum alkaline phosphatase, increased serum alanine transaminase, increased serum aspartate transaminase, increased serum alkaline phosphatase, and increased serum gamma-glutamyl transpeptidase.

- Increased serum alkaline phosphatase, increased serum alanine transaminase, increased serum aspartate transaminase, increased serum alkaline phosphatase, and increased serum gamma-glutamyl transpeptidase.

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- Increased serum alkaline phosphatase, increased serum alanine transaminase, increased serum aspartate transaminase, increased serum alkaline phosphatase, and increased serum gamma-glutamyl transpeptidase.

OVERDOSAGE

Oral doses up to 5000 mg/kg in rats (approximately 1300 times the recommended human dose based on body surface area) and more (about 850 times the recommended human dose based on body surface area) did not produce deaths or any clinical signs.

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

DOSEAGE AND ADMINISTRATION

Treatment of Duodenal Ulcer

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

Treatment of Erosive Esophagitis

The recommended adult oral dose is 30 mg once daily before eating for 8 weeks. (See INDICATIONS AND USAGE.)

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

Pathological Hypersensitivity Conditions Including Zollinger-Ellison Syndrome

The dosage of PREVACID in patients with pathological hypersensitivity 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.

Doses up to 90 mg bid 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.

HOW SUPPLIED

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

NDC 4300-1541-30
- Unit of use bottles of 30 15 mg capsules
- NDC 4300-1541-13
- Bottles of 100 15 mg capsules
- NDC 4300-1541-11
- NDC 4300-3046-30
- Unit dose package of 100 15 mg capsules
- NDC 4300-3046-13
- Bottles of 30 30 mg capsules
- NDC 4300-3046-11
- NDC 4300-3046-11
- Unit dose package of 100 30 mg capsules

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

Store between 59°F and 86°F.

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

U.S. Patent Nos. 4,630,098; 4,689,331; 5,011,743; 3,908,500 and 3,947,321.

Manufactured for:

TAP Pharmaceuticals Inc.

Deerfield, Illinois 60015-1355, U.S.A.

by Takeda Chemical Industries Limited,
Osaka, Japan 541

® Registered Trademark
OVERDOSAGE
Oral doses up to 5000 mg/day in rats (approximately 1300 times the recommended human dose based on body surface area) and mice (about 875 times the recommended human dose based on body weight) did not produce deaths or any clinical signs.
Lanogastost is not removed from the circulation by hemodialysis. In one reported case of overdose, the patient consumed 600 mg of lanogastost with no adverse reaction.

DOSE AND ADMINISTRATION
Treatment of Duodenal Ulcer
The recommended adult oral dose is 15 mg once daily before eating for 4 weeks. (See INDICATIONS AND USAGE.)

Treatment of Erosive Esophagitis
The recommended adult oral dose is 20 mg every 12 hours before eating for up to 8 weeks. For patients who do not respond to PREVACID therapy for 8 weeks (5-10% of patients), treatment with PREVACID may be continued for an additional 4 weeks. (See INDICATIONS AND USAGE.)

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

Pathological Hypersensitivity Conditions Including Zollinger-Ellison Syndrome
The dosage of PREVACID in patients with histologic and/or endoscopic evidence of Zollinger-Ellison syndrome is usually 15 mg once daily for 8 weeks. Dosages of up to 30 mg bid have been administered. The dosage of greater than 120 mg/day should be administered in divided doses. Dosage adjustment should be individualized, allowing for a dosage of up to 60 mg/day in divided doses. Patients with Zollinger-Ellison syndrome have been treated continuously with PREVACID for more than 4 years.

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

- Unit of 20 bottles of 30: 15 mg capsules
- Unit of 30: 15 mg capsules
- Unit of 100: 15 mg capsules
- Unit of 100: 30 mg capsules
- Unit of 100: 30 mg capsules
- Unit of 100: 30 mg capsules
- Unit of 100: 30 mg capsules
- Unit of 100: 30 mg capsules
- Unit of 100: 30 mg capsules

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

Store between 59°F and 86°F.

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

U.S. Patent Nos. 4,628,098, 4,689,333; 5,013,743; 5,026,300 and 5,043,321.

(Tm) Registered Trademark

Manufactured for
TAP Pharmaceuticals Inc.
Downers Grove, IL, U.S.A.
by Taisho Chemical Industries Limited,
Osaka, Japan 541

PREVACID®
(DEXLOROPRIME)
PREVACID®
(DEXLOROPRIME)
PREVACID®
(DEXLOROPRIME)
PREVACID®
(DEXLOROPRIME)
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-406/S004

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS
September 25, 1995

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

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

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

Special Supplement
Changes Being Effecte

Dear Dr. Fredd:

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

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

Sincerely,

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

JDW:ppj
Attachments