CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 21-428/S-004

Trade Name: Prevacid Delayed Release Capsules, SOLUTab Delayed-Release Orally Disintegrating Tablet, and Delayed-Release Oral Suspension

Generic Name: lansoprazole

Sponsor: TAP Pharmaceutical Products, Inc.

Approval Date: June 17, 2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-428/S-004

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-428/S-004

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-406/S-057
NDA 21-281/S-014
NDA 21-428/S-004

TAP Pharmaceutical Products Inc.
Attention: Nancianne Knipfer, Ph.D.
Product Manager, Regulatory Affairs
675 North Field Drive
Lake Forest, IL 60045

Dear Dr. Knipfer:

Please refer to your supplemental new drug applications dated December 19, 2003, received December 22, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prevacid (lansoprazole) Delayed-Release Capsules, Prevacid (lansoprazole) For Delayed-Release Oral Suspension, and Prevacid SoluTab (lansoprazole) Delayed-Release Orally Disintegrating Tablet.

We acknowledge receipt of your submissions dated February 24, April 16, May 4, and June 10, 2004.

These supplemental new drug applications propose the following changes: in the labeling sections **SPECIAL POPULATIONS - PEDIATRICS, PEDIATRIC USE, DOSAGE AND ADMINSTRATION** and **DESCRIPTION** section of the package insert for the treatment of symptomatic GERD, nonerosive esophagitis and erosive esophagitis in patients 12-17 years of age.

We completed our review of these applications, as amended. These applications are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert,) and/or submitted labeling (package insert submitted June 10, 2004).

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplement NDA 20-406/S-057, NDA 21-281/S-014, and NDA 21-428/S-004." Approval of these submissions by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have completed studies for ages 1-11 (NDA 20-406/S-047) and ages 12-17 (with this submission), and plan to initiate studies in children less than 1 year of age after the completion of your required rat toxicity study.

In addition, submit three copies of the introductory promotional materials that you propose to use for these products. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42

Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Melissa Hancock Furness, Regulatory Health Project Manager, at (301) 827-7450.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Gastrointestinal & Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Joyce Korvick
6/17/04 01:54:36 PM
for Dr. Robert Justice

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-428/S-004

APPROVED LABELING

(Nos. 1541, 1543, 1544, 3046, 7309, 7311)

03-5366-R24 Rev. July, 2004

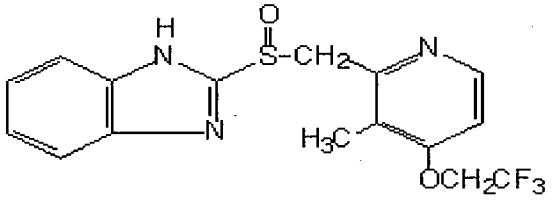
PREVACID®
(lansoprazole)
Delayed-Release Capsules

PREVACID®
(lansoprazole)
For Delayed-Release Oral Suspension

PREVACID® SoluTab™
(lansoprazole)
Delayed-Release Orally Disintegrating Tablets

DESCRIPTION

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



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

Lansoprazole is stable when exposed to light for up to two months. The rate of degradation of the compound in aqueous solution increases with decreasing pH. The degradation half-life of the drug substance in aqueous solution at 25°C is approximately 0.5 hour at pH 5.0 and approximately 18 hours at pH 7.0.

PREVACID is supplied in delayed-release capsules, in delayed-release orally disintegrating tablets for oral administration and in a packet for delayed-release oral suspension.

The delayed-release capsules contain the active ingredient, lansoprazole, in the form of enteric-coated granules and are available in two dosage strengths: 15 mg and 30 mg of lansoprazole per capsule. Each delayed-release capsule contains enteric-coated granules consisting of lansoprazole, hydroxypropyl cellulose, low substituted hydroxypropyl cellulose, colloidal silicon dioxide, magnesium carbonate, methacrylic acid copolymer, starch, talc, sugar sphere, sucrose, polyethylene glycol, polysorbate 80, and

titanium dioxide. Components of the gelatin capsule include gelatin, titanium dioxide, D&C Red No. 28, FD&C Blue No. 1, FD&C Green No. 3*, and FD&C Red No. 40.

PREVACID for Delayed-Release Orally Disintegrating Tablets contain the active ingredient, lansoprazole in the form of enteric-coated microgranules. The tablets are available in 15 mg and 30 mg dosage strengths. Each tablet contains lansoprazole and the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, magnesium carbonate, hydroxypropyl cellulose, hypromellose, titanium dioxide, talc, mannitol, methacrylic acid, polyacrylate, polyethylene glycol, glyceryl monostearate, polysorbate 80, triethyl citrate, ferric oxide, citric acid, crospovidone, aspartame**, artificial strawberry flavor and magnesium stearate.

PREVACID for Delayed-Release Oral Suspension is composed of the active ingredient, lansoprazole, in the form of enteric-coated granules and also contains inactive granules. The packets contain lansoprazole granules which are identical to those contained in PREVACID Delayed-Release Capsules and are available in 15 mg and 30 mg strengths. Inactive granules are composed of the following ingredients: confectioner's sugar, mannitol, docusate sodium, ferric oxide, colloidal silicon dioxide, xanthan gum, crospovidone, citric acid, sodium citrate, magnesium stearate, and artificial strawberry flavor. The lansoprazole granules and inactive granules, present in unit dose packets, are constituted with water to form a suspension and consumed orally.

* PREVACID 15-mg capsules only.

** **Phenylketonurics: Contains Phenylalanine 2.5 mg per 15 mg Tablet and 5.1 mg per 30 mg Tablet.**

CLINICAL PHARMACOLOGY

Pharmacokinetics and Metabolism

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

Absorption

The absorption of lansoprazole is rapid, with mean C_{max} occurring approximately 1.7 hours after oral dosing, and relatively complete with absolute bioavailability over 80%. In healthy subjects, the mean (±SD) plasma half-life was 1.5 (±1.0) hours. Both C_{max} and AUC are diminished by about 50% to 70% if the drug is given 30 minutes after food as opposed to the fasting condition. There is no significant food effect if the drug is given before meals.

Distribution

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

Metabolism

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

Elimination

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

Special Populations

Geriatric

The clearance of lansoprazole is decreased in the elderly, with elimination half-life increased approximately 50% to 100%. Because the mean half-life in the elderly remains between 1.9 to 2.9 hours, repeated once daily dosing does not result in accumulation of lansoprazole. Peak plasma levels were not increased in the elderly. No dosage adjustment is necessary in the elderly.

Pediatric

The pharmacokinetics of lansoprazole were studied in pediatric patients with GERD aged 1 to 11 years and 12 to 17 years in two separate clinical studies. In children aged 1 to 11 years, lansoprazole was dosed 15 mg q.d. for subjects weighing ≤ 30 kg and 30 mg q.d. for subjects weighing > 30 kg. Mean C_{max} and AUC values observed on Day 5 of dosing were similar between the two dose groups and were not affected by weight or age within each weight-adjusted dose group used in the study. In adolescent subjects aged 12 to 17 years, subjects were randomized to receive lansoprazole at 15 mg or 30 mg q.d. Mean C_{max} and AUC values of lansoprazole were not affected by body weight or age; and nearly dose-proportional increases in mean C_{max} and AUC values were observed between the two dose groups in the study. Overall, lansoprazole pharmacokinetics in pediatric patients aged 1 to 17 years were similar to those observed in healthy adult subjects.

Gender

In a study comparing 12 male and 6 female human subjects, no gender differences were found in pharmacokinetics and intragastric pH results. (Also see **Use in Women**.)

Renal Insufficiency

In patients with severe renal insufficiency, plasma protein binding decreased by 1.0%-1.5% after administration of 60 mg of lansoprazole. Patients with renal insufficiency had a shortened elimination half-life and decreased total AUC (free and bound). AUC for free lansoprazole in plasma, however, was not related to the degree of renal impairment, and C_{max} and T_{max} were not different from subjects with healthy kidneys. No dosage adjustment is necessary in patients with renal insufficiency.

Hepatic Insufficiency

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

Race

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

Pharmacodynamics

Mechanism of Action

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

Antisecretory Activity

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

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

Mean Antisecretory Effects After Single and Multiple Daily Dosing

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

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

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

Acid suppression may enhance the effect of antimicrobials in eradicating *Helicobacter pylori (H. pylori).* The percentage of time gastric pH was elevated above 5 and 6 was evaluated in a crossover study of PREVACID given q.d., b.i.d. and t.i.d.

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

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

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

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

Enterochromaffin-like (ECL) Cell Effects

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

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

Other Gastric Effects in Humans

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

Serum Gastrin Effects

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

Endocrine Effects

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

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

Other Effects

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

Microbiology

Lansoprazole, clarithromycin and/or amoxicillin have been shown to be active against most strains of *Helicobacter pylori in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section.

Helicobacter

Helicobacter pylori

Pretreatment Resistance

Clarithromycin pretreatment resistance (≥2.0 µg/mL) was 9.5% (91/960) by E-test and 11.3% (12/106) by agar dilution in the dual and triple therapy clinical trials (M93-125, M93-130, M93-131, M95-392, and M95-399).

Amoxicillin pretreatment susceptible isolates (≤0.25 µg/mL) occurred in 97.8% (936/957) and 98.0% (98/100) of the patients in the dual and triple therapy clinical trials by E-test and agar dilution, respectively. Twenty-one of 957 patients (2.2%) by E-test and 2 of 100 patients (2.0%) by agar dilution had amoxicillin pretreatment MICs of >0.25 µg/mL. One patient on the 14-day triple therapy regimen had an unconfirmed pretreatment amoxicillin minimum inhibitory concentration (MIC) of >256 µg/mL by E-test and the patient was eradicated of *H. pylori.*

Clarithromycin Susceptibility Test Results and Clinical/Bacteriological Outcomes[a]

Clarithromycin Pretreatment Results		Clarithromycin Post-treatment Results				
		H. pylori negative – eradicated	*H. pylori* positive – not eradicated			
			Post-treatment susceptibility results			
			S[b]	I[b]	R[b]	No MIC
Triple Therapy 14-Day (lansoprazole 30 mg b.i.d./amoxicillin 1 gm b.i.d./clarithromycin 500 mg b.i.d.) (M95-399, M93-131, M95-392)						
Susceptible[b]	112	105				7
Intermediate[b]	3	3				
Resistant[b]	17	6			7	4
Triple Therapy 10-Day (lansoprazole 30 mg b.i.d./amoxicillin 1 gm b.i.d./clarithromycin 500 mg b.i.d.) (M95-399)						
Susceptible[b]	42	40	1		1	
Intermediate[b]						
Resistant[b]	4	1			3	

[a]Includes only patients with pretreatment clarithromycin susceptibility test results
[b]Susceptible (S) MIC ≤0.25 µg/mL, Intermediate (I) MIC 0.5 - 1.0 µg/mL, Resistant (R) MIC ≥2 µg/mL

Patients not eradicated of *H. pylori* following lansoprazole/amoxicillin/clarithromycin triple therapy will likely have clarithromycin resistant *H. pylori.* Therefore, for those patients who fail therapy, clarithromycin susceptibility testing should be done when possible. Patients with clarithromycin resistant *H. pylori* should not be treated with lansoprazole/amoxicillin/clarithromycin triple therapy or with regimens which include clarithromycin as the sole antimicrobial agent.

Amoxicillin Susceptibility Test Results and Clinical/Bacteriological Outcomes

In the dual and triple therapy clinical trials, 82.6% (195/236) of the patients that had pretreatment amoxicillin susceptible MICs (≤0.25 µg/mL) were eradicated of *H. pylori.* Of those with pretreatment amoxicillin MICs of >0.25 µg/mL, three of six had the *H. pylori* eradicated. A total of 30% (21/70) of the patients failed lansoprazole 30 mg t.i.d./amoxicillin 1 gm t.i.d. dual therapy and a total of 12.8% (22/172) of the patients failed the 10- and 14-day triple therapy regimens. Post-treatment susceptibility results were not obtained on 11 of the patients who failed therapy. Nine of the 11 patients with amoxicillin post-treatment MICs that failed the triple therapy regimen also had clarithromycin resistant *H. pylori* isolates.

Susceptibility Test for *Helicobacter pylori*

The reference methodology for susceptibility testing of *H. pylori* is agar dilution MICs.[1] One to three microliters of an inoculum equivalent to a No. 2 McFarland standard ($1 \times 10^7 - 1 \times 10^8$ CFU/mL for *H. pylori*) are inoculated directly onto freshly prepared antimicrobial-containing Mueller-Hinton agar plates with 5% aged defibrinated sheep blood (≥ 2 weeks old). The agar dilution plates are incubated at 35°C in a microaerobic environment produced by a gas generating system suitable for campylobacters. After 3 days of incubation, the MICs are recorded as the lowest concentration of antimicrobial agent

required to inhibit growth of the organism. The clarithromycin and amoxicillin MIC values should be interpreted according to the following criteria:

Clarithromycin MIC (µg/mL)[a]	Interpretation
≤0.25	Susceptible (S)
0.5-1.0	Intermediate (I)
≥2.0	Resistant (R)

Amoxicillin MIC (µg/mL)[b]	Interpretation
≤0.25	Susceptible (S)

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

[b] There were not enough organisms with MICs >0.25 µg/mL to determine a resistance breakpoint.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard clarithromycin and amoxicillin powders should provide the following MIC values:

Microorganism	Antimicrobial Agent	MIC (µg/mL)[a]
H. pylori ATCC 43504	Clarithromycin	0.015-0.12 µg/mL
H. pylori ATCC 43504	Amoxicillin	0.015-0.12 µg/mL

[a] These are quality control ranges for the agar dilution methodology and they should not be used to control test results obtained using alternative methods.

Reference

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

CLINICAL STUDIES

Duodenal Ulcer

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

Duodenal Ulcer Healing Rates

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

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

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

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

Duodenal Ulcer Healing Rates

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

* ($p \leq 0.05$) versus placebo.
** ($p \leq 0.05$) versus placebo and ranitidine.

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

Randomized, double-blind clinical studies performed in the U.S. in patients with *H. pylori* and duodenal ulcer disease (defined as an active ulcer or history of an ulcer within one year) evaluated the efficacy of PREVACID in combination with amoxicillin capsules and clarithromycin tablets as triple 14-day therapy or in combination with amoxicillin capsules as dual 14-day therapy for the eradication of *H. pylori.* Based on the results of these studies, the safety and efficacy of two different eradication regimens were established:

Triple therapy:	PREVACID 30 mg b.i.d./ amoxicillin 1 gm b.i.d./ clarithromycin 500 mg b.i.d.
Dual therapy:	PREVACID 30 mg t.i.d./ amoxicillin 1 gm t.i.d.

All treatments were for 14 days. *H. pylori* eradication was defined as two negative tests (culture and histology) at 4-6 weeks following the end of treatment.

Triple therapy was shown to be more effective than all possible dual therapy combinations. Dual therapy was shown to be more effective than both monotherapies. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence.

A randomized, double-blind clinical study performed in the U.S. in patients with *H. pylori* and duodenal ulcer disease (defined as an active ulcer or history of an ulcer within one year) compared the efficacy of PREVACID triple therapy for 10 and 14 days. This study established that the 10-day triple therapy was equivalent to the 14-day triple therapy in eradicating *H. pylori.*

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

Study	Duration	Triple Therapy Evaluable Analysis*	Triple Therapy Intent-to-Treat Analysis#
M93-131	14 days	92† [80.0-97.7] (N=48)	86† [73.3-93.5] (N=55)
M95-392	14 days	86‡ [75.7-93.6] (N=66)	83‡ [72.0-90.8] (N=70)
M95-399+	14 days	85 [77.0-91.0] (N=113)	82 [73.9-88.1] (N=126)
	10 days	84 [76.0-89.8] (N=123)	81 [73.9-87.6] (N=135)

* Based on evaluable patients with confirmed duodenal ulcer (active or within one year) and *H. pylori* infection at baseline defined as at least two of three positive endoscopic tests from CLOtest®, histology and/or culture. Patients were included in the analysis if they completed the study. Additionally, if patients dropped out of the study due to an adverse event related to the study drug, they were included in the evaluable analysis as failures of therapy.

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

† ($p<0.05$) versus PREVACID/amoxicillin and PREVACID/clarithromycin dual therapy

‡ ($p<0.05$) versus clarithromycin/amoxicillin dual therapy

\+ The 95% confidence interval for the difference in eradication rates, 10-day minus 14-day is (-10.5, 8.1) in the evaluable analysis and (-9.7, 9.1) in the intent-to-treat analysis.

H. pylori Eradication Rates – 14-Day Dual Therapy
(PREVACID/amoxicillin)
Percent of Patients Cured
[95% Confidence Interval]
(Number of patients)

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

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

Long-Term Maintenance Treatment of Duodenal Ulcers

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

Endoscopic Remission Rates

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

%=Life Table Estimate
* ($p\leq0.001$) versus placebo.

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

Gastric Ulcer

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

Gastric Ulcer Healing Rates

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

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

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

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

Healing of NSAID-Associated Gastric Ulcer

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

NSAID-Associated Gastric Ulcer Healing Rates [1]

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

[1] Actual observed ulcer(s) healed at time points $\pm$ 2 days

[2] Dose for healing of gastric ulcer

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

Risk Reduction of NSAID-Associated Gastric Ulcer

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

NSAID-Associated Gastric Ulcer Risk Reduction Rates

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

[1] % = Life Table Estimate

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

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

Gastroesophageal Reflux Disease (GERD)

Symptomatic GERD

In a U.S. multicenter, double-blind, placebo-controlled study of 214 patients with frequent GERD symptoms, but no esophageal erosions by endoscopy, significantly greater relief of heartburn associated with GERD was observed with the administration of lansoprazole 15 mg once daily up to 8 weeks than with placebo. No significant additional benefit from lansoprazole 30 mg once daily was observed.

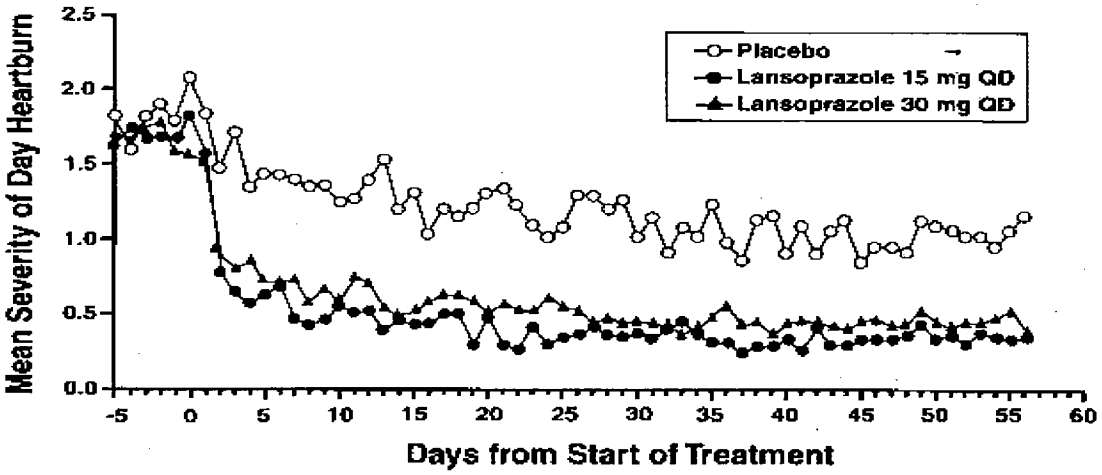
The intent-to-treat analyses demonstrated significant reduction in frequency and severity of day and night heartburn. Data for frequency and severity for the 8-week treatment period were as follows:

Frequency of Heartburn

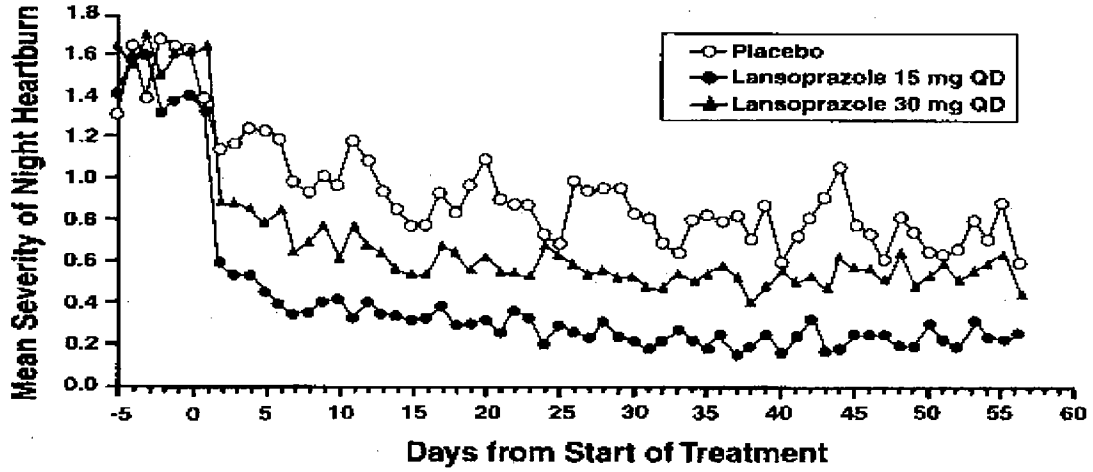
Variable	Placebo (n=43)	PREVACID 15 mg (n=80)	PREVACID 30 mg (n=86)
		Median	
% of Days without Heartburn			
Week 1	0%	71%*	46%*
Week 4	11%	81%*	76%*
Week 8	13%	84%*	82%*
% of Nights without Heartburn			
Week 1	17%	86%*	57%*
Week 4	25%	89%*	73%*
Week 8	36%	92%*	80%*

* ($p<0.01$) versus placebo.

Mean Severity of Day Heartburn By Study Day For Evaluable Patients (3=Severe, 2=Moderate, 1=Mild, 0=None)



Mean Severity of Night Heartburn By Study Day For Evaluable Patients (3=Severe, 2=Moderate, 1=Mild, 0=None)



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

Erosive Esophagitis

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

Erosive Esophagitis Healing Rates

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

* ($p \leq 0.001$) versus placebo.
† ($p \leq 0.05$) versus PREVACID 15 mg.

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

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

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

Erosive Esophagitis Healing Rates

Week	PREVACID 30 mg q.d. (N=115)	Ranitidine 150 mg b.i.d. (N=127)
2	66.7%*	38.7%
4	82.5%*	52.0%
6	93.0%*	67.8%
8	92.1%*	69.9%

* ($p \leq 0.001$) versus ranitidine.

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

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

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

In a U.S. multicenter, double-blind, active-controlled study, 30 mg of PREVACID was compared with ranitidine 150 mg b.i.d. in 151 patients with erosive reflux esophagitis that was poorly responsive to

a minimum of 12 weeks of treatment with at least one H_2-receptor antagonist given at the dose indicated for symptom relief or greater, namely, cimetidine 800 mg/day, ranitidine 300 mg/day, famotidine 40 mg/day or nizatidine 300 mg/day. PREVACID 30 mg was more effective than ranitidine 150 mg b.i.d. in healing reflux esophagitis, and the percentage of patients with healing were as follows. This study does not constitute a comparison of the effectiveness of histamine H_2-receptor antagonists with PREVACID, as all patients had demonstrated unresponsiveness to the histamine H_2-receptor antagonist mode of treatment. It does indicate, however, that PREVACID may be useful in patients failing on a histamine H_2-receptor antagonist.

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

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

* ($p \leq 0.001$) versus ranitidine.

Long-Term Maintenance Treatment of Erosive Esophagitis

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

Endoscopic Remission Rates

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

%=Life Table Estimate

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

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

In a U.S., randomized, double-blind, study, PREVACID 15 mg q.d. (n = 100) was compared with ranitidine 150 mg b.i.d. (n = 106), at the recommended dosage, in patients with endoscopically-proven healed erosive esophagitis over a 12-month period. Treatment with PREVACID resulted in patients remaining healed (Grade 0 lesions) of erosive esophagitis for significantly longer periods of time than

those treated with ranitidine ($p<0.001$). In addition, PREVACID was significantly more effective than ranitidine in providing complete relief of both daytime and nighttime heartburn. Patients treated with PREVACID remained asymptomatic for a significantly longer period of time than patients treated with ranitidine.

Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome

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

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

INDICATIONS AND USAGE

PREVACID Delayed-Release Capsules, PREVACID SoluTab Delayed-Release Orally Disintegrating Tablets and PREVACID For Delayed-Release Oral Suspension are indicated for:

Short-Term Treatment of Active Duodenal Ulcer

PREVACID is indicated for short-term treatment (for 4 weeks) for healing and symptom relief of active duodenal ulcer.

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

Triple Therapy: PREVACID/amoxicillin/clarithromycin

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

Dual Therapy: PREVACID/amoxicillin

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

Maintenance of Healed Duodenal Ulcers

PREVACID is indicated to maintain healing of duodenal ulcers. Controlled studies do not extend beyond 12 months.

Short-Term Treatment of Active Benign Gastric Ulcer
PREVACID is indicated for short-term treatment (up to 8 weeks) for healing and symptom relief of active benign gastric ulcer.

Healing of NSAID-Associated Gastric Ulcer
PREVACID is indicated for the treatment of NSAID-associated gastric ulcer in patients who continue NSAID use. Controlled studies did not extend beyond 8 weeks.

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

Gastroesophageal Reflux Disease (GERD)
Short-Term Treatment of Symptomatic GERD
PREVACID is indicated for the treatment of heartburn and other symptoms associated with GERD.

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

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

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

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

Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome
PREVACID is indicated for the long-term treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome.

CONTRAINDICATIONS
PREVACID is contraindicated in patients with known hypersensitivity to any component of the formulation of PREVACID.

Amoxicillin is contraindicated in patients with a known hypersensitivity to any penicillin.

Clarithromycin is contraindicated in patients with a known hypersensitivity to clarithromycin, erythromycin, and any of the macrolide antibiotics.

Concomitant administration of clarithromycin with cisapride, pimozide, astemizole, or terfenadine is contraindicated. There have been post-marketing reports of drug interactions when clarithromycin and/or erythromycin are co-administered with cisapride, pimozide, astemizole, or terfenadine resulting in cardiac arrhythmias (QT prolongation, ventricular tachycardia, ventricular fibrillation, and torsades de pointes) most likely due to inhibition of metabolism of these drugs by erythromycin and clarithromycin. Fatalities have been reported.

(Please refer to full prescribing information for amoxicillin and 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 is available as a capsule, orally disintegrating tablet and oral suspension, and is available in 15 mg and 30 mg strengths. Directions for use specific to the route and available methods of administration for each of these dosage forms is presented below. PREVACID should be taken before eating. PREVACID products SHOULD NOT BE CRUSHED OR CHEWED.

Phenylketonurics: Contains Phenylalanine 2.5 mg per 15 mg Tablet and 5.1 mg per 30 mg Tablet.

Administration Options

1. PREVACID Delayed-Release Capsules

PREVACID Delayed-Release Capsules should be swallowed whole.

Alternatively, for patients who have difficulty swallowing capsules, PREVACID Delayed-Release Capsules can be opened and administered as follows:

- Open capsule.
- Sprinkle intact granules on one tablespoon of either applesauce, ENSURE® pudding, cottage cheese, yogurt or strained pears.
- Swallow immediately.

PREVACID Delayed-Release Capsules may also be emptied into a small volume of either apple juice, orange juice or tomato juice and administered as follows:

- Open capsule.
- Sprinkle intact granules into a small volume of either apple juice, orange juice or tomato juice (60 mL – approximately 2 ounces).
- Mix briefly.
- Swallow immediately.
- To ensure complete delivery of the dose, the glass should be rinsed with two or more volumes of juice and the contents swallowed immediately.

USE IN OTHER FOODS AND LIQUIDS HAS NOT BEEN STUDIED CLINICALLY AND IS THEREFORE NOT RECOMMENDED.

2. PREVACID SoluTab Delayed-Release Orally Disintegrating Tablets

PREVACID SoluTab should not be chewed. Place the tablet on the tongue and allow it to disintegrate, with or without water, until the particles can be swallowed. The tablet typically disintegrates in less than 1 minute.

Alternatively, for children or other patients who have difficulty swallowing tablets, PREVACID SoluTab can be delivered in two different ways.

PREVACID SoluTab – Oral Syringe

For administration via oral syringe, PREVACID SoluTab can be administered as follows:

- Place a 15 mg tablet in oral syringe and draw up approximately 4 mL of water, or place a 30 mg tablet in oral syringe and draw up approximately 10 mL of water.
- Shake gently to allow for a quick dispersal.
- After the tablet has dispersed, administer the contents within 15 minutes.
- Refill the syringe with approximately 2 mL (5 mL for the 30 mg tablet) of water, shake gently, and administer any remaining contents.

PREVACID SoluTab – Nasogastric Tube Administration (≥ 8 French)

For administration via a nasogastric tube, PREVACID SoluTab can be administered as follows:

- Place a 15 mg tablet in a syringe and draw up 4 mL of water, or place a 30 mg tablet in a syringe and draw up 10 mL of water.
- Shake gently to allow for a quick dispersal.
- After the tablet has dispersed, inject through the nasogastric tube into the stomach within 15 minutes.
- Refill the syringe with approximately 5 mL of water, shake gently, and flush the nasogastric tube.

3. *PREVACID for Delayed-Release Oral Suspension*

PREVACID for Delayed-Release Oral Suspension should be administered as follows:

- Open packet.
- To prepare a dose, empty the packet contents into a container containing 2 tablespoons of **WATER**. DO NOT USE OTHER LIQUIDS OR FOODS.
- Stir well, and drink immediately.
- If any material remains after drinking, add more water, stir, and drink immediately.
- **This product should not be given through enteral administration tubes.**

Drug Interactions

Lansoprazole is metabolized through the cytochrome P_{450} system, specifically through the CYP3A and CYP2C19 isozymes. Studies have shown that lansoprazole does not have clinically significant interactions with other drugs metabolized by the cytochrome P_{450} system, such as warfarin, antipyrine, indomethacin, ibuprofen, phenytoin, propranolol, prednisone, diazepam, or clarithromycin in healthy subjects. These compounds are metabolized through various cytochrome P_{450} isozymes including

CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A. When lansoprazole was administered concomitantly with theophylline (CYP1A2, CYP3A), a minor increase (10%) in the clearance of theophylline was seen. Because of the small magnitude and the direction of the effect on theophylline clearance, this interaction is unlikely to be of clinical concern. Nonetheless, individual patients may require additional titration of their theophylline dosage when lansoprazole is started or stopped to ensure clinically effective blood levels.

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

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

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

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

In two 24-month carcinogenicity studies, Sprague-Dawley rats were treated orally with doses of 5 to 150 mg/kg/day, about 1 to 40 times the exposure on a body surface (mg/m^2) basis, of a 50-kg person of average height (1.46 m^2 body surface area) given the recommended human dose of 30 mg/day (22.2 mg/m^2). Lansoprazole produced dose-related gastric enterochromaffin-like (ECL) cell hyperplasia and ECL cell carcinoids in both male and female rats. It also increased the incidence of intestinal metaplasia of the gastric epithelium in both sexes. In male rats, lansoprazole produced a dose-related increase of testicular interstitial cell adenomas. The incidence of these adenomas in rats receiving doses of 15 to 150 mg/kg/day (4 to 40 times the recommended human dose based on body surface area) exceeded the low background incidence (range = 1.4 to 10%) for this strain of rat. Testicular interstitial cell adenoma also occurred in 1 of 30 rats treated with 50 mg/kg/day (13 times the recommended human dose based on body surface area) in a 1-year toxicity study.

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

receiving 75 to 600 mg/kg/day (10 to 80 times the recommended human dose based on body surface area).

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

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

Pregnancy: Teratogenic Effects.

Pregnancy Category B

Lansoprazole

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

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

Pregnancy Category C

Clarithromycin

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

Nursing Mothers

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

Pediatric Use

The safety and effectiveness of PREVACID have been established in pediatric patients 1 to 17 years of age for short-term treatment of symptomatic GERD and erosive esophagitis. Use of PREVACID in this population is supported by evidence from adequate and well-controlled studies of PREVACID in adults with additional clinical, pharmacokinetic, and pharmacodynamic studies performed in pediatric patients. The adverse events profile in pediatric patients is similar to that of adults. There were no adverse events reported in U.S. clinical studies that were not previously observed in adults. The safety and effectiveness of PREVACID in patients <1 year of age have not been established.

1 to 11 years of age

In an uncontrolled, open-label, U.S. multicenter study, 66 pediatric patients (1 to 11 years of age) with GERD were assigned, based on body weight, to receive an initial dose of either PREVACID 15 mg

q.d. if ≤ 30 kg or PREVACID 30 mg q.d. if > 30 kg administered for 8 to 12 weeks. The PREVACID dose was increased (up to 30 mg b.i.d.) in 24 of 66 pediatric patients after 2 or more weeks of treatment if they remained symptomatic. At baseline 85% of patients had mild to moderate overall GERD symptoms (assessed by investigator interview), 58% had non-erosive GERD and 42% had erosive esophagitis (assessed by endoscopy).

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

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

GERD symptom improvement and Erosive Esophagitis healing rates in pediatric patients age 1 to 11

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

[a] At Week 8 or Week 12

[b] Symptoms assessed by patients diary kept by caregiver.

[c] No data were available for 4 pediatric patients.

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

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

The most frequently reported (2 or more patients) treatment-related adverse events in patients 1 to 11 years of age (N=66) were constipation (5%) and headache (3%).

12 to 17 years of age

In an uncontrolled, open-label, U.S. multicenter study, 87 adolescent patients (12 to 17 years of age) with symptomatic GERD were treated with PREVACID for 8 to 12 weeks. Baseline upper endoscopies classified these patients into two groups: 64 (74%) nonerosive GERD and 23 (26%) erosive esophagitis (EE). The nonerosive GERD patients received PREVACID 15 mg q.d. for 8 weeks and the EE patients received PREVACID 30 mg q.d. for 8 to 12 weeks. At baseline, 89% of these patients had mild to moderate overall GERD symptoms (assessed by investigator interviews). During 8 weeks of PREVACID treatment, adolescent patients experienced a 63% reduction in frequency and a 69% reduction in severity of GERD symptoms based on diary results.

Twenty-one of 22 (95.5%) adolescent erosive esophagitis patients were healed after 8 weeks of PREVACID treatment. One patient remained unhealed after 12 weeks of treatment.

GERD symptom improvement and Erosive Esophagitis healing rates in pediatric patients age 12 to 17

GERD	Final Visit % (n/N)
Symptomatic GERD (All Patients) Improvement in Overall GERD Symptoms[a]	73.2% (60/82)[b]
Nonerosive GERD Improvement in Overall GERD Symptoms[a]	71.2% (42/59)[b]
Erosive Esophagitis Improvement in Overall GERD Symptoms[a] Healing Rate[c]	78.3% (18/23) 95.5% (21/22)[c]

[a]Symptoms assessed by patient diary (parents/caregivers as necessary).
[b]No data available for 5 patients.
[c]Data from one healed patient was excluded from this analysis due to timing of final endoscopy.

In these 87 adolescent patients, increases in serum gastrin levels were similar to those observed in adult studies, median fasting serum gastrin levels increased 42% from 45 pg/mL at baseline to 64 pg/mL [interquartile range (25^{th} – 75^{th} percentile) of 44 – 88 pg/mL] at the final visit. (Normal serum gastrin levels are 25 to 111 pg/mL.)

The safety of PREVACID Delayed-Release Capsules has been assessed in these 87 adolescent patients. Of the 87 adolescent patients with GERD, 6% (5/87) took PREVACID for <6 weeks, 93% (81/87) for 6-10 weeks, and 1% (1/87) for >10 weeks.

The most frequently reported (at least 3%) treatment-related adverse events in these patients were headache (7%), abdominal pain (5%), nausea (3%) and dizziness (3%). Treatment-related dizziness, reported in this package insert as occurring in <1% of adult patients, was reported in this study by 3 adolescent patients with nonerosive GERD, who had dizziness concurrently with other events (such as migraine, dyspnea, and vomiting).

Use in Women

Over 4,000 women were treated with lansoprazole. Ulcer healing rates in females were similar to those in males. The incidence rates of adverse events were also similar to those seen in males.

Use in Geriatric Patients

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

ADVERSE REACTIONS

Clinical

Worldwide, over 10,000 patients have been treated with lansoprazole in Phase 2-3 clinical trials involving various dosages and durations of treatment. The adverse reaction profiles for PREVACID Delayed-Release Capsules and PREVACID for Delayed-Release Oral Suspension are similar. In general, lansoprazole treatment has been well-tolerated in both short-term and long-term trials.

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

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

Body System/Adverse Event	PREVACID (N= 2768) %	Placebo (N= 1023) %
Body as a Whole		
Abdominal Pain	2.1	1.2
Digestive System		
Constipation	1.0	0.4
Diarrhea	3.8	2.3
Nausea	1.3	1.2

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

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

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

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

Body as a Whole – abdomen enlarged, allergic reaction, asthenia, back pain, candidiasis, carcinoma, chest pain (not otherwise specified), chills, edema, fever, flu syndrome, halitosis, infection (not otherwise specified), malaise, neck pain, neck rigidity, pain, pelvic pain; *Cardiovascular System* - angina, arrhythmia, bradycardia, cerebrovascular accident/cerebral infarction, hypertension/hypotension, migraine, myocardial infarction, palpitations, shock (circulatory failure), syncope, tachycardia, vasodilation; *Digestive System* – abnormal stools, anorexia, bezoar, cardiospasm, cholelithiasis, colitis, dry mouth, dyspepsia, dysphagia, enteritis, eructation, esophageal stenosis, esophageal ulcer, esophagitis, fecal discoloration, flatulence, gastric nodules/fundic gland polyps, gastritis, gastroenteritis, gastrointestinal anomaly, gastrointestinal disorder, gastrointestinal hemorrhage, glossitis, gum hemorrhage, hematemesis, increased appetite, increased salivation, melena, mouth ulceration, nausea and vomiting, nausea and vomiting and diarrhea, oral moniliasis, rectal disorder, rectal hemorrhage, stomatitis, tenesmus, thirst, tongue disorder, ulcerative colitis, ulcerative stomatitis; *Endocrine System* - diabetes mellitus, goiter, hypothyroidism; *Hemic and Lymphatic System* - anemia, hemolysis, lymphadenopathy; *Metabolic and Nutritional Disorders* - gout, dehydration, hyperglycemia/hypoglycemia, peripheral edema, weight gain/loss; *Musculoskeletal System* - arthralgia, arthritis, bone disorder, joint disorder, leg cramps, musculoskeletal pain, myalgia, myasthenia, synovitis; *Nervous System* – abnormal dreams, agitation, amnesia, anxiety, apathy, confusion, convulsion, depersonalization, depression, diplopia, dizziness, emotional lability, hallucinations, hemiplegia, hostility aggravated, hyperkinesia, hypertonia, hypesthesia, insomnia, libido decreased/increased, nervousness, neurosis, paresthesia, sleep disorder, somnolence, thinking abnormality, tremor, vertigo;

Respiratory System - asthma, bronchitis, cough increased, dyspnea, epistaxis, hemoptysis, hiccup, laryngeal neoplasia, pharyngitis, pleural disorder, pneumonia, respiratory disorder, upper respiratory inflammation/infection, rhinitis, sinusitis, stridor; *Skin and Appendages* - acne, alopecia, contact dermatitis, dry skin, fixed eruption, hair disorder, maculopapular rash, nail disorder, pruritus, rash, skin carcinoma, skin disorder, sweating, urticaria; *Special Senses* – abnormal vision, blurred vision, conjunctivitis, deafness, dry eyes, ear disorder, eye pain, otitis media, parosmia, photophobia, retinal degeneration, taste loss, taste perversion, tinnitus, visual field defect; *Urogenital System* - abnormal menses, breast enlargement, breast pain, breast tenderness, dysmenorrhea, dysuria, gynecomastia, impotence, kidney calculus, kidney pain, leukorrhea, menorrhagia, menstrual disorder, penis disorder, polyuria, testis disorder, urethral pain, urinary frequency, urinary tract infection, urinary urgency, urination impaired, vaginitis.

Postmarketing

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

Body as a Whole - anaphylactoid-like reaction; *Digestive System* - hepatotoxicity, pancreatitis, vomiting; *Hemic and Lymphatic System* - agranulocytosis, aplastic anemia, hemolytic anemia, leukopenia, neutropenia, pancytopenia, thrombocytopenia, and thrombotic thrombocytopenic purpura; *Skin and Appendages* – severe dermatologic reactions including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (some fatal); *Special Senses* - speech disorder; *Urogenital System* - urinary retention.

Combination Therapy with Amoxicillin and Clarithromycin

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

Triple Therapy: PREVACID/amoxicillin/clarithromycin

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

Dual Therapy: PREVACID/amoxicillin

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

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

Laboratory Values

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

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

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

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

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

OVERDOSAGE

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

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

DOSAGE AND ADMINISTRATION

PREVACID is available as a capsule, orally disintegrating tablet and oral suspension, and is available in 15 mg and 30 mg strengths. Directions for use specific to the route and available methods of administration for each of these dosage forms is presented below. PREVACID should be taken before eating. PREVACID products SHOULD NOT BE CRUSHED OR CHEWED. In the clinical trials, antacids were used concomitantly with PREVACID.

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

Indication	Recommended Dose	Frequency	For Additional Information, See
Duodenal Ulcers			
Short-Term Treatment	15 mg	Once daily for 4 weeks	**INDICATIONS AND USAGE**
Maintenance of Healed	15 mg	Once daily	**CLINICAL STUDIES**
***H. pylori* Eradication to Reduce the Risk of Duodenal Ulcer Recurrence†**			
Triple Therapy:			**INDICATIONS AND USAGE**
PREVACID	30 mg	Twice daily (q12h) for 10 or 14 days	
Amoxicillin	1 gram	Twice daily (q12h) for 10 or 14 days	
Clarithromycin	500 mg	Twice daily (q12h) for 10 or 14 days	
Dual Therapy:			**INDICATIONS AND USAGE**
PREVACID	30 mg	Three times daily (q8h) for 14 days	
Amoxicillin	1 gram	Three times daily (q8h) for 14 days	
Benign Gastric Ulcer			**CLINICAL STUDIES**
Short-Term Treatment	30 mg	Once daily for up to 8 weeks	
NSAID-associated GastricUlcer			**CLINICAL STUDIES**
Healing	30 mg	Once daily for 8 weeks*	
Risk Reduction	15 mg	Once daily for up to 12 weeks*	
Gastroesophageal Reflux Disease (GERD)			
Short-Term Treatment of Symptomatic GERD	15 mg	Once daily for up to 8 weeks	**CLINICAL STUDIES**
Short -Term Treatment of Erosive Esophagitis	30 mg	Once daily for up to 8 weeks**	**INDICATIONS AND USAGE**
Pediatric (1 to 11 years of age) Short-Term Treatment of Symptomatic GERD and Short-Term Treatment of Erosive Esophagitis			**PEDIATRIC USE**
≤ 30 kg	15 mg	Once daily for up to 12 weeks+	
> 30 kg	30 mg	Once daily for up to 12 weeks+	
(12 to 17 years of age) Short-Term Treatment of Symptomatic GERD			
Nonerosive GERD	15 mg	Once daily for up to 8 weeks	
Erosive Esophagitis	30 mg	Once daily for up to 8 weeks	
Maintenance of Healing of Erosive Esophagitis	15 mg	Once daily	**CLINICAL STUDIES**
Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome	60 mg	Once daily***	**CLINICAL STUDIES**

† Please refer to amoxicillin and clarithromycin full prescribing information for **CONTRAINDICATIONS** and **WARNINGS**, and for information regarding dosing in elderly and renally-impaired patients.

* Controlled studies did not extend beyond indicated duration.

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

*** Varies with individual patient. Recommended adult starting dose is 60 mg once daily. 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 dose 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 4 years.

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

Administration Options

1. PREVACID Delayed-Release Capsules

PREVACID Capsules-Oral Administration

PREVACID Delayed-Release Capsules should be swallowed whole.

Alternatively, for patients who have difficulty swallowing capsules, PREVACID Delayed-Release Capsules can be opened and administered as follows:

- Open capsule.
- Sprinkle intact granules on one tablespoon of either applesauce, ENSURE® pudding, cottage cheese, yogurt or strained pears.
- Swallow immediately.

PREVACID Delayed-Release Capsules may also be emptied into a small volume of either apple juice, orange juice or tomato juice and administered as follows:

- Open capsule.
- Sprinkle intact granules into a small volume of either apple juice, orange juice or tomato juice (60 mL – approximately 2 ounces).
- Mix briefly.
- Swallow immediately.
- To ensure complete delivery of the dose, the glass should be rinsed with two or more volumes of juice and the contents swallowed immediately.

USE IN OTHER FOODS AND LIQUIDS HAS NOT BEEN STUDIED CLINICALLY AND IS THEREFORE NOT RECOMMENDED.

PREVACID Capsules - Nasogastric Tube Administration

For patients who have a nasogastric tube in place, PREVACID Delayed-Release Capsules can be administered as follows:

- Open capsule.
- Mix intact granules into 40 mL of apple juice. DO NOT USE OTHER LIQUIDS.
- Inject through the nasogastric tube into the stomach.
- Flush with additional apple juice to clear the tube.

2. *PREVACID SoluTab Delayed-Release Orally Disintegrating Tablets*

PREVACID SoluTab should not be chewed. Place the tablet on the tongue and allow it to disintegrate, with or without water, until the particles can be swallowed. The tablet typically disintegrates in less than 1 minute.

Alternatively, for children or other patients who have difficulty swallowing tablets, PREVACID SoluTab can be delivered in two different ways.

PREVACID SoluTab – Oral Syringe

For administration via oral syringe, PREVACID SoluTab can be administered as follows:

- Place a 15 mg tablet in oral syringe and draw up approximately 4 mL of water, or place a 30 mg tablet in oral syringe and draw up approximately 10 mL of water.
- Shake gently to allow for a quick dispersal.
- After the tablet has dispersed, administer the contents within 15 minutes.
- Refill the syringe with approximately 2 mL (5 mL for the 30 mg tablet) of water, shake gently, and administer any remaining contents.

PREVACID SoluTab – Nasogastric Tube Administration (≥ 8 French)

For administration via a nasogastric tube, PREVACID SoluTab can be administered as follows:

- Place a 15 mg tablet in a syringe and draw up 4 mL of water, or place a 30 mg tablet in a syringe and draw up 10 mL of water.
- Shake gently to allow for a quick dispersal.
- After the tablet has dispersed, inject through the nasogastric tube into the stomach within 15 minutes.
- Refill the syringe with approximately 5 mL of water, shake gently, and flush the nasogastric tube.

3. *PREVACID for Delayed-Release Oral Suspension*

PREVACID for Delayed-Release Oral Suspension should be administered as follows:

- Open packet.
- To prepare a dose, empty the packet contents into a container containing 2 tablespoons of **WATER**. DO NOT USE OTHER LIQUIDS OR FOODS.
- Stir well, and drink immediately.
- If any material remains after drinking, add more water, stir, and drink immediately.
- **This product should not be given through enteral administration tubes.**

HOW SUPPLIED

PREVACID Delayed-Release Capsules, 15 mg, are opaque, hard gelatin, colored pink and green with the TAP logo and "PREVACID 15" imprinted on the capsules. The 30 mg capsules are opaque, hard gelatin, colored pink and black with the TAP logo and "PREVACID 30" imprinted on the capsules. They are available as follows:

NDC 0300-1541-30	Unit of use bottles of 30: 15-mg capsules
NDC 0300-1541-19	Bottles of 1000: 15-mg capsules
NDC 0300-1541-11	Unit dose package of 100: 15-mg capsules
NDC 0300-3046-13	Bottles of 100: 30-mg capsules
NDC 0300-3046-19	Bottles of 1000: 30-mg capsules
NDC 0300-3046-11	Unit dose package of 100: 30-mg capsules

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

NDC 0300-7309-30	Unit dose carton of 30: 15-mg packets
NDC 0300-7311-30	Unit dose carton of 30: 30-mg packets

PREVACID SoluTab Delayed-Release Orally Disintegrating Tablets, 15 mg, are white to yellowish white uncoated tablets with orange to dark brown speckles, with "15" debossed on one side of the tablet. The 30 mg are white to yellowish white uncoated tablets with orange to dark brown speckles, with "30" debossed on one side of the tablet. The tablets are available as follows:

NDC 0300-1543-30	Unit dose packages of 30: 15-mg tablets
NDC 0300-1544-30	Unit dose packages of 30: 30-mg tablets

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature]

R_x only

U.S. Patent Nos. 4,628,098; 4,689,333; 5,013,743; 5,026,560; 5,045,321; 5,093,132; 5,433,959; 5,464,632; 6,123,962 and 6,328,994.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-428/S-004

MEDICAL REVIEW(s)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research

DATE: 6/16/2004

FROM: Joyce A Korvick, MD, MPH

DGCDP/ODE III

SUBJECT: **Director (Deputy) Summary Approval Comments**
NDA 20-406/SE5-057
NDA 21-281/SE8-014
NDA 21-428/SE8-004

APPLICANT: TAP Pharmaceutical Products, Inc.

DRUG: Prevacid®(lansoprazole) Delayed-Release Capsules
Prevacid®(lansoprazole) Delayed-Release Oral Suspension
Prevacid® Solu Tab™(lansoprazole) Delayed-Release Orally Disintegrating Tablets

DIVISION RECOMMENDATION:
The Division recommends approval of the oral formulations of Prevacid (listed above) for the pediatric indication of Symptomatic GERD and Erosive Esophagitis in patients 12-17 years of age.

There are no post-marketing commitments.

I. BACKGROUND:

The oral formulations of Prevacid are approved for the treatment of Symptomatic GERD and erosive esophagitis in adults as well as use in the pediatric patients 1-11 years of age. This supplemental application provides data to support the use of oral formulations of Prevacid in pediatric Symptomatic GERD and erosive esophagitis patients. Two studies were submitted in these supplemental NDAs. One was a clinical study (M00-158) and the other a PK/PD study (M97-640).

II. DISCIPLINE REVIEW SUMMARY AND COMMENTARY:

A. OPDRA/DDMAC/DMETS:

There are no concerns or comments from these divisions regarding this labeling change.

B. Chemistry:

No changes are requested for the chemistry or manufacturing of this product.

C. Pharmacology/Toxicology:
There was no pre-clinical data submitted in this application.

D. Biopharmaceutics:
Study M97-640 is a PK/PD study in GERD patients aged 12-17 years. The patients were treated with 15 or 30 mg doses of Prevacid for a 5 day period. This resulted in similar mean AUC and Cmax values for the pediatric GERD patients relative to healthy adult subjects. In addition there was a corresponding improvement in PD parameters (24-hr mean intragastric pH, % time pH > 3 & 4) in these pediatric patients over the 5 day period.

From the biopharmaceutics standpoint, this application is approvable.

E. Clinical Efficacy/Safety:

The clinical study was an open-label study in adolescents with GERD, ages 12 to 17 years. According to disease status (non-erosive GERD or erosive esophagitis) of the 84 enrolled pediatric patients, 64 with non-erosive GERD, were assigned to receive lansoprazole 15 mg QD dose for 8 weeks and the remainder with erosive esophagitis were assigned to receive lansoprazole 30 mg QD for 8 to 12 weeks to assess efficacy and safety of lansoprazole. The primary efficacy endpoint was the change in frequency a severity of GERD symptoms based on subjects' diary data from the pretreament period to the Week 8 treatment period. Repeat endoscopy was performed in patients with erosive esophagitis at the end of this treatment period. The majority of erosive esophagitis patients had Grade 2 erosions and none of the patients had Grade 4 at baseline. The majority of patients enrolled in this study had moderate GERD Symptoms. Some were in the Severe category.

The outcomes revealed similar symptomatic improvement rates and endoscopic healing rates to those seen in adult patients.

There were no additional safety issues raised in either study in this pediatric age group compared to those already labeled.

III. PHASE 4 COMITTMENTS:
None

IV. LABELING:
This submission requests changes in the label for the following sections relevant to the pediatric indication: **PHARMACOLOGY – SPECIAL POPULATIONS-PEDIATRICS, PEDIATRIC USE, DOSEAGE AND ADMINISTRATION AND DESCRIPTION.**
(See below)

PHARMACOLOGY – SPECIAL POPULATIONS-PEDIATRICS: The following additional pharmacokinetic statements regarding Cmax and AUC were found to be acceptable:

> "In adolescent subjects aged 12 to 17 years, subjects were randomized to receive lansoprazole at 15 mg or 30 mg q.d. [redacted] Mean C_{max} and AUC values of lansoprazole were not affected by body weight or age; and nearly dose-proportional increases in [redacted] mean C_{max} and AUC values were observed between the two dose groups in the study. Overall, lansoprazole pharmacokinetics in pediatric patients aged 1 to 17 years were similar to those observed in healthy adult subjects."

PEDIATRIC USE: In order to parallel the presentation of the clinically meaningful data which is already approved for pediatric patients 1-11 years of age the following table was agreed upon by TAP and the Division.

GERD symptom improvement and Erosive Esophagitis healing rates in pediatric patients age 12 to 17

GERD	Final Visit % (n/N)
Symptomatic GERD (All Patients) Improvement in Overall GERD Symptoms[a]	73.2% (60/82)[b]
Nonerosive GERD Improvement in Overall GERD Symptoms[a]	71.2% (42/59)[b]
Erosive Esophagitis Improvement in Overall GERD Symptoms[a] Healing Rate[c]	78.3% (18/23) 95.5% (21/22)[c]

[a]Symptoms assessed by patient diary (parents/caregivers as necessary).
[b]No data available for 5 patients.
[c]Data from one healed patient [redacted] was excluded from this analysis due to timing of final endoscopy.

DOSAGE AND ADMINISTRATION: The ages of 12-17 were added to the indications for Symptomatic GERD (15 mg) and Erosive Esophagitis (30 Mg). These doses are the same doses listed for adult patients in these indications.

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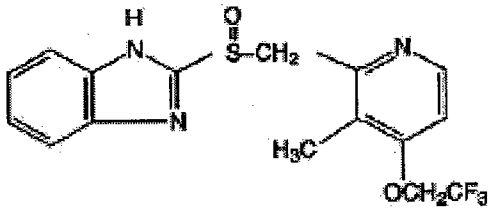
/s/

Joyce Korvick
6/17/04 01:47:29 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF GASTROINTESTINAL & COAGULATION DRUG PRODUCTS

EXECUTIVE SUMMARY OF MEDICAL AND CLINICAL PHARMACOLOGY REVIEWS

PREVACID® (lansoprazole)



NDA#/Supplement#:	**20-406/S-057, 21-281/S-014, and 21-428/S-004**
Proposed Indications:	**The short-term treatment of non-erosive GERD and EE in pediatric patients between 12 and 17 years old**
Drug Class:	Substituted benzimidazole proton pump inhibitor
Formulation and Route of administration:	Oral capsule
Proposed regimens:	Non-erosive GERD: 15 mg once daily for up to 8 weeks EE: 30 mg once daily for up to 8 weeks
Applicant:	TAP Pharmaceutical Products Inc.
Medical Reviewer:	Eric Brodsky, M.D.
Medical Team Leader:	Ruyi He, M.D.
Biopharmaceutics Reviewer:	Suliman Al-Fayoumi, Ph.D.
Biopharmaceutics Team Leader:	Suresh Doddapaneni, Ph.D.
Project Manager:	Melissa Furness
Date of Submission:	December 19, 2004
Review Date:	June 7, 2004

BACKGROUND

Lansoprazole is a proton pump inhibitor which was approved in the United States on May 10, 1995 for the treatment of a variety of acid-related esophageal, gastric, and duodenal disorders in adults. Lansoprazole inhibits gastric acid secretion by blocking the proton pump [(H+,K+)-ATPase enzyme system] at the secretory surface of the gastric parietal cell. Inhibition of the proton pump, the final step of stomach acid secretion, decreases intra-gastric acid concentration (increases intra-gastric pH). Based upon submitted adult and pediatric studies, lansoprazole was approved for the treatment of non-erosive gastro-esophageal reflux disease (GERD) and erosive esophagitis (EE) in adults and pediatric patients between the ages of 1 and 11 years old.

Lansoprazole is available by prescription in three oral formulations — prevacid® (lansoprazole) delayed-release capsules, prevacid® (lansoprazole) delayed-release oral suspension, and prevacid® (lansoprazole) delayed-release orally disintegrating tablets (solutab) — and one intravenous formulation, prevacid I.V. (lansoprazole) for injection. All three oral formulations contain 15 mg or 30 mg of lansoprazole and the intravenous formulation contains 30 mg of lansoprazole.

TAP Pharmaceutical Products Inc. (TAP) provided two study reports, M97-640 and M00-158, to support the following new lansoprazole indications: the treatment of non-erosive GERD and EE in pediatric patients between ages 12 to 17 years old.

EXECUTIVE SUMMARY

1.0 RECOMMENDATIONS

1.1 Recommendations on Approvability

From a clinical perspective, prevacid® (lansoprazole) delayed-release capsules, prevacid® (lansoprazole) delayed-release oral suspension, and prevacid® (lansoprazole) delayed-release orally disintegrating tablets (solutab) are recommended for approval for the treatment of GERD (non-erosive GERD and EE) in pediatric patients between 12 and 17 years old.

1.2 Recommendation on Phase 4 Studies and/or Risk Management Steps

From a clinical perspective, this medical officer does not recommend phase 4 studies or risk management steps in pediatric GERD patients between 12 and 17 years old.

2.0. SUMMARY OF CLINICAL FINDINGS

2.1 Brief Overview of Clinical Program

TAP submitted two clinical study reports (Studies M97-640 and M00-158) to support the efficacy and safety of lansoprazole in the treatment of non-erosive GERD and EE in pediatric patients between 12 and 17 years old. These studies, conducted exclusively in the United States, included a total of 150 pediatric GERD patients (between 12 and 17 years old) who all received upper endoscopies at baseline.

Study M97-640 was a randomized, double-blinded, multi-center (10 sites), pharmacokinetic (PK), and pharmacodynamic (PD) trial of lansoprazole in the treatment of pediatric GERD patients, ages 12 to 17 years old. Patients were randomized to two lansoprazole treatment groups: 15 mg/day (n = 32) or 30 mg/day (n = 31) for 5 consecutive days. The PK and PD of lansoprazole were assessed by plasma concentrations and 24-hour pH monitoring, respectively.

Study M00-158 was an uncontrolled, open-label, multi-center (20 sites) trial of lansoprazole in the treatment of GERD in pediatric patients, ages 12 to 17 years. Baseline upper endoscopies categorized pediatric GERD patients into two groups: non-erosive GERD (n = 64) and EE (n = 23). Non-erosive GERD patients received 15 mg of oral lansoprazole once daily for 8 weeks and EE patients received 30 mg of lansoprazole once daily for 8 weeks. EE patients with completely healed EE after 8 weeks of treatment were considered to have completed the therapy. In contrast, EE patients with unhealed EE after 8 weeks of treatment were treated with 30 mg of lansoprazole for an additional 4 weeks (12 weeks of total treatment).

The safety evaluation included assessment of the data from the two clinical studies and post-marketing data and literature reports in pediatric patients between 12 and 17 years old, who received lansoprazole.

2.2 Efficacy

Study M00-158: Sixty-four non-erosive GERD patients were treated with 15 mg of lansoprazole for 8 weeks and 23 EE patients were treated with 30 mg of lansoprazole for 8 to 12 weeks. The efficacy results are summarized below.

The co-primary endpoints were the change from baseline in the frequency and severity of GERD symptoms during the 8 week treatment period based on patient diary data. The patient diary results demonstrated an improvement in GERD symptoms during 8 weeks of lansoprazole treatment. The median percentage of days with GERD symptoms decreased from 88.9% to 33.3%. This was a statistically significant change ($p<0.001$). Furthermore, the average severity of GERD symptoms (0 = none; 1 = mild; 2 = moderate; 3 = severe; 4 = very severe) decreased from 1.6 (mild to moderate) to 0.5 (none to mild) and this was statistically significant ($p<0.001$). No placebo group was included in this trial.

The most important secondary endpoint was the proportion of patients who had endoscopically-documented complete esophageal healing at the week 8 and 12 visits. In this study, the appearance of the esophagus was scored by the TAP Esophagitis Grading Scale (developed by a committee of the sponsor's consultant gastroenterologists). Patients with normal appearing mucosa (grade 0) or mucosal edema, hyperemia and/or friability (grade 1) were classified to have non-erosive GERD. Patients with the appearance of at least one erosion/ulceration in the esophagus mucosa (grades 2, 3, or 4) were categorized to have EE.

Complete healing of EE was defined as the return of the esophageal mucosa to grade 0 or 1 (non-erosive GERD). Twenty-one of twenty-two (95.5%) EE patients were completely healed after 8 weeks of lansoprazole treatment. One patient remained unhealed after 12 weeks of lansoprazole treatment. However, all EE patients had grade 2 or 3 lesions; no EE patient had a grade 4 lesion in this study. These efficacy results support the proposed EE indication in pediatric patients between 12 and 17 years old.

Additional secondary endpoints were the change from baseline in the amount and frequency of antacid use during the first 8 weeks of lansoprazole treatment based on patient diary data. Rescue antacid use decreased from a median of 54.5% of the days during the pretreatment period to a median of 5.5% of the days during the lansoprazole treatment period ($p<0.001$). Furthermore, the amount of rescue antacid used, decreased from a median of 1.4 teaspoons/day during the baseline pretreatment period to a median of 0.2 teaspoons/day during the lansoprazole treatment period ($p<0.001$).

An additional secondary endpoint was the change from baseline in the severity of GERD symptoms at the week 8 visit based on investigator interviews. Investigators classified the patient's overall GERD symptoms on a 0 to 3 scale (none = 0, mild = 1, moderate = 2, and severe = 3). After 8 weeks of lansoprazole treatment, GERD patients who had severe (3) baseline symptoms, moderate (2) baseline symptoms, mild (1) baseline symptoms, improved their average GERD score to 0.67., 0.71, 0.71, respectively.

Study M97-640: The major endpoints evaluated were pharmacokinetic (C_{max} and AUC_{0-24}) and pharmacodynamic (after 5 days of lansoprazole treatment, the change from baseline in the mean 24 hour intra-gastric pH and the percentages of time that the pH exceeded 3 and 4) variables.

The results of this study demonstrated that the pharmacokinetics of lansoprazole are similar between the adolescents GERD patients in this study and previously observed healthy adult subjects. The mean dose-normalized C_{max} variables for the adolescent GERD patients who received 15 mg of lansoprazole, 30 mg of lansoprazole, and a historical population of healthy adult subjects were 27.7, 33.5, and 27.5 ng/mL/mg, respectively. The mean dose-normalized AUC_{0-24} values for the adolescent patients who received 15 mg of lansoprazole, 30 mg of lansoprazole, and a historical population of healthy adult subjects were 67.8, 83.0, and 71.1 ng•hour/mL/mg, respectively.

For both lansoprazole treatments, compared to baseline measurements, the increase in the mean 24-hour intra-gastric pH and the percentages of time the mean intra-gastric pH were above 3 and 4 at the Day 5 Visit were statistically significant. The mean 24-hour intra-gastric pH for the adolescent GERD patients was 2.71 at baseline and 3.84 after 5 days of lansoprazole (15 mg/day), and was 2.81 at baseline and 3.89 after 5 days of lansoprazole (30 mg/day). The percentage of time that the intra-gastric pH was over 3 for the adolescent GERD patients was 26.7% at baseline and 58.9% after 5 days of lansoprazole (15 mg/day) and was 29.1% at baseline and 59.6% after 5 days of lansoprazole (30 mg/day). The percentage of time that the intra-gastric pH was over 4 for the adolescent GERD patients was 20.0% at baseline and 46.9% after 5 days of lansoprazole (15 mg/day) and was 20.4% at baseline and 48.9% after 5 days of lansoprazole (30 mg/day) .

Summary: The efficacy of lansoprazole in the proposed indication was demonstrated by similar lansoprazole pharmacokinetics in adolescent GERD patients compared to healthy adult subjects; by the increase in intra-gastric pH after 5 days of lansoprazole treatment in adolescent GERD patients; by the efficacy in the complete healing of EE after 8 weeks of lansoprazole treatment (95.5%) in adolescent GERD patients; and efficacy results of lansoprazole treatment in adult GERD patients.

2.3 Safety

All patients in Studies M97-640 and M00-158 who received at least one dose of lansoprazole were included in the safety analyses. The Integrated Summary of Safety (ISS) included data on 150 pediatric GERD patients between 12 and 17 years old. Of the total population, 64 (43%) and 81 (54%) patients received 1 to 9 days and 42 to 70 days of lansoprazole, respectively.

Five patients had serious adverse drug events [gastroenteritis, a suicide attempt, a torn hamstring muscle, and a collection of symptoms (including chest pain, abdominal pain, and increased cough)] that required hospitalization. All of these serious adverse events were not likely related to lansoprazole and all of these patients were able to continue in the trials.

Two patients withdrew from the lansoprazole trials due to adverse drug events (AEs). The investigators believed that both of the AEs were possibly related to the study drug. One patient discontinued lansoprazole treatment after 40 days of therapy because of mild dizziness and moderate vomiting. Another patient with a past medical history of asthma, allergies, and eosinophilic esophagitis, developed hives, peripheral edema, and a generalized papular rash after 3 days of lansoprazole treatment.

The most frequent experienced AEs that were possibly, probably, or definitely caused by lansoprazole treatment included headache, abdominal pain, nausea, and dizziness occurring in 4%, 3%, 2%, and 3% of patients, respectively. The AE profile in these pediatric patients resembled that of adult patients and pediatric patients (between ages 1 and 11) taking lansoprazole.

No hematology or chemistry serum test, urine test, or vital sign abnormality were likely due to lansoprazole therapy. Five patients in Study M00-158 developed serum gastrin levels over 200 pg/mL (normal gastrin range is 25 to 111 pg/mL) after 8 weeks of lansoprazole. Similar high serum levels of gastrin are seen in adults treated with lansoprazole. Hypergastrinemia is a well-documented effect of all the PPIs in adults. Furthermore, hypergastrinemia was documented in GERD studies in pediatric patients between ages 1 to 11 years old.

No drug interaction studies of lansoprazole were conducted in adolescents. Based on the known potential drug interactions of lansoprazole with theophylline, digoxin, phenobarbital, carbamazepine, and/or phenytoin in adults; similar precautions should be taken when these medications are given concomitantly with lansoprazole in adolescent patients.

2.4 Dosing

This medical officer recommends a lansoprazole dose of 15 mg once daily for 4 to 8 weeks for the treatment of non-erosive GERD and a lansoprazole dose of 30 mg once daily for 6 to 8 weeks for the treatment of EE in pediatric patients between the ages of 12 to 17 years old. The evidence for this dosing recommendation is from numerous GERD studies in adult patients and the two supportive pediatric studies submitted in these sNDAs.

Since the efficacy of non-erosive GERD and EE treatment with lansoprazole in adolescent patients is primarily based on the safety and efficacy of lansoprazole in adult patients, the pediatric regimen should be similar to the safe and effective adult regimen. The treatment of

non-erosive GERD in adults with lansoprazole for 2 weeks is less effective than 4 to 8 weeks of lansoprazole treatment. Similarly, the treatment of EE in adults with lansoprazole for 2 to 4 weeks is less effective than 6 to 8 weeks of lansoprazole treatment. Therefore, the adolescent dose of lansoprazole in the treatment of non-erosive GERD and EE should be at least 4 weeks and 6 weeks, respectively.

2.5 Special Populations

2.5.1 Gender: The total pediatric GERD population included 66 males and 84 females. A similar percentage of females and males experienced AEs (55% and 48%, respectively) in the two studies. There was no evidence that gender affected the development of AEs during treatment with lansoprazole.

2.5.2 Age: The treatment of non-erosive GERD and EE in pediatric patients between 12 and 17 years old is the focus of this review. The mean age of all patients was 14.1 years.

Lansoprazole is approved for the treatment of non-erosive GERD and EE in adults and in pediatric patients between 1 and 11 years old.

2.5.3 Race: No safety or efficacy evaluation of racial subgroups was conducted in this pediatric population because the overwhelming majority (80.0%) of the adolescent patients was Caucasian.

2.5.4 Hepatic and Renal Impairment: Patients with severe renal or hepatic impairment were excluded from participating in the two studies; therefore, no comment can be made regarding pediatric patients with these conditions. Given similar PK of lansoprazole in pediatric patients between 12 and 17 years old and healthy adults, the adult recommendations should be applicable to this age group. The current lansoprazole label recommends no dosage adjustment for adult patients with renal insufficiency and dose adjustment should be considered for adults with severe hepatic disease.

2.5.5 Pregnancy: No patient was or became pregnant during the two studies. According to the current label, lansoprazole is considered Pregnancy Category B for adult patients.

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/s/

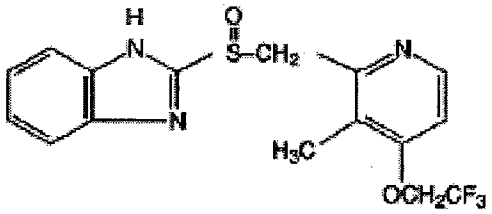
Ruyi He
6/15/04 11:40:46 AM

Suresh Doddapaneni
6/15/04 11:53:20 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF GASTROINTESTINAL & COAGULATION DRUG PRODUCTS

Medical Officer's Review of Efficacy Supplements: 20-406/S-057, 21-281/S-014, and 21-428/S-004

PREVACID (lansoprazole)



NDA#/Supplement#:	**20-406/S-057, 21-281/S-014, and 21-428/S-004**
Proposed Indications:	**The short-term treatment of non-erosive GERD and erosive esophagitis (EE) in pediatric patients between 12 and 17 years old**
Drug Class:	Substituted benzimidazole proton pump inhibitor
Formulation and Route of administration:	Oral capsule
Proposed regimens:	Non-erosive GERD: 15 mg once daily for up to 8 weeks EE: 30 mg once daily for up to 8 weeks
Applicant:	TAP Pharmaceutical Products Inc.
Documents Reviewed:	Electronic submitted sNDA and Data Sets
Division Director:	Robert Justice, M.D., M.S.
Deputy Director:	Joyce Korvick, M.D., M.P.H.
Medical Team Leader:	Ruyi He, M.D.
Medical Officer:	Eric Brodsky, M.D.
Biopharmaceutics Reviewer:	Suliman Al-Fayoumi, Ph.D.
Statistician:	Wen-Jen Chen, Ph.D.
Project Manager:	Melissa Furness

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Medical Officer's Review of Efficacy Supplements: 20-406/S-057, 21-281/S-014, and 21-428/S-004

Executive Summary

I. Recommendations

A. Recommendation on Approvability

From a clinical perspective, prevacid® (lansoprazole) delayed-release capsules, prevacid® (lansoprazole) delayed-release oral suspension, and prevacid® (lansoprazole) delayed-release orally disintegrating tablets (solutab) are recommended for approval for the treatment of GERD [non-erosive gastroesophageal reflux disease (GERD) and erosive esophagitis (EE)] in pediatric patients between 12 and 17 years old.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

From a clinical perspective, this medical officer does not recommend phase 4 studies or risk management steps in pediatric GERD patients between 12 and 17 years old.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

TAP Pharmaceutical Products Inc. (TAP) submitted two clinical study reports (Studies M97-640 and M00-158) to support the efficacy and safety of lansoprazole in the treatment of non-erosive GERD and EE in pediatric patients between 12 and 17 years old. These studies, conducted exclusively in the United States, included a total of 150 adolescent GERD patients (between 12 and 17 years old) who all received upper endoscopies at baseline.

Study M97-640 was a randomized, double-blinded, multi-center (10 sites), pharmacokinetic (PK), and pharmacodyamic (PD) trial of lansoprazole in the treatment of pediatric GERD patients, ages 12 to 17 years old. Patients were randomized to two lansoprazole treatment groups: 15 mg/day (n = 32) or 30 mg/day (n = 31) for 5 consecutive days. The PKs and PDs of lansoprazole were assessed by plasma concentrations and 24-hour pH monitoring, respectively.

Study M00-158 was an uncontrolled, open-label, multi-center (20 sites) trial of lansoprazole in the treatment of GERD in pediatric patients, ages 12 to 17 years. Baseline upper endoscopies categorized pediatric GERD patients into two groups: non-erosive GERD (n = 64) and EE (n = 23). Non-erosive GERD patients received 15 mg of oral lansoprazole once daily for 8 weeks and EE patients received 30 mg of lansoprazole once daily for 8 weeks. EE patients with completely healed

EE after 8 weeks of treatment were considered to have completed the therapy. In contrast, EE patients with unhealed EE after 8 weeks of treatment were treated with 30 mg of lansoprazole for an additional 4 weeks (12 weeks of total treatment).

The safety evaluation included assessment of the data from the two clinical studies, post-marketing data, and literature reports in pediatric patients between 12 and 17 years old, who received lansoprazole.

B. Efficacy

Study M00-158: Sixty-four non-erosive GERD patients were treated with 15 mg of lansoprazole for 8 weeks and 23 EE patients were treated with 30 mg of lansoprazole for 8 to 12 weeks. The efficacy results are summarized below.

The co-primary endpoints were the change from baseline in the frequency and severity of GERD symptoms during the 8 week treatment period based on patient diary data. The patient diary results demonstrated an improvement in GERD symptoms during 8 weeks of lansoprazole treatment. The median percentage of days with GERD symptoms decreased from 88.9% to 33.3%. This was a statistically significant change ($p<0.001$). Furthermore, the average severity of GERD symptoms (0 = none; 1 = mild; 2 = moderate; 3 = severe; 4 = very severe) decreased from 1.6 (mild to moderate) to 0.5 (none to mild) and this was statistically significant ($p<0.001$). No placebo group was included in this trial.

The most important secondary endpoint was the proportion of patients who had endoscopically-documented complete esophageal healing at the week 8 and 12 visits. In this study, the appearance of the esophagus was scored by the TAP Esophagitis Grading Scale (developed by a committee of the sponsor's consultant gastroenterologists). Patients with normal appearing mucosa (grade 0) or mucosal edema, hyperemia and/or friability (grade 1) were classified to have non-erosive GERD. Patients with the appearance of at least one erosion/ulceration in the esophagus mucosa (grades 2, 3, or 4) were categorized to have EE.

Complete healing of EE was defined as the return of the esophageal mucosa to grade 0 or 1 (non-erosive GERD). Twenty-one of twenty-two (95.5%) EE patients were completely healed after 8 weeks of lansoprazole treatment. One patient remained unhealed after 12 weeks of lansoprazole treatment. However, all EE patients had grade 2 or 3 lesions; no EE patient had a grade 4 lesion in this study. These efficacy results support the proposed EE indication in pediatric patients between 12 and 17 years old.

Additional secondary endpoints were the change from baseline in the amount and frequency of antacid use during the first 8 weeks of lansoprazole treatment based on patient diary data. Rescue antacid use decreased from a median of 54.5% of the days during the pretreatment period to a median of 5.5% of the days during the lansoprazole treatment period ($p<0.001$). Furthermore, the amount of rescue antacid used, decreased from a median of 1.4 teaspoons/day during the baseline pretreatment period to a median of 0.2 teaspoons/day during the lansoprazole treatment period ($p<0.001$).

An additional secondary endpoint was the change from baseline in the severity of GERD symptoms at the week 8 visit based on investigator interviews. Investigators classified the patient's overall GERD symptoms on a 0 to 3 scale (none = 0, mild = 1, moderate = 2, and severe = 3). After 8 weeks of lansoprazole treatment, GERD patients who had severe (3) baseline symptoms, moderate (2) baseline symptoms, mild (1) baseline symptoms, improved their average GERD score to 0.67., 0.71, 0.71, respectively.

Study M97-640: The major endpoints evaluated were pharmacokinetic (C_{max} and AUC_{0-24}) and pharmacodynamic (after 5 days of lansoprazole treatment, the change from baseline in the mean 24 hour intra-gastric pH and the percentages of time that the pH exceeded 3 and 4) variables .

The results of this study demonstrated that the pharmacokinetics of lansoprazole are similar between the adolescents GERD patients in this study and previously observed healthy adult subjects. The mean dose-normalized C_{max} variables for the adolescent GERD patients who received 15 mg of lansoprazole, 30 mg of lansoprazole, and a historical population of healthy adult subjects were 27.7, 33.5, and 27.5 ng/mL/mg, respectively. The mean dose-normalized AUC_{0-24} values for the adolescent patients who received 15 mg of lansoprazole, 30 mg of lansoprazole, and a historical population of healthy adult subjects were 67.8, 83.0, and 71.1 ng·hour/mL/mg, respectively.

For both lansoprazole treatments, compared to baseline measurements, the increase in the mean 24-hour intra-gastric pH and the percentages of time the mean intra-gastric pH were above 3 and 4 at the Day 5 Visit were statistically significant. The mean 24-hour intra-gastric pH for the adolescent GERD patients was 2.71 at baseline and 3.84 after 5 days of lansoprazole (15 mg/day), and was 2.81 at baseline and 3.89 after 5 days of lansoprazole (30 mg/day). The percentage of time that the intra-gastric pH was over 3 for the adolescent GERD patients was 26.7% at baseline and 58.9% after 5 days of lansoprazole (15 mg/day) and was 29.1% at baseline and 59.6% after 5 days of lansoprazole (30 mg/day). The percentage of time that the intra-gastric pH was over 4 for the adolescent GERD patients was 20.0% at baseline and 46.9% after 5 days of lansoprazole (15 mg/day) and was 20.4% at baseline and 48.9% after 5 days of lansoprazole (30 mg/day).

Summary: The efficacy of lansoprazole in the proposed indication was demonstrated by similar lansoprazole pharmacokinetics in adolescent GERD patients compared to healthy adult subjects; by the increase in intra-gastric pH after 5 days of lansoprazole treatment in adolescent GERD patients; by the efficacy in the complete healing of EE after 8 weeks of lansoprazole treatment (95.5%) in adolescent GERD patients; and efficacy results of lansoprazole treatment in adult GERD patients.

C. Safety

All patients in Studies M97-640 and M00-158 who received at least one dose of lansoprazole were included in the safety analyses. The Integrated Summary of Safety (ISS) included data on 150 pediatric GERD patients between 12 and 17 years old. Of the total population, 64 (43%) and 81 (54%) patients received 1 to 9 days and 42 to 70 days of lansoprazole, respectively.

Five patients had serious adverse drug events [gastroenteritis, a suicide attempt, a torn hamstring muscle, and a collection of symptoms (including chest pain, abdominal pain, and increased cough)]

that required hospitalization. All of these serious adverse events were not likely related to lansoprazole and all of these patients were able to continue in the trials.

Two patients withdrew from the lansoprazole trials due to adverse drug events (AEs). The investigators believed that both of the AEs were possibly related to the study drug. One patient discontinued lansoprazole treatment after 40 days of therapy because of mild dizziness and moderate vomiting. Another patient with a past medical history of asthma, allergies, and eosinophilic esophagitis, developed hives, peripheral edema, and a generalized papular rash after 3 days of lansoprazole treatment.

The most frequent experienced AEs that were possibly, probably, or definitely caused by lansoprazole treatment included headache, abdominal pain, nausea, and dizziness occurring in 4%, 3%, 2%, and 3% of patients, respectively. The AE profile in these pediatric patients resembled that of adult patients and pediatric patients (between ages 1 and 11) taking lansoprazole.
No hematology or chemistry serum test, urine test, or vital sign abnormality were likely due to lansoprazole therapy. Five patients in Study M00-158 developed serum gastrin levels over 200 pg/mL (normal gastrin range is 25 to 111 pg/mL) after 8 weeks of lansoprazole. Similar high serum levels of gastrin are seen in adults treated with lansoprazole. Hypergastrinemia is a well-documented effect of all the PPIs in adults. Furthermore, hypergastrinemia was documented in GERD studies in pediatric patients between ages 1 to 11 years old.

No drug interaction studies of lansoprazole were conducted in adolescents. Based on the known potential drug interactions of lansoprazole with theophylline, digoxin, phenobarbital, carbamazepine, and/or phenytoin in adults; similar precautions should be taken when these medications are given concomitantly with lansoprazole in adolescent patients.

D. Dosing

This medical officer recommends a lansoprazole dose of 15 mg once daily for 4 to 8 weeks for the treatment of non-erosive GERD and a lansoprazole dose of 30 mg once daily for 6 to 8 weeks for the treatment of EE in pediatric patients between the ages of 12 to 17 years old. The evidence for this dosing recommendation is from numerous GERD studies in adult patients and the two supportive pediatric studies submitted in this sNDA.

Since the efficacy of non-erosive GERD and EE treatment with lansoprazole in adolescent patients is primarily based on the safety and efficacy of lansoprazole in adult patients, the pediatric regimen should be similar to the safe and effective adult regimen. The treatment of non-erosive GERD in adults with lansoprazole for 2 weeks is less effective than 4 to 8 weeks of lansoprazole treatment. Similarly, the treatment of EE in adults with lansoprazole for 2 to 4 weeks is less effective than 6 to 8 weeks of lansoprazole treatment. Therefore, the adolescent dose of lansoprazole in the treatment of non-erosive GERD and EE should be at least 4 weeks and 6 weeks, respectively.

E. Special Populations

1. **Gender:** The total pediatric GERD population included 66 males and 84 females. A similar percentage of females and males experienced AEs (55% and 48%, respectively) in the two studies. There was no evidence that gender affected the development of AEs during treatment with lansoprazole.

2. **Age:** The treatment of non-erosive GERD and EE in pediatric patients between 12 and 17 years old is the focus of this review. The mean age of all patients was 14.1 years.

   Lansoprazole is approved for the treatment of non-erosive GERD and EE in adults and in pediatric patients between 1 and 11 years old.

3. **Race:** No safety or efficacy evaluation of racial subgroups was conducted in this pediatric population because the overwhelming majority (80.0%) of the adolescent patients was Caucasian.

4. **Hepatic and Renal Impairment:** Patients with severe renal or hepatic impairment were excluded from participating in the two studies; therefore, no comment can be made regarding pediatric patients with these conditions. Given similar PKs of lansoprazole in pediatric patients between 12 and 17 years old and healthy adults, the adult recommendations should be applicable to this age group. The current lansoprazole label recommends no dosage adjustment for adult patients with renal insufficiency and dose adjustment should be considered for adults with severe hepatic disease.

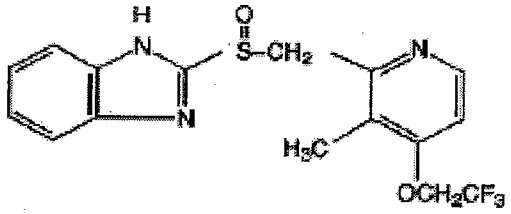
5. **Pregnancy:** No patient was or became pregnant during the two studies. According to the current label, lansoprazole is considered Pregnancy Category B for adult patients.

Clinical Review

I. Introduction and Background

A. Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

1 Drug: **PREVACID (lansoprazole)**



2 **Proposed indications:** **The short-term treatment of non-erosive GERD and EE in pediatric patients between 12 and 17 years old.**

3 Proposed regimens: GERD: 15 mg once daily for up to 8 weeks
EE: 30 mg once daily for up to 8 weeks

4 Proposed age group: Pediatric patients between 12 to 17 years old

5 Molecular formula: $C_{16}H_{14}F_3N_3O_2S$

6 Chemical name: 2-[[[3-methyl-4-(2,2,2-trifluorethoxy)-2-pyridyl]methyl]sulfinyl] benzimidazole

7 Drug class: Substituted benzimidazole proton pump inhibitor

8 Formulation and route of administration: Oral capsule

Lansoprazole is a proton pump inhibitor which has been approved in the United States since May 10, 1995 for the treatment of a variety of acid-related esophageal, gastric, and duodenal disorders. Lansoprazole inhibits gastric acid secretion by blocking the proton pump [(H+,K+)-ATPase enzyme system] at the secretory surface of the gastric parietal cell. Inhibition of the proton pump, the final step of stomach acid secretion, decreases intra-gastric acid concentration (increases intra-gastric pH).

Lansoprazole is available by prescription in three oral formulations — prevacid® (lansoprazole) delayed-release capsules, prevacid® (lansoprazole) delayed-release oral suspension, and prevacid® (lansoprazole) delayed-release orally disintegrating tablets (solutab) — and an intravenous formulation, prevacid I.V. (lansoprazole) for injection. All three oral formulations contain 15 mg or 30 mg of lansoprazole and the intravenous formulation contains 30 mg of lansoprazole.

Lansoprazole was approved for the treatment of non-erosive GERD and EE in adults and pediatric patients between the ages of 1 and 11 years old; but not for pediatric patients between 12 and 17 years old. On August 8, 1999, the Division of Gastrointestinal and Coagulation Drug Products (The Division) issued the Pediatric Written Request (WR) to the sponsor. The Lansoprazole Pediatric WR was amended several times and the final amended version was issued on June 3, 2003. The Division requested the sponsor to conduct two lansoprazole studies in pediatric GERD patients between ages 12 to 17 years old: a PK, PD, symptom assessment, 5-day study in at least 30 patients with symptomatic and/or endoscopically proven GERD (Study Three) and a 8-week, open-label, parallel group, clinical outcome study in at least 80 pediatric sGERD patients (Study Four).

In this sNDA submission, the sponsor provided one resubmitted study report (M97-640) and one new study report (M00-158) in response to Studies Three and Four of the Lansoprazole Pediatric WR to support the following new lansoprazole indications: the treatment of non-erosive GERD and EE in pediatric patients between ages 12 to 17 years old.

B. State of Armamentarium for Indication(s)

Prevacid® (lansoprazole) was approved for the following indications: the treatment of GERD (non-erosive GERD and EE) in adults and pediatric patients between the ages of 1 and 11 years old; but not for pediatric patients between 12 and 17 years old.

Prilosec® (omeprazole) is the only proton pump inhibitor (PPI) approved for the treatment of non-erosive esophagitis and EE in pediatric patients between 12 and 17 years old, in the United States. Please see Table 1 for the recommended starting doses of PPIs in the treatment of GERD in adolescents. Safe and effective use of other PPIs including aciphex® (rabeprazole), protonix® (pantoprazole), and nexium® (esomeprazole) have not been established in the treatment of acid-related gastrointestinal disorders for pediatric patients between 12 and 17 years old.

Several histamine-2 receptor antagonists (H_2RAs) including zantac® (ranitidine), pepcid® (famotidine), and tagamet® (cimetidine) are approved for the treatment of GERD in adolescents in the U.S. Please see Table 1 for the recommended doses of H_2RAs in the treatment of GERD in adolescents. Safe and effective use of axid® (rizatidine) has not been established for the treatment of pediatric patients with GERD.

Table 1: Recommended starting doses of PPIs and H_2RAs in the treatment of GERD in adolescents

DRUG	DRUG CLASS	NON-EROSIVE GERD	EE
Omeprazole (Prilosec®)	PPI	20 mg/day	20 mg/day
Lansoprazole (Prevacid®)	**PPI**	**Proposed dose is 15 mg/day**	**Proposed dose is 30 mg/day**
Rabeprazole (Aciphex®)	PPI	Not Established	Not Established
Pantoprazole (Protonix®)	PPI	Not Established	Not Established
Esomeprazole (Nexium®)	PPI	Not Established	Not Established
Ranitidine (Zantac®)	H_2RA	150 mg BID	150 mg QID
Famotidine (Pepcid®)	H_2RA	0.5 mg/kg BID	0.5 mg/kg BID
Cimetidine (Tagamet®)	H_2RA	800 mg BID or 400 mg QID	800 mg BID or 400 mg QID
Rizatidine (Axid®)	H_2RA	Not Established	Not Established

PPI = proton pump inhibitor; H_2RAs = histamine-2 receptor antagonists; Adapted from most recent approved labels

C. Important Milestones in Product Development

On October 8, 1998, TAP submitted a Proposed Pediatric Study Request (PPSR) for lansoprazole. In response, on August 8, 1999, The Division issued a Lansoprazole Pediatric Written Request (WR) pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act to obtain needed information about the use of lansoprazole in pediatric patients.

The Division made additional minor amendments to the Lansoprazole Pediatric WR on June 18, 2002, December 18, 2002, and June 3, 2003. The most recent amended Lansoprazole Pediatric WR required that all pediatric studies be submitted to the FDA by December 31, 2005 to obtain an additional six months of lansoprazole marketing exclusivity. This amended WR asked the sponsor to complete four major studies in the treatment of GERD in pediatric patients. The following is a summary of the 4 major studies:

Study One: This study will consist of four parts: two PK, PD, and safety studies of lansoprazole and two randomized withdrawal efficacy and safety studies of lansoprazole will be conducted in infants with GERD.

Study Two: This study will be a multi-center, open-label, 8 to 12-week, PK, PD, and clinical outcome study with age-appropriate formulation(s) of lansoprazole in at least 60 pediatric patients aged 1 to 11 years with symptomatic and/or endoscopically proven GERD.

Study Three: This study will be a multi-center, randomized, double-blind, 5-day, PK, PD, and symptom assessment study of lansoprazole in at least 30 patients with symptomatic and/or endoscopically proven GERD in pediatric patients aged 12 to 17 years.

Study Four: This study will be a multi-center, open-label, parallel group, 8 to 12-week, clinical outcome study of lansoprazole in at least 80 pediatric symptomatic GERD (sGERD) patients aged 12 to 17 years in whom gastrointestinal endoscopy has been performed.

On December 19, 2003, the sponsor submitted this sNDA for priority review for the treatment of GERD in pediatric patients between 12 and 17 years old, for the three oral lansoprazole formulations: capsules (NDA 20-406/S-57), suspension (NDA 21-281/S-14), and disintegrating tablets (NDA 21-428/S-4). All of the studies submitted in this sNDA follow the design of the Lansoprazole Pediatric WR. Study M97-640 follows Study Three and Study M00-158 follows Study Four of the Lansoprazole Pediatric WR.

D. Other Relevant Information

On May 10, 1995, The Division approved the first lansoprazole formulation for the treatment of several acid related conditions in adults. Please see Table 2 for the approval dates of all the lansoprazole formulations in adults.

Table 2: Approval dates of lansoprazole in adults

DATE	NDA #	FORMULATION	INDICATION	POPULATION
May, 5, 1995	20-406	oral capsules	several acid-related disorders	adults
May 31, 2001	21-281	oral suspension	several acid-related disorders	adults
August 30, 2002	21-428	oral disintegrating tablets (solutab)	several acid-related disorders	adults

Lansoprazole is approved for the treatment of the following conditions in adults in the U.S.:

1) Active duodenal and active gastric ulcers
2) Active NSAID-associated gastric ulcers in patients that continue NSAID use
3) Maintenance of healed duodenal ulcers
4) Prevention of NSAID-associated gastric ulcers in patients with a past history of a gastric ulcer (who require NSAID treatment)
5) Eradication of *H. pylori* in patients with an active duodenal ulcer or a history of a duodenal ulcer within the last year
6) Pathologic hypersecretory conditions (like Zollinger-Ellison Syndrome)
7) Symptomatic GERD, active EE, and maintenance of healed EE

On July 31, 2002, The Division approved lansoprazole for the treatment of GERD in pediatric patients between the ages of 1 to 11 years old (NDA 20-406/S-47, NDA 21-281). Please see Table 3 for the approved lansoprazole regimens in pediatric GERD patients. The safety and effectiveness of lansoprazole in pediatric patients between 12 and 17 years old and less than 1 year old have not been established.

Table 3: FDA-approved indications of lansoprazole in pediatric patients

	INDICATION	DOSE
1	Treatment of GERD	15 mg q day for pediatrics (1 to 11 years old) less than or equal to 30 kg and 30 mg q day for pediatrics (1 to 11 years old) greater than 30 kg for 12 weeks*
2	Treatment of EE	15 mg q day for pediatrics (1 to 11 years old) less than or equal to 30 kg and 30 mg q day for pediatrics (1 to 11 years old) greater than 30 kg for 12 weeks*

* The prevacid dose was increased up to 30 mg BID in some pediatric patients after 2 or more weeks of treatment if they remained symptomatic.
Reference: last approved labeling in August 2003

Lansoprazole is approved for use to treat adults with GERD in over 100 countries in North America, South America, Africa, Asia, and Europe.

E. Important Issues with Pharmacologically Related Agents

Five proton pump inhibitors [omeprazole (prilosec®), lansoprazole (prevacid®), rabeprazole (aciphex®), pantoprazole (protonix®), and esomeprazole (nexium®)] are currently approved for several acid-related conditions in the U.S.

The sponsor of prilosec® fulfilled their Pediatric WR and obtained pediatric exclusivity. Prilosec is approved for pediatric patients older than 2 years of age for the treatment of symptomatic GERD and EE. The FDA-approved dose of prilosec® for the treatment of sGERD or EE is 10 mg/day for pediatric patients $\leq$ 20 kg and 20 mg/day for pediatric patients > 20 kg.

Pediatric WRs have been issued to all sponsors who have approved reference listed proton pump inhibitors. At the time of this sNDA submission, the sponsors of aciphex, protonix, and nexium have not submitted any pediatric study reports in response to their pediatric WRs.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

Chemistry: The chemistry study reports of this sNDA were reviewed by Dr. Ramesh Raghavachari, the chemistry reviewer in The Division. Dr. Raghavachari found that the chemistry, manufacture, and controls of lansoprazole in this sNDA were unchanged from the original NDA submission (NDA 20-406) except that over-encapsulation of the drug product was performed in the double-

blind M97-640 study. Dr. Raghavachari required that the sponsor provide "comparative dissolution data for the over-encapsulated drug product used in (Study M97-640) and the commercial drug product." Dr. Raghavachari recommended approval of this sNDA, pending evaluation of the dissolution data for the over-encapsulated drug product. Please see Dr. Raghavachari's review of this sNDA dated April 1, 2004 for details.

Animal Pharmacology and Toxicology: No new non-clinical studies or non-clinical information were submitted in this sNDA.

Microbiology: This sNDA has no pertinent microbiology issues.

Statistics: Dr. Wen Jen Chen conducted the statistical review of this sNDA. Dr. Chen concluded that from a statistical perspective, the efficacy of lansoprazole in the treatment of GERD in pediatric patients between 12 and 17 years old is supported by the study data.

III. Human Pharmacokinetics and Pharmacodynamics

Dr. Suliman Al-Fayoumi, the biopharmaceutics reviewer in The Division, performed the PK and PD review. In this sNDA submission, Study M97-640 contained the only PK and PD data of lansoprazole in pediatric GERD patients between ages 12 and 17 years old. No PK or PD data were obtained in Study M00-158.

Study M97-640 was a randomized, double-blinded, multi-center study of lansoprazole in the treatment of pediatric GERD patients, ages 12 to 17 years old. Patients were randomized to two treatments: 15 mg/day (n=32) or 30 mg/day (n=31) of lansoprazole for 5 consecutive days. Baseline upper endoscopies were performed on all patients. The major efficacy endpoints were PK variables (C_{max}, T_{max}, AUC_{0-24}, and the half-life), PD variables (the change from baseline in the mean 24 hour intra-gastric pH and the percentages of time that the pH exceeded 3 and 4), and symptom relief.

Please see Dr. Al-Fayoumi's review of this sNDA for details regarding study M97-640.

IV. Description of Clinical Data and Sources

A. Overall Data

The sponsor provided one new study report (Study M00-158) and one resubmitted study report (Study M97-640) in this sNDA submission. Study M97-640 included 63 GERD patients and the primary objective was to assess the PKs and intra-gastric pH of lansoprazole in the treatment of GERD (non-erosive GERD and EE) in pediatric patients between 12 to 17 years. Study M00-158 included 87 GERD (non-erosive GERD and EE) patients and the primary objectives were to assess the safety and efficacy of once daily administration of 15 mg or 30 mg of lansoprazole in pediatric patients, ages 12 to 17 with symptomatic GERD.

Because the efficacy of lansoprazole in the treatment of GERD in pediatric patients between 12 and 17, is primarily based on efficacy data in adult GERD patients, lansoprazole GERD trials in adult patients were used as a source in this review. Studies M95-300 and M87-092 were previously-submitted adult lansoprazole trials in non-erosive GERD and EE patients, respectively. Study M95-300 was a U.S. multi-center, double-blind, placebo-controlled, lansoprazole 8-week study of 214 adult patients with frequent GERD symptoms, but no esophageal erosions by endoscopy. Study M87-092 was a U.S., multi-center, double-blind, placebo-controlled, lansoprazole, 8-week study of 269 adult patients with an endoscopic diagnosis of esophagitis.

Post-marketing data and literature reports served as supportive evidence for the efficacy and safety of lansoprazole in adolescent GERD patients.

B. Tables Listing the Clinical Trials

Table 4 lists the two clinical studies submitted in this sNDA.

Table 4: Tabular listing of all clinical trials in this NDA

Type of Study	Study Identifier	Objective(s) of Study	Study Design and Type of Control	Test Product(s); Dose Regimen; Route of Administration and Duration of Treatment	Number of Subjects	Healthy Subjects or Diagnosis of Patients
Phase II Efficacy	M00-158	Safety and efficacy of QD administration of lansoprazole 15 mg or 30 mg in adolescents, ages 12-17 years with GERD	Open-label, multi-center	Lansoprazole 15 mg capsule QD orally (for subjects with non-erosive GERD) Lansoprazole 30 mg capsule QD orally (for subjects with erosive esophagitis) Duration: 8 weeks; if erosive esophagitis was unhealed at Week 8 endoscopy, subjects were treated for an additional 4 weeks with 30 mg QD	64 23	Adolescents, aged 12 to 17 years, with a history of GERD symptoms for at least 3 months and currently symptomatic
Phase I PK, PD	M97-640	Safety, PK, and PD of QD administration of lansoprazole 15 mg or 30 mg in pediatric subjects, ages 12 to 17 years with symptomatic GERD	Randomized, double-blind, multi-center	Lansoprazole 15 mg capsule QD orally Lansoprazole 30 mg capsule QD orally Duration: 5 days	32 31	Adolescents, aged 12 to 17 years, with symptomatic, endoscopically and/or histologically proven GERD

Reference: Study M00-158 — "A study to evaluate the safety and efficacy of lansoprazole in adolescents with GERD after 8 to 12 weeks of treatment."

C. Postmarketing Experience

According to the National Disease and Therapeutic Index (NDTI), physicians in the United States recommended the use of lansoprazole in the treatment of pediatric patients (between 12 and 16 years old) approximately 56,000 times in 2001. The NDTI is a survey conducted by IMS HEALTH, designed to provide statistical information about the patterns and treatment of disease encountered in office-based practices in the United States. The Division has not received or

identified any significant safety issues from post-marketing reports related to the use of lansoprazole in this population.

D. Literature Review

The sponsor submitted published literature regarding the treatment of non-erosive GERD and EE in adolescents with lansoprazole. With PK, PD, safety, and efficacy data, the literature supported the conclusions of this medical officer that lansoprazole is safe and effective for the treatment of pediatric GERD patients between 12 and 17 years old.

V. Clinical Review Methods

A. How the Review was Conducted

The efficacy evaluation of the proposed indication is based on lansoprazole trials in adult GERD patients; the bioequivalence of lansoprazole in pediatric GERD patients between the ages of 12 to 17 years old (Study M97-640) to historical adult subjects; and the efficacy of EE healing after 8-12 weeks of lansoprazole administration in pediatric patients between the ages of 12 to 17 years old (Study M00-158).

The safety evaluation of the proposed indication is based on lansoprazole trials in adult GERD patients; 150 pediatric GERD patients between the ages of 12 to 17 years old who used lansoprazole from 5 days to 12 weeks (Studies M97-640 and M00-158); post-marketing reports from the use of lansoprazole in pediatric adolescent patients; and literature assessment of the use of lansoprazole in pediatric adolescent patients.

B. Overview of Materials Consulted in Review

Supplemental NDA 20-406/S-057, NDA 21-281/S-014, and NDA 21-428/S-004 are completely electronic submissions which included the following sections: Labeling (Volume 2), CMC (Volume 5), and Clinical (Volume 6). In this review, I have examined material in the Labeling (Volume 2) and Clinical (Volume 6) Sections.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

No DSI audit was done of the study sites since the phase II study was multicenter involving 20 sites and no one site contributed more than 10 patients or 11% of the total number of GERD patients in the phase II trial.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

According to the sponsor, the study was conducted in accordance with the protocol, International Conference on Harmonisation (ICH), Good Clinical Practice (GCP) guidelines governing clinical study conduct, all applicable local regulations, and the ethical principles stated in the Declaration of Helsinki (1996 revision). The investigators assured that the study was conducted in accordance

with prevailing local laws and customs and complied with the provisions as stated in the ICH guidelines.

E. Evaluation of Financial Disclosure

The sponsor has submitted FDA Form 3454 certifying that no investigator of any of the covered clinical studies had any financial interests to disclose.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

In Study M00-158, the frequency and severity of the adolescent's GERD symptoms significantly decreased during 12-weeks of lansoprazole therapy compared to the baseline Pretreatment Period. The frequency and amount of rescue antacid used during the 12-week treatment period was significantly lower compared to the baseline Pretreatment Period. Furthermore, the trial demonstrated 95.5% complete healing of EE after 8 weeks of lansoprazole therapy. Study M00-158 demonstrated support of the efficacy of lansoprazole in the treatment of non-erosive GERD and EE in pediatric patients between 12 and 17 years old.

B. General Approach to Review of the Efficacy of the Drug

Two study reports (Studies M97-640 and M00-158) were submitted in this sNDA. Study M97-640, a PK and PD study, was reviewed by Dr. Suliman Al-Fayoumi, the biopharmaceutics reviewer in The Division (see his review for details). This medical officer reviewed Study M00-158, the safety and efficacy study, in this sNDA.

C. Detailed Review of Trials by Indication

Study M00-158.

1 Title: "A study to evaluate the safety and efficacy of lansoprazole in adolescents with GERD after eight to twelve weeks of treatment."

2 Objectives: Assess the safety and efficacy of lansoprazole in the treatment of GERD (non-erosive GERD and EE) in pediatric patients, ages 12 to 17 years.

3 Study Design: This was an open-label, multi-center (20 sites), U.S. trial of lansoprazole in the treatment of GERD (non-erosive GERD and EE) in pediatric patients, ages 12 to 17 years, for 8 to 12 weeks. All of the pediatric patients had baseline upper endoscopies to categorize their GERD into one of two groups:

1) Treatment Group I: Patients with non-erosive GERD at the Pretreatment Visit were treated with 15 mg of oral lansoprazole once daily for eight weeks.

2) Treatment Group II: Patients with EE at the Pretreatment Visit were treated with 30 mg of oral lansoprazole once daily for eight weeks. Patients with completely healed EE at the Week 8 Visit completed study participation at this Week 8 Visit. In contrast, patients with unhealed EE at the Week 8 Visit were to be treated with 30 mg of oral lansoprazole once daily for an additional four weeks (12 weeks of total treatment) and completed study participation at the Week 12 Visit.

Therefore, all EE patients had post-treatment upper endoscopies to assess esophageal healing.

Medical Reviewer's Comments: The design's inclusion of baseline upper endoscopies in all of the GERD patients and the post-treatment upper endoscopies in EE patients is acceptable.
The design of Study M00-158 follows the design of Study Four of the LPWR issued by the Division of Gastrointestinal and Coagulation Drug Products (The Division). The LPWR was equivocal in its request for a controlled study; therefore, the sponsor has satisfied Study Four of the LPWR.

4 Study Population:
4.1 Number of patients: The sponsor's intention was to enroll a minimum of 20 patients with non-erosive GERD and a minimum of 20 patients with EE. The remaining patients were to be enrolled in the appropriate treatment group based on endoscopic findings. The sponsor aimed for a total number of 80 GERD patients.

4.2 and 4.3 Inclusion and Exclusion Criteria: Please see Table 5 for the eligibility criteria in this study.

Table 5: Eligibility criteria

Inclusion Criteria: To be eligible to participate in the study, patients had to have met the following criteria:	**Exclusion Criteria:** If patients had the following conditions, they were not eligible to participate in the study:
➢ 12 to 17 years of age at the time he/she received the first dose of study drug. ➢ Patients with GERD symptoms (for example: regurgitation, sour taste, heartburn, retro-sternal pain, vomiting, etc.) for at least 3 months prior to the Pretreatment Period. Patients had to be symptomatic with GERD at screening. ➢ Patients' pretreatment diaries reflected at least one episode of moderate, severe, or very severe GERD symptom(s) within the 6 days prior to the Treatment Period. ➢ Patients with Barrett's esophagus, with no known dysplastic changes in the esophageal mucosal, were eligible to enter the study. ➢ Laboratory, biochemical, and hematology parameters within normal laboratory limits as listed in the [illegible] except: alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were less than 2 times the upper limit of normal; creatinine was less than or equal to 2.0 mg/dL; patients with Gilbert's disease were eligible for the study; or if the blood tests were abnormal, the tests were judged clinically acceptable by the investigator. ➢ Females had a negative pregnancy test; were not lactating; and were using and agreed to continue to use effective means of birth control (documentation of abstinence was acceptable) if sexually active. ➢ Discontinue use of antacids (other than the Mylanta provided during the study), histamine (type 2) receptor antagonists, sucralfate, anticholinergics, and	➢ Duodenal and/or gastric ulcer(s) ≥3 mm in diameter at the Pretreatment Visit. ➢ Current esophageal stricture requiring dilatation. Strictures could not have been dilated within the 12 weeks prior to the pretreatment upper endoscopy. ➢ Acute upper gastrointestinal (UGI) bleed. Patients stabilized after an acute UGI bleed were eligible for the study provided they were hemodynamically stable (for example: hemoglobin ≥10.0 g/dL with no associated hypotension or tachycardia) at the time of the pretreatment upper endoscopy. ➢ Coexisting disease affecting the esophagus (for example: scleroderma; eosinophilic esophagitis; viral, bacterial, or fungal infection). Furthermore, recent esophageal radiation or esophageal trauma. ➢ Patients with evidence of Zollinger-Ellison syndrome, esophageal varices, symptomatic pancreatobiliary tract disease, cholecystitis, rheumatoid arthritis, or lupus. ➢ Patients had no evidence of malignancy (except basal cell carcinoma) requiring active treatment. ➢ Evidence of uncontrolled, clinically significant cardiovascular, pulmonary, renal, hepatic, metabolic, gastrointestinal, neurologic, or endocrine disease, or other abnormality (other than the disease being studied). Patients with neurologic impairment such as, but not limited to, cerebral palsy or Down's syndrome were eligible; however, they had to be able to understand and cooperate with study requirements. ➢ History of gastric, duodenal, or esophageal surgery. (Exceptions: simple oversew of an ulcer, esophageal atresia repair, fundoplication, or gastrostomy tube placement.) ➢ Evidence of alcohol abuse, illegal drug use, or drug abuse in the 12 months prior to the Pretreatment Period. ➢ Received blood products within the 12 weeks prior to the first dose of study drug. ➢ Received an investigational drug within one month prior to the first dose of study drug.

prokinetics prior to the Pretreatment Period. ➢ If they required continuous treatment with theophylline derivatives, phenytoin, phenobarbital, digoxin, and/or carbamazepine, then they were eligible. However, they had serum drug levels monitored during the study to assure that proper levels of these drugs were being maintained. ➢ Patients receiving chronic tricyclic antidepressant therapy were eligible; however, they could not begin a new course of therapy during participation in the study (including the Pretreatment Period). ➢ The parent or legal guardian, with agreement of the patient, had to understand, sign, and date the informed consent form prior to the patient having any study related procedures. The patient had to be able to understand and cooperate with study requirements.	➢ Known allergy to proton pump inhibitors. ➢ Required chronic anticoagulant therapy. ➢ Chronic use (> 12 doses per month) of the following medications within 30 days prior to the pretreatment upper endoscopy: a) Non-steroidal anti-inflammatory drugs including COX-2 inhibitors. b) Oral or intravenous corticosteroids ≥ the equivalent of 10 mg of prednisone per day. ➢ Received bisphosphonates, tetracycline, doxycycline, ferrous sulfate, or the oral formulation of cromolyn sodium within the 30 days prior to the pretreatment upper endoscopy. ➢ Received proton pump inhibitors within 14 days prior to the Pretreatment Period. ➢ Received antacids (other than the mylanta provided during the study), histamine (type 2) receptor antagonists, sucralfate, anticholinergics, and prokinetics during the Pretreatment Period ➢ GERD symptoms were manifested by only extra-esophageal symptoms (for example: cough, hoarseness, wheezing, etc.)

Reference: Study M00-158: "A study to evaluate the safety and efficacy of lansoprazole in adolescents with GERD after 8 to 12 weeks of treatment."

Medical Reviewer's Comments: The inclusion and exclusion criteria were appropriate for this study. The eligibility criteria suitably selected for adolescent GERD patients and provided for a rescue medication for treatment failure.

The eligibility criteria appropriately precluded the use of concomitant medications that treat EE (including antihistamines and PPIs) and properly prohibited patients with other esophageal disease. The inclusion criteria allowed for patients with significant renal disease; however, this is acceptable because the current lansoprazole label states that no dose adjustment is needed for adult patients with significant renal failure.

4.4 Premature Discontinuation of Patients

All patients had the right to withdraw from the study at any time without prejudice to future treatment. The investigator could discontinue any patient, without consent, at any time due to an adverse event; treatment with another drug which would interfere with the evaluation of study drug; pregnancy; poor compliance; therapeutic failure; personal reasons; or if the study had been terminated by the sponsor.

5 <u>Drugs used in study</u>: Non-erosive GERD patients received 15 mg of oral lansoprazole capsules daily for eight weeks and EE patients received 30 mg of oral lansoprazole capsules daily for 8 to 12 weeks. No placebo medication was used in this trial.

All GERD patients in the trial were supplied with mylanta® to take if necessary. The patients, who did not achieve relief of their heartburn symptoms, were permitted to take the approved dose of mylanta®, the rescue medication, anytime during the Pretreatment and Treatment Periods (except within 30 minutes of study drug administration.) The approved dose of mylanta® is 10 to 20 mL every 4 hours, if necessary, for the relief of heartburn, acid indigestion, or sour stomach. Ten milliliters of mylanta® contains the following active ingredients: 400 mg of aluminum hydroxide, 400 mg of magnesium hydroxide, and 40 mg of simethicone.

Medical Reviewer's Comments: The approved dose of lansoprazole for the treatment of sGERD and EE in pediatric patients from one year to eleven years is 15 mg/day for patients $\leq$ 30 kg and 30 mg/day for pediatrics > 30 kg. The approved lansoprazole dose for the treatment of sGERD in adult patients is 15mg/day and the approved lansoprazole dose for the treatment of EE in adult patients is 30 mg/day. Therefore, the proposed lansoprazole doses for pediatric patients, ages 12 to 17, are acceptable. Furthermore, the lansoprazole doses used in this trial were the exact doses recommended by the PPWR.

6 Schedule of Procedures and Evaluations: The study consisted of two periods: a Pretreatment Period (7 to 14 days) and a Treatment Period (8 to 12 weeks). Please see Table 6 for the Schedule of Procedures and Evaluations. All non-erosive GERD patients had an 8-week Treatment Period. EE patients who had completely healed EE at 8 weeks had an 8-week Treatment Period and EE patients who were not healed at 8 weeks had a 12-week Treatment Period.

Table 6: Schedule of procedures and evaluations for Study M00-158

Study Procedures	Pretreatment Period (7 to 14 days)		Treatment Period (8 to 12 weeks)			
	Pretreatment Visit(s) (Day -14 to Day -2)	Day -1 Visit	Day 1[a]	Week 4 Visit	Week 8 Visit[b]	Final Visit[c] (Week 8 Visit or Week 12 Visit)
Informed Consent and Assent	X			→		
Complete Medical and Social History	X					
Interim Medical History		X				
Brief Physical Examination		X		X	X	
Complete Physical Examination	X					X
Vital Signs	X	X		X	X	X
Endoscopy with Biopsies	X[d]	X[d]			X[e]	X[e]
Routine Fasting Laboratory Evaluations	X			X	X	X
Fasting Serum Gastrin Determinations	X			X	X	X
Pregnancy Test (females)	X			X	X	X
Theophylline, Phenytoin, Phenobarbital, Digoxin, and/or Carbamazepine Levels (if applicable)	X			X	X	X
Overall GERD Symptom Assessment Based on Investigator Interview	X	X		X	X	X
Prior and Concomitant Medication Record	X	X		X	X	X
Adverse Event Assessment				X	X	X
Dispense Study Drug/Drug Accountability		X		X	X	
Diary Instruction/Dispense Diary	X	X		X	X	
Return Study Drug/Drug Accountability				X	X	X
Return/Review Diary		X		X	X	X
Dispense Mylanta	X	X		X	X	
First Day of Study Drug Administration			X			
Follow-up Instructions (eg, non-study follow-up visit/therapy)						X

a This was the first day of treatment; it was not a study visit.
b Week 8 Visit applied to patients with unhealed EE at the Week 8 Visit. These patients were treated for an additional 4 weeks, and completed study participation at the Week 12 Visit.
c Final Visit was the Week 8 Visit for all non-erosive GERD patients and EE patients with complete healing at the Week 8 Visit. Whereas, the Final Visit was the Week 12 Visit for EE patients who had unhealed EE at the Week 8 Visit. Finally, the Final Visit was the last visit in the Treatment Period for patients who prematurely terminated from the study.
d The endoscopy was to be performed at any time during the Pretreatment Period (Day -14 through Day -1).
e Follow-up endoscopies were performed only on patients who had EE at the Pretreatment Visit. They were performed at the Week 8 Visit, Week 12 Visit (if unhealed at the Week 8 Visit), and the Final Visit for patients who prematurely terminated study participation.
Reference: Study M00-158 — "A study to evaluate the safety and efficacy of lansoprazole in adolescents with GERD after 8 to 12 weeks of treatment."

Medical Reviewer's Comments: The schedule of procedures and evaluations appears to be organized, clear, and sufficient for this study.

6.1 Pretreatment Period: During the Pretreatment Period, between Day -14 and Day -1, informed consent/assent was obtained and the patients underwent the following procedures to determine eligibility for the Treatment Period: complete medical histories; overall GERD symptoms; prior and concomitant medications; social histories; physical examinations including height, weight, and vital signs; routine fasting laboratory evaluations including serum gastrin levels and pregnancy tests,

phenytoin, digoxin, phenobarbital, carbamazepine, and/or theophylline drug levels if applicable; and **upper endoscopies** with biopsies.

Patients were not permitted to use bisphosphonates, tetracycline, doxycycline, ferrous sulfate, oral cromolyn sodium, investigational drugs (other than the study medication), chronic anticoagulant therapy, antacids (other than the mylanta® provided during the study), prescription and over-the-counter type 2 histamine receptor antagonists, sucralfate, anticholinergics, prokinetics, and proton pump inhibitors (other than the study medication). Patients were not permitted to use more than 12 doses per month of the following medications: NSAIDS including COX-2 inhibitors and corticosteriods greater than or equal to the equivalent to 10 mg of prednisone per day.

During the Pretreatment Period, mylanta® was dispensed to patients. If the GERD patients did not achieve relief of their heartburn symptoms, they were permitted to take the approved dose of mylanta®, the rescue medication, anytime.

During the Pretreatment Period, diaries were dispensed to patients. Patients, their parents, or their caregivers (PPC) maintained the daily diary, in which they recorded the severity of their GERD symptoms and the amount and frequency of their mylanta usage.

Medical Reviewer's Comments: The study procedure lacked specific dietary instructions for the patients to observe. The treatment of GERD includes dietary and lifestyle changes. Patients should be on a consistent diet between the two comparative periods (throughout the Pretreatment and Treatment Periods) because the dietary changes can influence the outcome of GERD treatment. Furthermore, some patients can completely treat their GERD, if they make dietary and lifestyle changes.

6.1.1 Pretreatment Endoscopies: All patients had baseline upper endoscopies during the Pretreatment Period. One upper endoscopy with three biopsies and photographic documentation was used to assess the presence and severity of the following: EE, Barrett's esophagus with dysplastic changes, esophageal stricture requiring dilatation, esophageal varices, acute UGI bleed, and gastric and/or duodenal ulcers ≥ 3 mm in diameter.

During the baseline endoscopies, the endoscopist graded the appearance of the esophageal mucosa using the TAP Esophagitis Grading Scale (developed by a committee of the sponsor's consultant gastroenterologists). According to the TAP Esophagitis Grading Scale (Table 7), patients with grade 0 or 1 were classified to have non-erosive GERD and patients with grade 2, 3, or 4 were classified to have EE. Therefore, the endoscopic appearance of the esophageal mucosa determined the assigned treatment: Patients with non-erosive GERD and EE were placed in Treatment Group I and Treatment Group II, respectively.

Table 7: TAP Esophagitis Grading Scale

GRADE	ESOPHAGEAL MUCOSA APPEARANCE BY UPPER ENDOSCOPY	CATEGORY
0	Normal appearing mucosa by endoscopy	Non-erosive GERD
1	Mucosal edema, hyperemia and/or friability or red streaks (linear erythematous areas)	Non-erosive GERD
2	One or more erosion(s)/ulcerations(s) involving less than 10% of the distal 5 cm of the esophagus	EE
3	Erosions/ulcerations involving 10 to 50% of the distal 5 cm of the esophagus or a single ulcer measuring 3 to 5 mm in diameter	EE
4	Multiple erosions/ulcerations involving greater than 50% of the distal 5 cm of the esophagus or a single large ulcer greater than 5 mm in diameter	EE

An ulcer is a discrete lesion with appreciable depth and ≥ 3 mm in diameter.
An erosion is a superficial break in the esophageal mucosa which is < 3 mm in diameter.
Reference: Study M00-158 — "A study to evaluate the safety and efficacy of lansoprazole in adolescents with GERD after 8 to 12 weeks of treatment." Volume 7, page 39, Table 9.5b

During the baseline endoscopies, the endoscopists also performed five full mucosal thickness gastric biopsies on each patient. The biopsies were evaluated for active and chronic inflammation, atrophy, intestinal metaplasia, endocrine cell evaluation, and *H. pylori* status by a blinded pathologist. Patients who tested positive for *H. pylori* were allowed to complete the study.

6.1.2 Pretreatment Patient Evaluations: At the Pretreatment Visit (7 to 14 days prior to Day 1), all of the patients' GERD symptoms (including the predominant symptom) were identified and documented by the investigators. The investigators instructed the patients, their parents, and/or their caregivers (PPCs) to daily classify the severity of their worst GERD symptoms (please see Table 8) and the amount and frequency of their mylanta use in their diaries.

Table 8: Patient's GERD symptoms severity grading scale

SEVERITY	GRADE	DEFINITIONS
0	None	No GERD symptoms.
1	Mild	Bothered a little and/or symptoms present part of the day or night but caused little or no discomfort. Did not interfere with sleep.
2	Moderate	Bothered some and/or symptoms present half of day or night, annoying. Did not interfere with daily routine and/or occasionally interfered with sleep.
3	Severe	Bothered a lot and/or symptoms present most of the day or night and/or interfere with daily routine or sleep.
4	Very Severe	Bothered intensely and/or experienced constant symptoms and/or marked interference with daily routine or sleep.

Reference: Study M00-158 – "A study to evaluate the safety and efficacy of lansoprazole in adolescents with GERD after 8 to 12 weeks of treatment." Volume 7, page 42, Table 9.5e.

6.1.3 Pretreatment Investigator Evaluations: On the last day of the Pretreatment Period (day -1), all patients had visits with the investigators. The investigators performed interim medical histories, recorded prior and concomitant medications, documented patient GERD symptoms, performed brief physical examinations, assessed the patient's diaries, and dispensed study and rescue drugs. The investigators documented the severity of the patient's overall GERD symptoms during the week (day -7 to day -1) prior to the last day of the Pretreatment Period. Please see Table 9.

Table 9: Investigator's GERD symptom severity grading scale

	GRADE	DEFINITION
0	None	No symptoms.
1	Mild	GERD symptoms do not last long and are easily tolerated
2	Moderate	GERD symptoms cause discomfort and interrupts usual activities
3	Severe	GERD symptoms cause great interference with usual activities and may be incapacitating

Reference: Study M00-158 – "A study to evaluate the safety and efficacy of lansoprazole in adolescents with GERD after 8 to 12 weeks of treatment." Adapted from Volume 7, page 42, Table 9.5f.

6.1.4 Pretreatment Laboratory Evaluations: All patients were instructed to fast at least 8 hours before the Pretreatment (baseline) laboratory samples were drawn. Laboratory evaluations included determinations of the following:

1) Hematology: hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelet count.

2) Blood Chemistry Determinations: total protein, glucose, blood urea nitrogen, creatinine, gamma glutamyl transferase, hepatic panel, total cholesterol, calcium, inorganic phosphorus, sodium, potassium, chloride, and uric acid.
3) Serum Gastrin Determinations: Samples were drawn before the endoscopy procedure or 24 hours after the endoscopy procedure. Gastrin specimens were frozen immediately and shipped to [redacted] 5 pounds of dry ice on the day of collection.
4) Urinalysis: specific gravity, pH, glucose, ketones, protein, and microscopic examination.
5) Pregnancy Tests: A serum pregnancy test was completed for all female patients and results were to be negative for the patient to enter and, subsequently, to continue in the study.
6) Theophylline, Phenytoin, Phenobarbital, Digoxin, and/or Carbamazepine Levels: Patients taking these drugs were to have serum drug levels monitored to assure that proper levels of these drugs were being maintained. The time of the last dose of medication was recorded each time a drug level was drawn.

When an individual patient had a laboratory value that was outside the sponsor's thresholds for potentially concerning laboratory results, a listing of all related values for that patient was generated and reviewed by the sponsor to determine whether further action was needed.

6.2 Treatment Period:

6.2.1 Treatment Period for non-erosive GERD patients: Non-erosive GERD patients who completed all pretreatment procedures and met all eligibility requirements were allowed to start the Treatment Period. The Treatment Period began when the first dose of study drug (15 mg of oral lansoprazole) was taken (Day 1) and ended after eight weeks of treatment or when the patient prematurely discontinued from the study. Non-erosive GERD patients did not have follow-up upper endoscopies.

Patients were not permitted to use bisphosphonates, tetracycline, doxycycline, ferrous sulfate, oral cromolyn sodium, investigational drugs (other than the study medication), chronic anticoagulant therapy, antacids (other than the mylanta® provided during the study), histamine2-receptor antagonists, sucralfate, anticholinergics, prokinetics, and PPIs (other than the study medication). Patients were not permitted to use more than 12 doses per month of the following medications: NSAIDS including COX-2 inhibitors and corticosteriods greater than or equal to the equivalent to 10 mg of prednisone per day.

Before the Treatment Period, mylanta® was dispensed to non-erosive GERD patients. If the patients did not achieve relief of their heartburn symptoms, they were permitted to take the approved dose of mylanta® anytime (except within 30 minutes of study drug administration.)

Patients, their parents, and/or their caregivers (PPC) maintained the daily diary, in which they recorded the severity of their GERD symptoms and the amount and frequency of their mylanta use.

Patient visits occurred at Week 4 and Week 8. If a patient withdrew from the study early, then the final visit occurred on the last day of study drug treatment. At all these visits, the following procedures were performed: concomitant medication assessments, brief physical exams, vital signs measurements, adverse event assessments, and laboratory evaluations including fasting serum

gastrin levels. Furthermore, the investigators documented the severity of the patient's overall GERD symptoms during the one-week prior to each visit (see Table 9).

6.2.2 Treatment Period for EE patients: EE patients followed similar procedures and evaluations as the non-erosive GERD patients. Below highlights some differences.

In contrast to the non-erosive patients, EE patients were treated for 8 weeks with 30 mg of oral lansoprazole per day. At the Week 8 Visit, all EE patients had follow-up upper endoscopies to assess EE healing. The endoscopist graded the appearance of the esophageal mucosa by using the TAP Esophagitis Grading Scale (see Table 7). If these patients achieved a grade of 0 or 1 (non-erosive GERD), then they were classified to have complete EE healing and they finished the study (in 8 weeks).

On the 8-week follow-up endoscopy, if patients had grades of 2, 3, or 4; then they were categorized to have incomplete healing — these patients continued to have EE. These EE patients were treated with 30 mg of oral lansoprazole per day for an additional 4 weeks (a total of 12 weeks of treatment). At the Week 12 Visit, these EE patients had a third (and final) upper endoscopy to assess EE healing. The appearance of the esophageal mucosa of these patients was graded by the identical TAP Esophagitis Grading Scale. At the Week 12 Visit patients also received: concomitant medication assessments, complete physical exams, vital signs measurements, adverse event assessments, and lab evaluations including fasting serum gastrin levels. Furthermore, the investigators documented the severity of the patient's overall GERD symptoms during the week prior to the Week 12 visit.

Medical Reviewer's Comments: The study procedures and evaluations were acceptable.

The change in weight of the GERD patients after 8-12 weeks of the Treatment Period was not measured. If overweight GERD patients lost weight (through reduction in calories consumed and an increase in exercise performed) during the 8-12 weeks of the Treatment Period, then their GERD symptoms may have improved by this lifestyle change in addition to the study medication.

7 <u>Endpoints</u>:
7.1 Primary Efficacy Endpoint: For all (non-erosive GERD and EE) patients, the primary efficacy endpoint was the change in the frequency and severity of GERD symptoms based on **patient diary** data in the one to two-week Pretreatment Period (day -14 to day -1) compared to the eight-week Treatment Period (day 1 to the week 8 visit).

Medical Reviewer's Comments: The efficacy of lansoprazole in the treatment of GERD is difficult to demonstrate without a control group (a placebo control, an active control, or dose-ranging control group). Pediatrics GERD patients can improve with dietary and lifestyle changes alone without medication. Therefore, the true efficacy of lansoprazole in the treatment of GERD will be difficult to demonstrate in this study alone.

However, this is a supportive study for the efficacy of lansoprazole in the treatment of GERD in adolescent patients. The sponsor will rely primarily on the efficacy of lansoprazole in the treatment

of GERD in adults. Furthermore, the sponsor will have supportive information from PK and PD studies and efficacy data in this study.

7.2 Secondary Efficacy Endpoints for all patients in this study: Four secondary efficacy endpoints for all patients were:

1) The change in frequency and severity of GERD symptoms based on **patient diary** data in the one to two-week Pretreatment Period (day -14 to day -1) compared to the first four weeks of the Treatment Period (starting on day 2 to day 29).
2) The change in frequency and severity of GERD symptoms based on **patient diary** data in the one to two-week Pretreatment Period (day -14 to day -1) compared to the entire Treatment Period (starting on day 2 to the Final Visit). The Final Visit for non-erosive GERD patients and EE patients, who had completely healed EE at the Week 8 Visit, was the Week 8 Visit. In contrast, the Final Visit for EE patients, who did not have completed healing at the Week 8 Visit, was the Week 12 Visit. Finally, the Final Visit for all (non-erosive GERD and EE) patients, who prematurely terminated from the study during the Treatment Period, was the last day that each patient received the study drug.
3) The change in antacid use based on **patient diary** data from the Pretreatment Period (day -14 to day -1) compared to the first four weeks of the Treatment Period (starting on day 2 to day 29), the first eight weeks of the Treatment Period (starting on day 2 to day 57), and the entire Treatment Period (starting on day 2 to the Final Visit).
4) Based on **investigator interview**, the change in the severity of the GERD symptoms from the week prior to the Treatment Period (day -7 to day -1) compared to the week prior to the Week 4 Visit (day 23 to day 29), the week prior to the Week 8 Visit (day 51 to day 57), and the week prior to the Week 12 Visit (day 79 to day 85).

7.3 Additional Secondary Efficacy Endpoint for only EE patients in this study: One additional secondary efficacy variable for only EE patients was: the percentage of patients with Pretreatment endoscopically-proven EE who had **completed healing** at the Week 8, the Week 12, and the Final Visits.

Medical Reviewer's Comments: Healing of esophageal erosions should be a co-primary endpoint for the EE patients in this study.

8 Statistical Methods: The primary endpoint and the three secondary endpoints for all patients will be analyzed using the sign test. The secondary endpoint for EE patients will be calculated.

9 Study Deviations:
Five non-erosive GERD patients were prematurely discontinued from the study (three for therapeutic failure, one due to an adverse event, and one for poor compliance) and no EE patient was prematurely discontinued from the study.

Overall, the most frequently reported study deviations were: visit date deviations; laboratory evaluations which were ill-timed, not performed, or performed without the patient fasting; missing diary data; missed doses of study drug; and biopsies not obtained. Nine patients enrolled in the study did not meet all of the admission criteria. Patient No. 422 did not have baseline laboratory

blood tests; Patient No. 105 took doxycycline throughout the pretreatment and treatment periods; Patient No. 251 started taking the study drug 27 days prior to his 12th birthday; Patient No. 121 was enrolled without having a urinalysis prior to enrollment; Patient No. 402 was enrolled with only three days of diary data in the Pretreatment Period; and Patient 463 took 4 chewable Tums on Day -13. Furthermore, some patients took concurrent medications not allowed by the study: Patient No. 105 took doxycycline throughout the pretreatment and treatment periods; Patient No. 463 took 4 chewable Tums on Day -13; Patient No. 107 took 30 mg of lansoprazole in addition to the study drug (15 mg of lansoprazole) for the last two days of the Treatment Period, Patients No. 613 and No. 321 took metoclopramide for at least 4 weeks during the Treatment Period.

Medical Officer Comments: The minor protocol deviations should not affect the overall efficacy results of the study.

10 Baseline Demographics and Other Characteristics:

10.1 Baseline Demographics: Eighty-seven adolescent patients were enrolled in the study and treated with lansoprazole. Sixty-four non-erosive GERD patients (grade 0 or 1 per the TAP Esophagitis Grading Scale) were assigned to receive 15 mg of lansoprazole and 23 EE patients (grade 2, 3, or 4 per the Grading Scale) were assigned to receive 30 mg of lansoprazole. The study was conducted at 20 centers in the United States. Table 10 delineates the baseline patient demographics including: gender, race, H. pylori status, weight, height, and age.

Table 10: Baseline patient demographics

Demographic Characteristic	All Subjects	Non-erosive GERD Lansoprazole 15 mg QD	Erosive Esophagitis Lansoprazole 30 mg QD
Gender			
N	87	64	23
Female	60.9% (53)	64.1% (41)	52.2% (12)
Male	39.1% (34)	35.9% (23)	47.8% (11)
Race			
N	87	64	23
Caucasian	80.5% (70)	79.7% (51)	82.6% (19)
Black	16.1% (14)	15.6% (10)	17.4% (4)
Other[a]	3.4% (3)	4.7% (3)	0
***H. pylori* Status**[b]			
N	86	63	23
Positive	3.5% (3)	1.6% (1)	8.7% (2)
Negative	96.5% (83)	98.4% (62)	91.3% (21)
Age (years)			
N	87	64	23
Mean (SD)	14.1 (1.6)	14.1 (1.7)	14.3 (1.3)
Range	11-17[c]	11-17[c]	13-17
Weight - Females (pounds)			
N	53	41	12
Mean (SD)	135.4 (31.3)	135.6 (32.3)	134.6 (28.9)
Range	74-222	74-222	100-198
Weight - Males (pounds)			
N	34	23	11
Mean (SD)	139.7 (49.4)	132.0 (46.8)	155.7 (52.9)
Range	65-290	65-225	86-290
Height - Females (inches)			
N	53	41	12
Mean (SD)	63.2 (2.5)	63.2 (2.7)	63.3 (2.0)
Range	57-69	57-69	60-66
Height - Males (inches)			
N	33	22	11
Mean (SD)	65.3 (4.8)	64.3 (5.1)	67.3 (3.6)
Range	54-73	54-73	62-72

SD = standard deviation

a Race categories other than Caucasian and Black were combined into one category.

b Histologic *H. pylori* results.

c Subject No. 251 started study drug 27 days prior to his 12th birthday.

Reference: Volume 7, page 62, Table 11.2a

Medical Reviewer's Comments: Overall, the baseline demographics of the study population were acceptable. The average age of the GERD patients was 14. All of the GERD patients satisfied the strict age criteria established in the eligibility criteria, except Patient No. 251 was 11 years and 11 months old. This patient, who is one month younger than the desired population, should have similar safety and efficacy outcomes in the treatment of GERD with lansoprazole.

The study population had a similar racial makeup to the United States' population except that the study population had less Hispanics and slightly more Caucasians.

The study population had a small percentage of GERD patients who were *H. pylori* positive. This is consistent with the adolescent pediatric population in the United States. *H. pylori* is more common in adults over 50 years old than in the pediatric population in the U.S.

The sponsor did not calculate the Body Mass Index (BMI) of the GERD patients. Overweight and obese subjects are more likely to develop GERD than normal weight subjects.

Although this study had more females than males, the distribution of patients according to age is adequate for a study of this size. There is no evidence that adolescent males with GERD and adolescent females with GERD have different outcomes.

Table 11 demonstrates additional baseline demographic characteristics of the GERD patients including tobacco, alcohol, and caffeine consumption.

Table 11: Baseline patient behaviors

VARIABLE	ALL SUBJECTS N= 87 n(%)	LANSOPRAZOLE 15 MG QD N= 64 n(%)	LANSOPRAZOLE 30 MG QD N= 23 n(%)	OVERALL P-VALUE#
TOBACCO				
TOBACCO NONUSER$	83 (95.4)	61 (95.3)	22 (95.7)	
TOBACCO USER	4 (4.6)	3 (4.7)	1 (4.3)	0.947
ALCOHOL				
NONDRINKER&	83 (95.4)	61 (95.3)	22 (95.7)	
DRINKER	3 (3.4)	2 (3.1)	1 (4.3)	
UNKNOWN	1 (1.1)	1 (1.6)	0	0.793
CAFFEINE				
CAFFEINE NONUSER	11 (12.6)	7 (10.9)	4 (17.4)	
CAFFEINE USER	73 (83.9)	56 (87.5)	17 (73.9)	
UNKNOWN	3 (3.4)	1 (1.6)	2 (8.7)	0.350

Reference: Study M00-158 — "A study to evaluate the safety and efficacy of lansoprazole in adolescents with GERD after 8 to 12 weeks of treatment." Volume 7, page 113, Table 14.1_2.1

Medical Reviewer's Comments: The pediatric patient GERD adolescent population in this study used less tobacco than the national average for adolescents.

This study did not provide a procedure for counseling patients on non-pharmacologic methods for treating GERD including decreasing alcohol, caffeine, and tobacco consumption. Standard medical practice in the treatment of pediatric GERD includes non-pharmacologic therapy.

10.2 <u>Past medical history of GERD in the study population</u>:
Of the 87 patients in this study, 30 had a history of GERD less than one year; 13 had a history of GERD one to two years; 28 had a history of GERD greater than two years, but less than five years; and 16 had a history of GERD greater than five years. The most frequently reported predominant GERD symptoms were heartburn, generalized abdominal pain, epigastric abdominal pain, chest pain, regurgitation, sour taste, nausea, and vomiting. Some patients reported several predominant symptoms.

Medical Reviewer's Comments: According to the inclusion criteria in this study, GERD patients must have a history of GERD for at least 3 months prior to the Pretreatment Period and must be symptomatic. Approximately 66% of the patients had a history of GERD over one year and

approximately 18% of the patients had a history of GERD more than five years. The study population satisfied the sponsor's anticipated GERD population.

10.3 Baseline GERD characteristics: Fifty-three (61%) of the 87 patients in this study had received previous medical therapy for their GERD within 12 months prior to the start of the study; 18 patients (21%) had been treated previously with a PPI.

Table 12 displays the baseline frequency and severity of GERD in the study population according to the patients' diaries. The severity of GERD symptoms is classified according to patient diaries as follows: 0 = none; 1 = mild; 2 = moderate; 3 = severe; 4 = very severe (see Table 8). Given that the data is not symmetric, the data is reported as the median values.

Table 12 also displays the baseline amount and frequency of the rescue antacid (mylanta) use according to the patients' diaries.

Table 12: Baseline frequency and severity of GERD and mylanta use based on patient diaries

	N	% of Days with GERD	Daily Severity[a] of GERD	% of Days Antacid Used	Amount of Antacid Used in Teaspoons/ Day
		Median	Median	Median	Median
All Patients	87	88.9	1.61	54.5	1.36
Non-Erosive GERD	64	90.7	1.56	55.1	1.35
EE	23	84.6	1.89	50.0	1.56

a GERD Severity scored as 0=none; 1 = mild; 2 = moderate; 3 = severe; 4 = very severe
Reference: Volume 7, page 116-7, Table 14.1_3.1

Medical Reviewer's Comments: The pediatric study population had considerable GERD because the median percentage of GERD symptoms was 89% of the days at baseline. Furthermore, they required antacids 55% of the days at baseline. The study population satisfied the sponsor's anticipated GERD population.

10.4 Baseline Upper Endscopy Results: From the baseline appearance of the esophageal mucosa, endoscopists classified patients into two treatment groups: Treatment Group I (non-erosive GERD patients) and Treatment Group II (EE patients). See Table 13 for a summary of the baseline appearance of the patients' esophageal mucosa.

Table 13: Baseline esophageal mucosa appearance by endoscopy

	Baseline Esophagitis Grade	All Subjects (N = 87) n (%)
Non-erosive GERD		
	Grade 0	18 (20.7%)
	Grade 1	46 (52.9%)
Erosive Esophagitis		
	Grade 2	20 (23.0%)
	Grade 3	3 (3.4%)
	Grade 4	0

Reference: Study M00-158 — "A study to evaluate the safety and efficacy of lansoprazole in adolescents with GERD after 8 to 12 weeks of treatment." Volume 7, page 64, Table 14.1_2.1

Medical Reviewer's Comments: The majority of all the GERD patients [79% (69/87)] had baseline abnormalities in the appearance of their esophageal mucosa: 72% (46/64) of the non-erosive GERD patients had a grade 1 appearance (mucosal edema, hyperemia, red streaks, and/or friability) and 100% (23/23) of the EE patients had a grade 2 or 3 appearance.

At baseline, 76% (66/87) of the GERD patients in this study had a grade 1 or grade 2 appearance.

All grades of EE were present in the study population except grade 4 EE.

10.5 Baseline Investigator Interview Results: During the Pretreatment Period interviews, investigators estimated the severity of the patients' GERD (please see Table 14).

Table 14: Baseline GERD severity according to the investigators

	Severity of Overall GERD Symptoms				
	N	None	Mild	Moderate	Severe
All Subjects	87	1	16	61	9
Non-erosive GERD Subjects (Lansoprazole 15 mg QD)	64	0	15	45	4
Erosive Esophagitis Subjects (Lansoprazole 30 mg QD)	23	1	1	16	5

Reference: Study M00-158 — "A study to evaluate the safety and efficacy of lansoprazole in adolescents with GERD after 8 to 12 weeks of treatment." Volume 7, page 66, Table 14.1_3.2

Medical Reviewer's Comments: Several patients with EE had moderate symptoms and several patients with non-erosive GERD had severe symptoms. These results are consistent with the lack of correlation of the severity of GERD symptoms with the severity of esophageal damage. Because symptoms do not correlate with esophageal healing, post-treatment upper endoscopies are required for the EE patients.

11 Efficacy Results:

11.1 Primary Efficacy Endpoint: The pre-specified primary efficacy endpoint was the change in the frequency and severity of GERD symptoms based on patient diary data in the one to two-week Pretreatment Period (day -14 to day -1) compared to the eight-week Treatment Period (day 1 to the Week 8 Visit). Table 15 displays the median percentage of days that patients had GERD symptoms in the Pretreatment Period and the first 8 weeks of the Treatment Period. The values are reported in the median because the data is not symmetric.

Table 15: Median frequency of GERD symptoms

		Entire Pretreatment Period	First 8 Weeks of Treatment Period	Change
	N[a]	Median	Median	Median
Non-Erosive GERD	64	90.7	43.1	-31.8*
EE	23	84.6	16.0	-54.4*
All Patients	87	88.9	33.3	-38.8*

a Patients who did not have any diary entries during the Pretreatment or Treatment Periods were not included in the analysis; * $p < 0.001$; Reference: Adapted from Volume 7, page 179, Table 14.2_1.2

For all GERD patients, the change in the median percentage of days with GERD symptoms in the Pretreatment Period compared to the Treatment Period was statistically significant ($p < 0.001$). Most patients decreased the frequency of their GERD symptoms by about half.

Table 16 displays the mean severity of GERD symptoms in the Pretreatment Period and the first eight weeks of the Treatment Period based on the patient diaries. Table 8 summarizes the grading system used in this study for the severity of GERD symptoms based on the patient diaries: GERD severity is scored as 0 = none; 1 = mild; 2 = moderate; 3 = severe; 4 = very severe.

Table 16: The severity[a] of GERD symptoms

		Entire Pretreatment Period	First 8 Weeks of Treatment Period	Change
	N[b]	Median	Median	Median
Non-Erosive GERD	64	1.6	0.6	-0.7*
EE	23	1.9	0.2	-1.1*
All Patients	87	1.6	0.5	-0.8*

a The severity scale includes: 0=none, 1=mild, 2=moderate, 3=severe, and 4=very severe;
b Patients who did not have any diary entries during the Pretreatment or Treatment Periods were not included in the analysis
* $p < 0.001$; The p-value is based on the sign test for significant change from the Pretreatment Period.
Reference: Adapted from Volume 7, page 179, Table 14.2_1.2

For the GERD patients in this study, the change in the median severity of GERD symptoms from the Pretreatment Period compared to the Treatment Period was statistically significant ($p < 0.001$). Patients at baseline had mild to moderate GERD symptoms and patients had none to mild GERD during lansoprazole treatment.

Medical Reviewer's Comments: These efficacy results are difficult to interpret because no placebo group was included in this study. GERD symptoms can improve after non-pharmacologic intervention including lifestyle and dietary changes. Furthermore, adolescent GERD patients may have random waxing and waning of their symptoms and as many as 50% of GERD symptoms may resolve long-term without medication. Therefore, the efficacy of the study medication at the reduction of frequency of GERD symptoms is difficult to assess in this trial.

However, this is a supportive study for the efficacy of lansoprazole in the treatment of GERD in adolescent patients. The sponsor will rely primarily on the efficacy of lansoprazole in the treatment of GERD in adults. Furthermore, the sponsor will have supportive information from PK and PD studies and efficacy data in this study.

11.2 Secondary Efficacy Results:

11.2.1 Secondary Efficacy Variable for EE patients: The percentage of patients with Pretreatment endoscopically-proven EE who had complete healing at the Week 8, the Week 12, and the Final Visits.

All EE patients had baseline esophageal mucosa grades of 2 or 3 in this study. Complete healing was defined as a return of the esophageal mucosa to an esophagitis grade of 0 or 1 (non-erosive GERD). The complete healing rates of the EE in this study are displayed in Table 17.

Twenty-one of twenty-two patients (95%) were completely healed at the Week 8 Visit. Patient No. 471 did not have complete healing at the Week 8 Visit; therefore, Patient No. 471 received an additional 4 weeks of lansoprazole (30 mg per day) for a total of 12 weeks of treatment. Patient No. 471's esophagitis (grade 2) remained unchanged from baseline at both the Week 8 and the Week 12 Visits.

Table 17: Esophageal healing rates for EE patients

Visit	% Healed	n/N
Week 8 Visit	95.5%	21/22
Final Visit	95.5%	21/22

% Healed is defined as the conversion of the esophageal mucosa from grade 2, 3, or 4 (EE) to grade 0 or grade 1 (non-erosive GERD)
n = the number of patients who had complete healing of their EE
N = the total number of EE patients
Reference: Volume 7, page 72, Table 14.2_3

Medical Reviewer's Comments: This secondary endpoint of complete healing in the EE group should have been a pre-specified co-primary endpoint. Many important EE trials have used the complete healing of EE by endoscopy appearance as a primary endpoint.

The endoscopists in this study were not blinded to the patient's clinical status. The endoscopists knew that all the EE patients who received post-treatment endoscopies were treated with 30 mg of lansoprazole for 8 weeks. This may have introduced observation bias to the study.

In addition, Study M00-158 had no control group (no placebo-control, no active control, and no dose-ranging control group.) However, the efficacy of complete healing of EE was 95.5% (21/22) in this study.

Furthermore, these results are similar (or slightly better) than the results of adult EE treatment studies with lansoprazole. In Study M88-269, complete EE healing at 8-weeks occurred in 89% of adult EE patients after treatment with 30 mg of lansoprazole. Similarly, in Study M87-092, complete healing at 8-weeks occurred in 82% of adult EE patients after treatment with 30 mg of lansoprazole.

11.2.2 Secondary Efficacy Variable for non-erosive GERD and EE patients: Another secondary efficacy variable was the change in rescue antacid use based on patient diary data from the Pretreatment Period (day -14 to day -1) compared the first eight weeks of the Treatment Period (starting on day 2 to day 57.) Table 18 summarizes the proportion of days of rescue antacid (mylanta) use during the Pretreatment and Treatment Periods based on the patient diaries. All values are reported in the median because the values are not symmetric. During the Treatment period, the median days patients required antacid was about 6%; in contrast, during the Pretreatment period, the median days patients required antacid was about 55%.

Table 18: Frequency of mylanta use in the Pretreatment and Treatment Periods

		Entire Pre-treatment Period	First 8 Weeks of Treatment Period	Change between the First 8 Weeks and the Pretreatment Period
	N[a]	Median	Median	Median
Non-Erosive GERD	64	55.1	7.3	-37.3*
EE	23	50.0	1.8	-28.6*
All Patients	87	54.5	5.5	-37.0*

a Patients who did not have any diary entries during the Pretreatment or Treatment Periods were not included in the analysis; * $p < 0.001$
Reference: Adapted from Volume 7, page 178 (Table 14.2_1.1) and page 180 (Table 14.2_1.2) and page 182 (Table 14.2_1.3)

Table 19 summarizes the average amount of mylanta used in teaspoons per day in the Pretreatment and Treatment Periods according to the patient diaries.

Table 19: Amount[a] of mylanta use in the Pretreatment and Treatment Periods

		Entire Pre-treatment Period	First 8 Weeks of Treatment Period	Change between the First 8 Weeks and the Pretreatment Period
	N[b]	Median	Median	Median
Non-Erosive GERD	64	1.3	0.3	-0.9*
EE	23	1,6	0.1	-1.1*
All Patients	87	1.4	0.2	-1.0*

a Amount of Mylanta is reported in teaspoons per day

b Patients who did not have any diary entries during the Pretreatment or Treatment Periods were not included in the analysis; * $p < 0.001$

Reference: Adapted from Volume 7, page 178 (Table 14.2_1.1) and page 180 (Table 14.2_1.2) and page 182 (Table 14.2_1.3)

Medical Reviewer's Comments: The improvement in the amount and frequency of rescue medication from baseline to the Treatment Period supports the efficacy of the use of lansoprazole for the treatment of GERD.

11.2.3 Secondary Efficacy Variable for non-erosive GERD and EE patients: Based on investigator interview, the change in the severity of the GERD symptoms from the week prior to the Treatment Period (day -7 to day -1) compared to the week prior to the Week 4 Visit (day 23 to day 29), the week prior to the Week 8 Visit (day 51 to day 57), and the week prior to the Week 12 Visit (day 79 to day 85). Table 9 outlines the grading system that the investigators used in their assessment of the severity of patients' GERD as follows: none = 0, mild = 1, moderate = 2, and severe = 3. Table 20 displays the results of this secondary variable according to the investigators' interviews during the baseline, Week 4, Week 8, and Final Visits.

Table 20: GERD severity according to the investigators' interviews

		SEVERITY OF OVERALL GERD SYMPTOMS			
VISIT	N	None	Mild	Moderate	Severe
Baseline Visit	87	1	16	61	9
Week 4 Visit	85	21	49	14	1
Week 8 Visit	80	35	34	11	0
Final Visit	86	36	36	13	1

Reference: Adapted from Volume 7, page 72, Table 11.4c

Medical Reviewer's Comments: According to the investigator interviews, as the GERD severity decreases after a longer duration of lansoprazole treatment in this study. This secondary endpoint supports the efficacy of the use of lansoprazole for the treatment of adolescent GERD.

Table 21 categorizes the GERD patients into subgroups based on their baseline GERD severity and shows the average GERD severity of all the subgroups after 8 weeks of lansoprazole.

Table 21: The change in GERD severity at the 8-week visit

BASELINE SYMPTOMS (0-3)	N	None (0)	Mild (1)	Moderate (2)	Severe (3)	Mean GERD Score (0-3) at the 8-week visit
None (0)	1	1	0	0	0	0.00
Mild (1)	14	5	8	1	0	0.71
Moderate (2)	56	25	22	9	0	0.71
Severe (3)	9	4	4	1	0	0.67

Reference: Adapted from Volume 7, page 191, Table 14.2_5.2

Medical Reviewer's Comments: All the GERD severity subgroups decreased their average GERD symptom severity after lansoprazole treatment. This secondary endpoint supports the efficacy of the use of lansoprazole for the treatment of adolescent GERD.

D. Efficacy Conclusions

In Study M00-158, the median frequency of the adolescent's GERD symptoms significantly decreased from 88.9% of the days in the baseline Pretreatment Period to 33.3% of the days in the 8-week lansoprazole Treatment Period based on patient diaries. Furthermore, compared to the baseline period, the median severity of the adolescent's GERD symptoms significantly decreased during the 8-week lansoprazole Treatment Period based on patient diaries. Therefore, the co-primary endpoints were achieved. Compared to the baseline period, the frequency and amount of rescue antacid use during 8 weeks of lansoprazole treatment decreased, based on patient diary data. Additionally, the severity of patients' GERD symptoms decreased after 8 weeks of lansoprazole treatment based on investigator interviews. Even though this trial had major design flaws — it was uncontrolled and open-labeled — and was subject to bias, the trial serves as a supportive study in the treatment of GERD and EE in adolescents. Furthermore, the trial demonstrated efficacy in the complete healing of EE after 8 weeks of lansoprazole administration; over 95% (21/22) of the EE patients achieved complete healing at 8 weeks.

Study M97-640 demonstrated that the pharmacokinetic variables (C_{max}, T_{max}, AUC_{0-24}, and the half-life) of adolescent GERD patients after 5 days of lansoprazole was similar to the pharmacokinetics in previously observed healthy adult subjects. Additionally, this study demonstrated that the intra-gastric pH of the adolescent GERD patients improved after 5 days of lansoprazole. Specifically, the mean 24 hour intra-gastric pH and the percentages of time that the intra-gastric pH exceeded 3 and 4 after 5 days of lansoprazole treatment was statistically significant compared to the baseline intra-gastric pH variables.

There was no difference in efficacy between non-erosive GERD and EE patients in overall GERD symptoms, pH parameters, and PK variables after lansoprazole treatment. The efficacy of

lansoprazole in complete healing of EE in adolescent patients with severe EE is not known. Study M00-158 included patients with grade 2 and grade 3 EE; but not patients with grade 4 EE.

Several patients with EE had moderate symptoms and several patients with non-erosive GERD had severe symptoms. These results are consistent with the lack of correlation of the severity of GERD symptoms with the severity of esophageal damage. Because symptoms do not correlate with esophageal healing, post-treatment upper endoscopies are required for the EE patients.

In summary, the efficacy of lansoprazole in the proposed indication was demonstrated by similar lansoprazole pharmacokinetics in pediatric patients between 12 and 17 years old in Study M97-640 compared to healthy adult subjects; by the improvement of intra-gastric pH after 5 days of lansoprazole treatment in Study M97-640; by the efficacy in the complete healing of EE after 8 weeks of lansoprazole treatment in Study M00-158; and efficacy results of lansoprazole treatment in adult GERD patients

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

The sponsor has demonstrated the safety of oral lansoprazole in the treatment of GERD and EE in pediatric patients between the ages of 12 and 17 years old (adolescents). A safety review of the two trials uncovered no safety concerns. Analysis of this data demonstrates that the safety profile of this drug in this pediatric population is similar to the safety profile in the adult population and in the pediatric population, between the ages of 1 year to 11 years old. In summary, the combination of data in this ISS, the data in the clinical GERD trials of adults and pediatrics between the ages of 1 year to 11 years old (children), and the post-marketing and literature GERD data from adults and pediatrics, all combine to establish the safety of oral lansoprazole in the treatment of GERD and EE in pediatric patients between the ages of 12 and 17 years old.

B. Description of Patient Exposure

The Integrated Summary of Safety (ISS) consisted of two studies containing 150 GERD patients who received at least one dose of lansoprazole. Table 22 shows the exposure of pediatric GERD patients ages 12 to 17 years old (adolescents), to lansoprazole in the two clinical trials in this supplemental NDA submission. Of the total ISS population, 96 patients received 15 mg of lansoprazole per day and 54 patients received 30 mg of lansoprazole per day. Of the 150 subjects who received lansoprazole in Studies M00-158 and M97-640, 80% were Caucasian and 56% were females. The mean age for all patients was 14.1 years (range: 11-17 years). Additionally, 4.7% were tobacco users, 2.7% were alcohol users, and 82.7% were caffeine users.

Table 22: Patient exposure to lansoprazole in the two studies

Study	# of Sites	Duration of Treatment	Dose of Oral Lansoprazole	# of Patients Entered in Each Group	# of Patient Withdrawals	# of Patient Withdrawals Due to an AE
M00-158	20	8 weeks	15 mg/ day for non-erosive GERD patients	64	5	1
			30 mg/day for EE patients	23	0	0
M97-640	10	5 days	15 mg per day	32	1	1
			30 mg per day	31	0	0
All Studies	30			150	6	2

Reference: Adapted from Integrated Summary of Safety, Volume 9, Page 76, Table 1

The distribution of study drug exposure during the lansoprazole adolescent GERD clinical program directly reflected the different study durations in the 12-week (M00-158) and 5-day (M97-640) studies. A summary of the duration of lansoprazole use in the adolescent GERD studies is presented in Table 23.

Table 23: Duration of lansoprazole use in adolescent patients

Total Duration of Treatment	n (%)		
	All Subjects (N=150)	M00-158 (8-12 weeks) (N=87)	M97-640 (5 days) (N=63)
0 - 9 Days	64 (42.7%)	1 (1.1%)	63 (100.0%)
>9 - 42 Days	4 (2.7%)	4 (4.6%)	0
>42 -70 Days	81 (54.0%)	81 (93.1%)	0
>70 Days	1 (0.7%)	1 (1.1%)	0
Range	4.0 - 88.0	4.0 - 88.0	4.0 - 9.0[a]

SD = Standard Deviation
a Some subjects received greater than 5 days of lansoprazole due to scheduling conflicts.
Reference: Adapted from Integrated Summary of Safety, Volume 9, Page 17, Table 2.4a

Medical Reviewer's Comments: The overall exposure to lansoprazole in the study population is small (N=150), considering that GERD is a chronic disorder. However, the sponsor intends to use this safety data as supportive evidence of the safety of lansoprazole in pediatric patients, ages 12 to

17 years old and additional copious data includes clinical trial and post-marketing safety data from adult and pediatric GERD patients.

C. Methods and Specific Findings of Safety Review

1 Safety Endpoints: Safety endpoints included changes in blood and urine tests, vital signs, gastritis findings (from endoscopies) from the Pretreatment Period compared to the Treatment Period.

2 Safety Analysis: The percentage of patients having adverse events (AEs) will be tabulated using Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART) and using body systems. Descriptive statistics for changes from the Pretreatment Period in laboratory tests and vital signs results will be presented. The changes will be analyzed by one-sample t-tests.

3 Adverse Events in the Adolescent GERD Studies:

3.1 Deaths: No patients died during the GERD studies in pediatric patients between 12 and 17 years old.

3.2 Serious Adverse Events (SAEs): Five patients in the adolescent GERD studies had serious adverse events (SAEs). During Study M00-158, four patients in the lansoprazole 15 mg per day dose group experienced SAEs and all required hospitalization. Three patients experienced events (suicide attempt, dehydration due to gastroenteritis, and a torn hamstring muscle) that were considered not related to the study drug and one experienced an AE (acute cholecystitis) that was considered unlikely to be related to the study drug.

During Study M97-640, one patient in the lansoprazole 30 mg per day dose group experienced a SAE (moderate gastrointestinal disorder with symptoms of chest pain, abdominal pain, and increased cough) and required hospitalization. The sponsor considered this SAE due to an exacerbation of the patient's GERD; but not related to lansoprazole, the study drug. Table 24 summarizes the five SAEs experienced by patients in Studies M00-158 and M97-640.

Table 24: Serious reported adverse events

	Study #	Patient #	Age	Sex	Total Days in Study	Treatment Day of Onset	Treatment Day Stopped	SAE	Severity
1	M00-158	301	13	F	40	53	54	Suicide Attempt	Mild
2	M00-158	107	14	M	55	52	57	Dehydration due to Gastroenteritis	Severe
3	M00-158	131	12	F	57	9	35	Torn Left Hamstring	Severe
4	M00-158	132	16	F	58	26	40	Acute Cholecystitis	Severe
5	M97-640	64	16	F	6	7	13	Exacerbation of GERD	Moderate

Reference: Adapted from Volume 7, page 222, Table 14.3.2_1 and Integrated Summary of Safety Volume 9, Page 137, Table 7.2

The following are the four SAEs narratives in Study M00-158:

1) Patient No. 301: A 13-year-old Caucasian female, with a history of depression, was hospitalized for a suicide attempt by intentional acetaminophen overdose on Day 53 (13 days post-treatment). The patient took approximately fifty 500 mg acetaminophen tablets. She was taken to the emergency room and treated with activated charcoal and mucomyst®. Four hours after ingestion, her acetaminophen level was 148, which was considered to be a borderline hepatotoxic level and she was hospitalized. The event was considered resolved on Day 54 and the patient began follow-up therapy with her psychologist.

Concomitant medications at the time of the event included paxil CR®. The investigator considered this SAE (suicide attempt) not related to the study drug. The patient was not taking the study drug (15 mg of lansoprazole) at the time of the SAE because the patient was previously discontinued from the study on treatment day 41 due to mild dizziness and moderate. The AEs on day 41 were considered possibly related to the study drug.

2) Patient No. 107: A 14-year-old Caucasian male with a history of a head injury due to a motor vehicle accident, attention deficit hyperactivity disorder, lower intestine bacterial overgrowth, and recent infections with mononucleosis and Streptococcal throat, developed 3 days of vomiting, diarrhea, and increased temperature. He was diagnosed with dehydration due to severe gastroenteritis and he required hospitalization on Day 55. He was treated with intravenous fluids, potassium, and Rocephin®. The events resolved on Day 57 and the patient was discharged from the hospital.

Concomitant medications at the time of admission included omnicef®, tussionex®, tylenol® with codeine, adderall®, zyrtec®, fibercon®, and hyoscyamine. The investigator considered this SAE

not related to the study drug. The patient developed this SAE after he completed the full 8-week treatment period with the study drug (15 mg of lansoprazole.)

3) Patient No. 131: A 12-year-old Caucasian female, with no significant past medical history, experienced a severe torn left hamstring while performing a cheerleading jump on Day 9. The investigator described the event as causing significant disability. The subject developed immediate pain and could not walk. She was treated with rest, leg elevation, and tylenol® and the event resolved on Day 35. No concomitant medications were reported.

The investigator considered the SAE not related to the study drug. The patient did not stop the study drug (15 mg of lansoprazole) during the SAE.

4) Patient No. 132: A 16-year-old Caucasian female patient with a history of recent weight loss and a healed gastric ulcer developed severe nausea on day 26. The patient had an ultrasound (normal) and a HIDA scan which indicated non-filling of the gallbladder consistent with acalculous cholecystitis. She was hospitalized and had a laparoscopic cholecystectomy. The event was considered resolved on Day 40.

The investigator considered this SAE not likely related to the study drug (lansoprazole 15 mg). Concomitant medications at the time of the hospital admission included lexapro®, zofran®, trazodone®, and birth control pills. During the nausea the study drug was temporarily discontinued and then restarted post-operatively.

The following is the one SAE narrative in Study M97-640:

5) Patient 64: A 16-year-old female, with a past medical history of headaches, received 30 mg of lansoprazole for six days and completed Study M97-640. On Post-Study Day 1, the investigator started her on 30 mg BID of lansoprazole for an exacerbation of GERD (moderate cough, abdominal pain, and chest pain.) On Post-Study Day 3, the investigator further increased the lansoprazole to 60 mg BID. However, the patient continued to have these symptoms; therefore, she was hospitalized on Post-Study Day 5. She was treated with intravenous zantac® and her chest pain improved. She experienced a mild-moderate headache for 6 days; therefore, on Post-Study Day 6, lansoprazole was discontinued. The investigator felt the headaches were not related to the study drug; but due to a tension headache. On Post-Study Day 7, she was started on prilosec® 20 mg BID; her GERD symptoms returned to baseline, her headache resolved, and she was discharged from the hospital. Following her discharge from the hospital, the patient reported recurring headaches, as well as persistent GERD symptoms despite increasing the prilosec® to 40 mg BID, and then to 40 mg TID. At the Post-Study Day 24 follow-up visit, her concomitant medications included prilosec® 40 mg TID, ranitidine 300 mg QHS, propulsid® 20 mg BID, and paxil® 30 mg QD.

The investigator felt that her SAE (chest pain, abdominal pain, and her cough) were not related to the study drug; but due to an exacerbation of her GERD.

Medical Reviewer's Comments: Based on the information presented, this reviewer is in agreement with the sponsor that the SAEs were not related or not likely related to the lansoprazole.

3.3 Withdrawals Due to Adverse Events:

Two patients withdrew from the lansoprazole studies due to AEs:

1) Patient No. 301 (see above) in Study M00-158 discontinued treatment after 40 days of therapy because of mild dizziness and moderate vomiting. The investigator believed that these AEs were possibly related to the study drug (15 mg of lansoprazole.)

2) Patient No. 69 in Study M97-640: A 14-year-old male with a past medical history of asthma, allergies, and eosinophilic esophagitis, developed hives, peripheral edema, and a generalized papular rash on Study Day 3. The patient was treated with Benadryl® on Study Day 3. The patient discontinued the study drug (lansoprazole 15 mg per day) on Study Day 4. The mild AEs resolved on Post-Study Day 3. The investigator felt that these AEs had a possible relationship to the study drug.

Medical Reviewer's Comments: Based on the information presented, this reviewer is in agreement with the sponsor that these two AEs were possibly related to the study drug (lansoprazole.)

3.4 Frequent Adverse Events: Among all patients, 78/150 (52%) experienced one or more treatment AEs. The most frequently reported treatment-related AEs in pediatric patients between 12 and 17 years old, were headache (13%), abdominal pain (9%), pharyngitis (9%), vomiting (6%), diarrhea(6%), and dizziness (5%). Table 25 displays the most frequent AEs (by body system) experienced by pediatric GERD patients between 12 and 17 years old, who received at least one dose of lansoprazole in Studies M00-158 or M97-640.

Table 25: Most frequently experienced AEs for all patients

Body System/ COSTART Term	All Subjects (N=150)	M00-158 (N=87)	M97-640 (N=63)
Any Event	78 (52%)	57 (66%)	21 (33%)
Body as a Whole			
Abdominal Pain	13 (9%)	12 (14%)	1 (2%)
Headache	19 (13%)	14 (16%)	5 (8%)
Infection	7 (5%)	6 (7%)	1 (2%)
Pain	7 (5%)	5 (6%)	2 (3%)
Accidental Injury	6 (4%)	5 (6%)	1 (2%)
Asthenia	4 (3%)	4 (5%)	0
Flu Syndrome	5 (3%)	5 (6%)	0
Fever	3 (2%)	3 (3%)	0
Viral Infection	2 (1%)	2 (2%)	0
Digestive System			
Vomiting	9 (6%)	9 (10%)	0
Diarrhea	9 (6%)	8 (9%)	1 (2%)
Nausea	7 (5%)	6 (7%)	1 (2%)
Dyspepsia	2 (1%)	2 (2%)	0
Gastroenteritis	2 (1%)	2 (2%)	0
Metabolic and Nutritional System			
SGOT Increased	2 (1%)	2 (2%)	0
Nervous System			
Dizziness	8 (5%)	7 (8%)	1 (2%)
Respiratory System			
Pharyngitis	13 (9%)	8 (9%)	5 (8%)
Cough Increased	5 (3%)	5 (6%)	0
Sinusitis	5 (3%)	4 (5%)	1 (2%)
Rhinitis	3 (2%)	3 (3%)	0
Skin and Appendages			
Urticaria	3 (2%)	2 (2%)	1 (2%)
Vesiculobullous Rash	2 (1%)	2 (2%)	0

To be included in this table, AEs had to have occurred in two or more patients. Adapted from Integrated Summary of Safety, Volume 9, Page 20, Table 3.1a

Table 26 displays the most frequent experienced AEs that are possibly, probably, or definitely caused by lansoprazole treatment according to the investigators.

Table 26: Most frequently experienced AEs that are possibly, probably, or definitely caused by lansoprazole treatment

Body System/ COSTART Term	All Subjects (N=150)	M00-158 (N=87)	M97-640 (N=63)
Any Event	18 (12%)	13 (15%)	5 (8%)
Body as a Whole			
Headache	6 (4%)	6 (7%)	0
Abdominal Pain	4 (3%)	4 (5%)	0
Digestive System			
Nausea	3 (2%)	3 (3%)	0
Nervous System			
Dizziness	4 (3%)	3 (3%)	1 (2%)

To be included in this table, AEs had to have occurred in two or more patients.
Adapted from Integrated Summary of Safety, Volume 9, Page 21, Table 3.1b

Medical Reviewer's Comments: Unfortunately, no comparison of the AE frequency can be made in these two studies, since both studies did not have a comparator group.

The adverse event profile in these pediatric patients resembled that of adult patients and pediatric patients (between ages 1 and 11) taking lansoprazole. The incidence of possibly, probably, or definitely treatment-related abdominal pain was 3%, 2.1%, and 1.2% in these pediatric patients, in lansoprazole-treated adults in the current label, and in placebo-treated adults in the current label, respectively. The incidence of possibly, probably, or definitely treatment-related nausea was 2%, 1.3%, and 1.2% in these pediatric patients, in lansoprazole-treated adults in the current label, and in placebo-treated adults in the current label, respectively.

There were no AEs reported in these two trials that were not previously reported in adults or pediatric patients between ages 1 and 11.

There was little difference in the pattern of AEs experienced by patients receiving lansoprazole 15 mg per day compared to patients receiving lansoprazole 30 mg per day in the analysis of AEs by dose in the adolescent GERD studies.

4 Clinical Laboratory Evaluations: Laboratory tests were preformed at baseline (during the Pretreatment Period), at the Week 4 Visit, at the Week 8 Visit, and the Final Visit (if applicable). The Final Visit for non-erosive GERD patients and EE patients, who had completely healed EE at the Week 8 Visit, was the Week 8 Visit. In contrast, the Final Visit for EE patients, who did not have completed healing at the Week 8 Visit, was the Week 12 Visit. Finally, the Final Visit for all (non-erosive GERD and EE) patients, who prematurely terminated from the study during the Treatment Period, was the last day that each patient received the study drug.

Laboratory evaluations included the following:

1) Hematology: hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelet count.
2) Blood chemistry determinations: total protein, glucose, blood urea nitrogen, creatinine, gamma glutamyl transferase, hepatic panel, total cholesterol, calcium, inorganic phosphorus, sodium, potassium, chloride, and uric acid.
3) Serum gastrin determinations: samples were drawn before the endoscopy procedure or 24 hours after the endoscopy procedure. Gastrin specimens were frozen immediately and shipped to [redacted] 5 pounds of dry ice on the day of collection.
4) Urinalysis: specific gravity, pH, glucose, ketones, protein, and microscopic examination.
5) Pregnancy Tests: a serum pregnancy test was completed for all female patients and results were to be negative for the patient to enter and, subsequently, to continue in the study.
6) Theophylline, phenytoin, phenobarbital, digoxin, and/or carbamazepine levels: patients taking these drugs were to have serum drug levels monitored to assure that proper levels of these drugs were being maintained. The time of the last dose of medication was recorded each time a drug level was drawn.

When an individual patient had a laboratory value that was outside the sponsor's thresholds for potentially concerning laboratory results, a listing of all related values for that patient was generated and reviewed by the sponsor to determine whether further action was needed.

No consistent clinical changes were identified in changes from baseline to the final visit for any hematology, chemistry, or urinalysis value. Among all laboratory variables, no trends were identified and no changes were medically relevant.

Statistically significant mean changes in several laboratory variables from baseline to final visit were identified in the two adolescent pediatric GERD studies. Most of these changes were small and not considered clinically significant.

Table 27 shows the fasting serum gastrin levels in both adolescent GERD studies. The normal serum gastrin range according to the laboratory used in the studies was 25 to 111 pg/mL.

Table 27: Fasting gastrin levels in Study M00-158

			QUARTILES			
VISIT	**N**	**MEAN (SD)** in pg/mL	**25%** in pg/mL	**MEDIAN** in pg/mL	**75%** in pg/mL	**P-VALUE**
Baseline	85	58.8 (92)	38.0	45.0	55.0	N/A
Week 4	78	89.9 (74)	52.0	71.0	99.0	0.005
Week 8	74	76.3 (51)	43.0	65.5	88.0	0.057
Final	86	80.1 (69)	44.0	64.0	88.0	0.015

Reference: Adapted from Integrated Summary of Safety, Volume 9, Page 51, Table 6.0a

Five subjects had fasting serum gastrin levels of ≥ 200 pg/mL during Study M00-158. Table 28 documents the five serum gastrin level outliers in pg/mL.

Table 28: Elevated serum gastrin values during Study M00-158

Subject No./ Gender/Age (years)	Lansoprazole Dose	Gastrin Level (pg/mL)		
		Baseline	Week 4 Visit	Week 8 Visit
245/F/12	15 mg QD	66	247	42 (Day 56, 1 Day Post-treatment)
621/F/13	30 mg QD	51	220	83 (Day 58, 1 Day Post-treatment)
213/F/13	15 mg QD	66	200	162 (Day 60, 1 Day Post-treatment)
511/F/15	30 mg QD	512 (Day -13) 880 (Day -1)	350	366 (Day 52, 1 Day Post-treatment)*
113/F/17	15 mg QD	106	538	No follow-up gastrin value available due to premature termination

Reference: Adapted from Integrated Summary of Safety, Volume 9, Page 52, Table 6.0b

Medical Reviewer's Comments: Hypergastrinemia is a well-documented effect of all the PPIs in adult subjects and patients. Furthermore, hypergastrinemia was documented in GERD studies in pediatric patients between ages 1 to 11 years old. PPIs significantly lower gastric acid output, which is thought to trigger a compensatory increase in gastrin production and finally an increase in gastrin serum levels.

Similar degrees of gastrin elevation were seen in the pediatric children, pediatric adolescent, and adult populations. The current labeling for lansoprazole states that "in over 210[redacted]patients, median fasting gastrin levels increased 50% to 100% from baseline but remained within normal range after treatment with lansoprazole." In these two adolescent GERD studies, post-treatment follow-up gastrin levels were not performed; therefore, no comment can be made on reversibility. However, these high levels will most likely return to normal after lansoprazole is withdrawn.

Elevated gastrin has been trophic for enterochromaffin-like (ECL) cells; which has been shown to lead to ECL carcinoid tumors in rats. However, long-term use of PPIs has not been shown to cause gastric carcinoids in human adults. Less data exists for the effects of elevated gastrin in the pediatric population.

5 Vital Signs and Physical Findings: Most of the vital signs and physical findings during treatment were unchanged from baseline in both adolescent GERD studies. Occasionally, statistically significant mean changes in physical exam findings including vital signs occurred.

Medical Reviewer's Comments: None of the statistically significant mean changes in the physical exams (including vital signs) were clinically significant.

6 Drug Interactions:

No drug interaction studies were conducted for lansoprazole in adolescents.

Based on the known potential drug interactions of lansoprazole in adults, theophylline, digoxin, phenobarbital, carbamazepine, and/or phenytoin levels, were to be monitored during the Treatment Periods of Studies M00-158 and M97-640. However, no patients took these drugs during these studies.

Medical Reviewer's Comments: According to the oral lansoprazole label, "lansoprazole is metabolized through the cytochrome P_{450} system, specifically through the CYP3A and CYP2C19 isozymes. Studies [redacted] have shown that lansoprazole does not have clinically significant interactions with other drugs metabolized by the cytochrome P450 system, such as warfarin, antipyrine, indomethacin, ibuprofen, phenytoin, propranolol, prednisone, diazepam, or clarithromycin in healthy subjects. When lansoprazole was administered concomitantly with theophylline [redacted], a minor (10%) increase 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."

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

Additionally, lansoprazole should be taken at least 30 minutes prior to sucralfate because lansoprazole's bioavailability was reduced by 17% when administered concomitantly with sucralfate in adult subjects.

Since pediatric GERD patients between ages 12 and 17 have similar PKs and PDs of lansoprazole as adult patients, similar precautions should be taken when medications are given concomitantly with lansoprazole in adolescent patients.

D. Adequacy of Safety Testing

Overall, the sponsor has adequately assessed the safety of lansoprazole for the proposed indications. The duration of lansoprazole exposure was sufficient, given that the indications are for short term therapies. Additional supportive safety data exists in adult GERD patients.

E. Summary of Critical Safety Findings and Limitations of Data

Overall, lansoprazole appears safe to use in pediatric patients, ages 12 to 17 years of age. In the two adolescent trials, no adverse events were reported that were not previously reported in adults or pediatric patients between ages 1 and 11 years old. Furthermore, adolescents that received 15 mg or 30 mg of lansoprazole per day experienced little difference in their pattern of adverse events. Long-term data is needed on the effect of hypergastrinemia on ECL cells in the adolescent population.

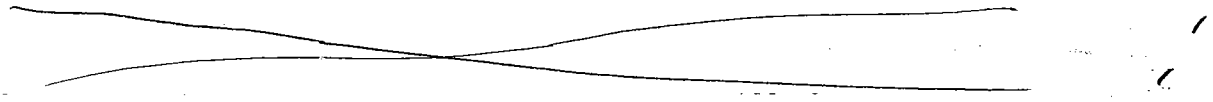
VIII. Dosing, Regimen, and Administration Issues

This medical officer recommends a lansoprazole dose of 15 mg once daily for 4 to 8 weeks for the treatment of non-erosive GERD and a lansoprazole dose of 30 mg once daily for 6 to 8 weeks for the treatment of EE in pediatric patients between the ages of 12 to 17 years old. The evidence for this dosing recommendation is from numerous GERD studies in adult patients and the two supportive pediatric studies submitted in this sNDA.

Since the efficacy of non-erosive GERD and EE treatment with lansoprazole in adolescent patients is primarily based on the safety and efficacy of lansoprazole in adult patients, the pediatric regimen should be similar to the safe and effective adult regimen. Two weeks of lansoprazole treatment of non-erosive GERD in adults is less effective than four to eight weeks of lansoprazole therapy. Similarly, four weeks of lansoprazole treatment of EE in adults is less effective than six to eight weeks of lansoprazole therapy. Therefore, the adolescent dose of lansoprazole in the treatment of non-erosive GERD and EE should be at least 4 weeks and 6 weeks, respectively.

Lansoprazole is available in three oral formulations: delayed-release capsules, delayed-release oral suspension, and delayed-release orally disintegrating tablets (solutab). Lansoprazole products should be taken before eating. No dosage adjustment is necessary in patients with renal insufficiency or the elderly. For patients with severe liver disease, dosage adjustment should be considered.

Lansoprazole delayed-release capsules should be swallowed whole; they should not be crushed or chewed. Alternatively, for patients who have difficulty swallowing capsules, lansoprazole delayed-release capsules can be opened and administered as follows: open capsule; sprinkle intact granules on one tablespoon of either applesauce, ensure®, pudding, cottage cheese, yogurt, or strained pears; and swallow immediately. The capsules may also be emptied into a small volume of either apple juice, orange juice or tomato juice and administered as follows: open capsule; sprinkle intact granules into a small volume of apple juice, orange juice, or tomato juice (60 mL); mix briefly; and then swallow immediately. To insure complete delivery of the dose, the glass should be rinsed with two or more volumes of juice and the contents swallowed immediately. The use of the capsules in other foods and liquids has not been studied clinically and is therefore not recommended.



The delayed-release orally disintegrating tablets (solutab) are not designed to be swallowed intact, chewed, or crushed. The tablet typically disintegrates in less than 1 minute. Place the tablet on the tongue and then allow it to disintegrate with or without water until the particles can be swallowed.

The delayed-release oral suspension should be administered as follows: open packet; to prepare a dose, empty the packet contents into a container containing 2 tablespoons of water (do not use other liquids or foods); stir well; and then drink immediately. If any material remains after drinking, add more water, stir, and drink immediately. This product should not be given through enteral administration tubes.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

A similar percentage of females and males experienced AEs (55% and 48%, respectively). A higher percentage of females experienced dizziness, infection, pain, cough increased, sinusitis, and asthenia (8%, 6%, 6%, 6%, 5%, and 4%, respectively) compared to males (2%, 3%, 3%, 0%, 2%, and 2%, respectively). Conversely, a higher percentage of males experienced abdominal pain and flu syndrome (12% and 6%, respectively) compared to females (6% and 1%, respectively). Table 29 demonstrates the most frequent AEs by gender in both adolescent GERD studies

Table 29: Most frequently experienced AEs by gender

Body System/ COSTART Term	n (%) Females (N=84)	Males (N=66)
Any Event	46 (55%)	32 (48%)
Body as a Whole		
Headache	9 (11%)	10 (15%)
Abdominal Pain	5 (6%)	8 (12%)
Infection	5 (6%)	2 (3%)
Pain	5 (6%)	2 (3%)
Accidental Injury	4 (5%)	2 (3%)
Asthenia	3 (4%)	1 (2%)
Fever	2 (2%)	1 (2%)
Flu Syndrome	1 (1%)	4 (6%)
Digestive System		
Diarrhea	6 (7%)	3 (5%)
Nausea	4 (5%)	3 (5%)
Vomiting	4 (5%)	5 (8%)
Nervous System		
Dizziness	7 (8%)	1 (2%)
Respiratory System		
Pharyngitis	6 (7%)	7 (11%)
Cough Increased	5 (6%)	0 (0%)
Sinusitis	4 (5%)	1 (2%)
Dyspnea	2 (2%)	0 (0%)
Rhinitis	2 (2%)	1 (2%)
Skin and Appendages		
Rash	2 (2%)	0 (0%)
Urticaria	2 (2%)	1 (2%)
Vesiculobullous Rash	0	2 (3%)

Reference: Integrated Summary of Safety, Volume 9, Page 26, Table 3.2c

Medical Reviewer's Comments: There was little difference in the pattern of AEs experienced by females compared to males in the analysis of AEs by gender in the adolescent GERD studies.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

Evaluations of AEs by race and age were not prepared by the sponsor, since the overwhelming majority of patients (80.0%) were Caucasian and all were between 11 and 17 years of age.

C. Evaluation of Pediatric Program

In the United States, lansoprazole is approved for the treatment of GERD and EE in pediatric patients between the ages of 1 to 11 years old. The treatment of GERD and EE in pediatric patients between the ages of 12 to 17 years old, with lansoprazole is the subject of this sNDA.

The sponsor has not started pediatric studies in pediatric GERD patients less than one year of age. Prior to initiation of these studies, the sponsor will need to develop an age-appropriate lansoprazole formulation and will need to perform a 4-week repeated dose toxicity study in neonatal rats and a 90-day repeated dose toxicity study in neonatal dogs.

D. Comments on Data Available or Needed in Other Populations

The sponsor has not started pediatric studies in pediatric GERD patients less than one year of age. Prior to initiation of these studies, the sponsor will need to develop an age-appropriate lansoprazole formulation and will need to perform a 4-week repeated dose toxicity study in neonatal rats and a 90-day repeated dose toxicity study in neonatal dogs.

X. Conclusions and Recommendations

A. Conclusions

Lansoprazole has a favorable benefit/risk profile in the treatment of GERD (non-erosive GERD and EE) in pediatric patients between 12 and 17 years old (adolescents). The safety and efficacy of prevacid® (lansoprazole) delayed-release capsules in the treatment of non-erosive GERD and EE are based on adequate and well-controlled trials in adult GERD patients and additional safety, efficacy, pharmacokinetic, and pharmacodynamic studies performed in pediatric GERD patients between 12 and 17 years old.

The safety and efficacy of prevacid® (lansoprazole) delayed-release oral suspension and prevacid® (lansoprazole) delayed-release orally disintegrating tablets for these indications in adolescents are based on adult PK and PD studies that demonstrated bioequivalence of these oral formulations to the delayed release capsules.

In the clinical trials presented in this efficacy supplement, lansoprazole administration decreased the frequency and severity of GERD symptoms in adolescents with GERD (the co-primary endpoints) and achieved complete healing of EE in over 95% of the pediatric adolescent EE patients. Furthermore, lansoprazole demonstrated an acceptable safety profile in these studies.

Studies M00-158 and M97-640 satisfy Studies Three and Four, respectively, of the Lansoprazole Pediatric Written Request issued by the Division of Gastrointestinal and Coagulation Drug Products.

B. Recommendations

From a clinical perspective, this medical officer recommends that this sNDA is approvable pending labeling changes. If the sponsor accepts the labeling changes, then this medical officer recommends approval of prevacid® (lansoprazole) delayed-release capsules, prevacid® (lansoprazole) delayed-release oral suspension, and prevacid® (lansoprazole) delayed-release orally disintegrating tablets (solutab) for the treatment of GERD (non-erosive GERD and EE) in pediatric patients between 12 and 17 years old. Please see my labeling recommendations in the Appendix.

Since the pharmacokinetics of lansoprazole are similar in pediatric adolescent GERD patients and healthy adult subjects; similar precautions should be taken when theophylline, digoxin, phenobarbital, carbamazepine, and/or phenytoin are given concomitantly with lansoprazole in adolescent patients.

4 Page(s) Withheld

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

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Medical- 21-428
S004

Table 30: List of abbreviations

AEs	adverse drug events
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC_{0-24}	area under the plasma concentration-time curve
BID	two times a day
BMI	body mass index
C_{max}	maximum observed plasma concentration
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CYP	cytochrome
ECL	enterochromaffin-like
EE	erosive esophagitis
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GERD	gastroesophageal reflux disease
H. pylori	*Helicobacter pylori*
H_2RAs	histamine-2 receptor antagonists
ICH	International Conference on Harmonisation
ISS	Integrated Summary of Safety
LPWR	Lansoprazole Pediatric Written Request
mg	milligram
mL	milliliter
NDTI	National Disease and Therapeutic Index
ng	nanogram
NSAID	non-steroidal anti-inflammatory drugs
PD	pharmacodynamic
pg/mL	picograms per milliliter
PK	pharmacokinetic
PPC	patients, their parents, or their caregivers
PPI	proton pump inhibitor
PPSR	Proposed Pediatric Study Request
q d	once daily
SAE	serious adverse event
sGERD	symptomatic GERD
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
TAP	TAP Pharmaceutical Products Inc. (the sponsor)
The Division	Division of Gastrointestinal and Coagulation Drug Products
T_{max},	time to reach the observed maximum plasma concentration
UGI	upper gastrointestinal
WR	written request

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/s/

Eric Brodsky
6/15/04 10:15:08 AM
MEDICAL OFFICER

Ruyi He
6/15/04 11:14:39 AM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-428/S-004

CLINICAL PHARMACOLOGY/ BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Review

NDA: **20-406 / SE5-057**
21-281 / SE8-014
21-428 / SE8-004

Generic Name: Prevacid® Delayed-Release Capsule

Sponsor: Tap Pharmaceutical Products Inc.

Reviewer: Suliman I. Al-Fayoumi, Ph.D.

Type of Submission: Efficacy Supplement for Pediatric Labeling

Proposed Indication: Short term treatment of symptomatic GERD (non-erosive GERD and erosive esophagitis)

Submission Date: 12/23/03

ORM Division: GI & Coagulation Drug Products

OCPB Division: DPE II

Team Leader: Suresh Doddapaneni, Ph.D.

Proposed Dosage Regimen: 15 QD for up to 8 weeks for treatment of non-erosive GERD
30 mg QD for up to 8 weeks for treatment of erosive esophagitis

I. Executive Summary

Lansoprazole (Prevacid® Delayed-Release Capsule), a proton pump inhibitor, was approved for marketing in the US on 5/10/95. It is currently indicated for the treatment and maintenance therapy of a variety of acid-related GI conditions. The recommended adult dosage is 15-30 mg QD for up to 8 weeks.

To obtain needed pediatric information on lansoprazole, the Agency issued a formal Pediatric Written Request (PWR) for Prevacid® (lansoprazole) Delayed-Release Capsules on 8/26/98. The Agency requested in the PWR that the sponsor conduct single and multiple dose pharmacokinetic/pharmacodynamic (PK/PD) studies along with clinical outcome and safety evaluation in pediatric patients aged 0-12 months. In addition, the sponsor was to conduct studies to evaluate PK/PD and clinical outcomes in pediatric patients aged 1-11 years and 12-17 years corresponding to studies 3 and 4, respectively, of the PWR for Prevacid®

Based on submitted PK/PD and clinical safety and efficacy data, the sponsor recently gained approval for the use of Prevacid® in pediatric patients 1-11 years of age (see approval letter for NDA 20-406/SE5-047, dated 7/31/02).

The current submission is provided in support of the use of lansoprazole in pediatric GERD patients aged 12-17 years. The submission consists of two studies; study **M97-640** (a PK/PD study in adolescent GERD patients) and study **M00-158** (an 8-12 week open label safety and efficacy study).

The findings of study M97-640 indicate that Administration of 15 and 30 mg QD doses of lansoprazole results in similar values of the mean PK parameters (AUC and C_{max}) for the pediatric GERD patients aged 12-17 years relative to healthy adult subjects. In addition, statistically significant increases in the values of the mean PD parameters (24-hr mean intragastric pH, % time pH > 3 & 4) are observed following 5 days of dosing relative to day 1.

The submitted studies are provided in partial fulfillment of the Agency's PWR for lansoprazole. Additional studies are currently being conducted by the sponsor in fulfillment of the remainder of the PWR.

A. Recommendations

From the view point of Office of Clinical Pharmacology and Biopharmaceutics, NDA 21-406 / S-057 is **acceptable** provided that a satisfactory agreement is reached between the Agency and the sponsor with respect to proposed language in the package insert. See Appendix 1 for the Agency proposed package insert.

The sponsor has adequately fulfilled the requirement for a study in pediatric GERD patients aged 12-17 years corresponding to study 3 in the Pediatric Written Request (PWR) for Prevacid®.

B. Phase IV Commitments

None.

II. Table of Contents

C. Summary of CPB Findings

NDA 20-406/S-057 consists of two studies; study **M00-158** (an 8-12 week open label safety and efficacy study), and study **M97-640** (a PK/PD study in adolescent GERD patients).

The current review solely addresses the Clinical Pharmacology and Biopharmaceutics-related results in the submission (i.e., study M97-640 which corresponds to study 3 of the PWR).

In study M97-640, the PK and PD profiles of lansoprazole in pediatric GERD patients aged 12-17 years were evaluated following administration of 15 or 30 mg capsules of Prevacid for a period of 5 days.

Administration of 15 and 30 mg doses of Prevacid resulted in similar mean AUC and C_{max} values for the pediatric GERD patients aged 12-17 years relative to healthy adult subjects. When compared on PD data (mean 24-hr intragastric pH and % time pH > 3, 4, 5 & 6), the higher lansoprazole dose (30 mg) resulted in similar changes in the PD parameters relative to the lower dose (15 mg). In addition, statistically significant increases in mean 24-hr intragastric pH and % time pH > 3 & 4 were observed on day 5 relative to day 1.

II. Question-Based Review

A. General Attributes

Lansoprazole is a substituted benzimidazole that inhibits gastric acid secretion via specific inhibition of H^+/K^+ ATPase enzyme system at the secretory surface of the gastric parietal cell.

Lansoprazole is currently approved for use in adults and pediatric patients aged 1 to 11 years. The approved indications for adults in the U.S. include the short-term treatment of symptomatic gastroesophageal reflux disease (GERD) (15 mg once daily up to 8 weeks), the short-term treatment of erosive esophagitis (30 mg QD up to 8 weeks) and the long-term maintenance treatment of healed erosive esophagitis.

B. General Clinical Pharmacology

1. Are pediatric GERD patients aged 12-17 years and adults comparable on their PK/PD profiles?

Study M97-640 evaluated the PK and PD aspects of lansoprazole Capsule 15 and 30 mg in pediatric GERD patients aged 12-17 years. Sixty male and female pediatric GERD patients aged 12-17 years received 15 or 30 mg QD doses of Prevacid Delayed-Release Capsules for 5 consecutive days. The study was conducted in a randomized, open label, double-blind multi-center fashion. Blood samples were drawn for determination of lansoprazole PK up to 12 hrs post-dose on day 5, while 24-hr intragastric pH monitoring was conducted on days 1 and 5 of each treatment group.

Table 1. Summary of the mean PK parameters for Lansoprazole, 15 mg and 30 mg QD on day 5 (n = 59)

Pharmacokinetic Parameter (unit)	N	Lansoprazole 15 mg QD	N	Lansoprazole 30 mg QD	N	Healthy Adult Subjects[a]
T_{max} (h)	30	1.6 ± 0.7	29	1.7 ± 0.7	345	1.7 ± 0.8
C_{max}[b] (ng/mL)	30	414.8 ± 215.5	29	1005 ± 604.9	515	824 ± 419
Dose-normalized C_{max} (ng/mL/mg)	30	27.7 ± 14.4	29	33.5 ± 20.2	515	27.5 ± 14.0
AUC[b] (ng•h/mL)	30	1017 ± 1737	29	2490 ± 2522	513	2133 ± 1797
Dose-normalized AUC (ng•h/mL/mg)	30	67.8 ± 115.8	29	83.0 ± 84.1	513	71.1 ± 59.9
$t_{1/2}$[c] (h)	30	0.84 ± 0.26	29	0.95 ± 0.31	285	1.19 ± 0.52

SD = Standard Deviation

a Data obtained from Abbott-65006 Drug Metabolism Report No. 32 – Overview and summary of the human pharmacokinetics and biopharmaceutics of lansoprazole[30].

b For healthy adult subjects normalized to a 30 mg dose.

c Harmonic mean ± pseudo-standard deviation.

Table 1. Summary of the primary PD parameters for lansoprazole in pediatric GERD patients aged 12-17 years and healthy adult subjects.

Lansoprazole Dose	Day	Mean 24-hour Intragastric pH	% of time pH >3	% of time pH >4
Adolescents with GERD (M97-640)				
15 mg QD (N=10)	Baseline	2.7	27	20
	Day 5	3.8	59	47
30 mg QD (N=9)	Baseline	2.8	29	20
	Day 5	3.9	60	49
Adults Aged ≥18 years				
15 mg QD[a]	Baseline	2.1	18	12
	Day 5	4.0	59	49
30 mg QD[a]	Baseline	2.1	18	12
	Day 5	4.9	72	66

Administration of 15 and 30 mg doses of lansoprazole resulted in similar values of the mean PK parameters (AUC and C_{max}) for the pediatric GERD patients aged 12-17 years relative to healthy adult subjects (Table 1).

When compared on PD data (mean 24-hr intragastric pH and % time pH > 3, 4, 5 & 6), both 15 mg and 30 mg doses resulted in similar changes in the PD parameters (Table 2). In addition, the PD data following administration of the 15 mg QD dose of lansoprazole seemed to be comparable between adolescent GERD patients and adults. As for the 30 mg dose of lansoprazole, values of the primary PD parameters appeared to be higher in adults relative to adolescent GERD patients.

Overall, the PK/PD data for Prevacid Delayed-Release Capsule in pediatric GERD patients aged 12-17 years indicate that the 15 mg and 30 mg QD doses of Prevacid are similar on their acid inhibitory effects in this age group. Based on the fact that PK was similar in adolescents and adults and 15 mg QD and 30 QD doses were found to be safe, in the safety and efficacy study M00-158, adolescent patients were dosed with 15 mg QD or 30 mg QD based on whether they had non-erosive GERD or erosive esophagitis (similar to adult dosing), respectively. In an uncontrolled, open-label, U.S. multicenter clinical study (study M00-158) involving 87 adolescent patients (12 to 17 years of age) with symptomatic GERD, both the 15 and 30 mg QD regimens were shown to be efficacious up to 8 to 12 weeks of treatment.

E. General Biopharmaceutics

None

F. Analytical Section

Plasma concentrations of lansoprazole were determined using a validated LC/MS/MS assay method over a range of 5 to 1200 ng/mL. The lower limit of quantitation was established at —

III. Appendices

A. Proposed Package Insert (original and Agency proposed)

B. Individual Study Review

C. Cover Sheet and OCPB Filing/Review Form

Appendix A

Proposed Package Insert

34 Page(s) Withheld

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

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Clin Pharm/Bio- 21-428 S004

Appendix B

Individual Study Reviews

NDA: 20-406/ S-057 - Study M97-640 Study Date: Mar 1998-Feb 1999

Type of Study: PK/PD Study in Adolescent GERD Patients

Study **M97-640** is entitled,

"A Study to Evaluate the Effects of Lansoprazole 15 mg and 30 mg in Pediatric Patients with Esophagitis"

Primary Objective(s)

- To assess the safety, PK & PD of QD administration of lansoprazole in pediatric patients aged 12 to 17 with symptomatic GERD.

Study Design

Open-label, randomized, double-blind multi-center study

Subjects	60 pediatric patients
Key Inclusion Criteria	Male and female pediatric patients aged 12-17 yrs Had symptomatic, endoscopically and/or histologically proven GERD
Treatment	Patients were randomly assigned to receive one of two treatments: lansoprazole 15 mg OR lansoprazole 30 mg for a 5-day period.
PK/PD Sampling Times	For determination of lansoprazole plasma concentrations on day 5, blood samples were collected at the following time points: 0 (pre-dose), 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10 and 12 hrs post-dose. For assessment of esophageal & gastric pH, a dual channel pH probe was placed nasogastrically and 24-hr pH measurements were continuously determined at baseline and during day 5 on treatment.

Pharmacokinetic/Pharmacodynamic Analysis

The following PK parameters were determined: AUC_{0-24}, C_{max}, t_{max}, $t_{1/2}$, CL/f & V_d/f. In addition, the following PD parameters were determined: mean 24-hr intragastric pH & % time pH > 3, 4, 5 & 6.

Results and Discussion

Table 1. Summary of the mean PK parameters for Lansoprazole, 15 mg and 30 mg QD on day 5 (n = 59)

Pharmacokinetic Parameter (unit)	N	Lansoprazole 15 mg QD	N	Lansoprazole 30 mg QD	N	Healthy Adult Subjects[a]
T_{max} (h)	30	1.6 ± 0.7	29	1.7 ± 0.7	345	4.7 ± 0.8
C_{max}[b] (ng/mL)	30	414.8 ± 215.5	29	1005 ± 604.9	515	824 ± 419
Dose-normalized C_{max} (ng/mL/mg)	30	27.7 ± 14.4	29	33.5 ± 20.2	515	27.5 ± 14.0
AUC[b] (ng•h/mL)	30	1017 ± 1737	29	2490 ± 2522	513	2133 ± 1797
Dose-normalized AUC (ng•h/mL/mg)	30	67.8 ± 115.8	29	83.0 ± 84.1	513	71.1 ± 59.9
$t_{1/2}$[c] (h)	30	0.84 ± 0.26	29	0.95 ± 0.31	285	1.19 ± 0.52

SD = Standard Deviation
a Data obtained from Abbott-65006 Drug Metabolism Report No. 32 – Overview and summary of the human pharmacokinetics and biopharmaceutics of lansoprazole[10].
b For healthy adult subjects normalized to a 30 mg dose.
c Harmonic mean ± pseudo-standard deviation.

Table 2. Summary of the mean PD parameters for Lansoprazole, 15 and 30 mg QD on day 5 and at baseline (n = 59)

	15 mg QD Lansoprazole (Mean ± SD)	
Variable Analyzed	Baseline (N=10)	Day 5 Visit (N=10)
24-hour Intragastric pH	2.71 ± 1.37	3.84 ± 1.34*
% of time pH >3	26.72 ± 28.40	58.92 ± 28.95*
% of time pH >4	19.99 ± 28.88	46.92 ± 30.92*
% of time pH >5	15.15 ± 29.42	31.97 ± 33.25
% of time pH >6	9.80 ± 24.61	13.96 ± 20.10
	30 mg QD Lansoprazole (Mean ± SD)	
Variable Analyzed	**Baseline (N=9)**	**Day 5 Visit (N=9)**
24-hour Intragastric pH	2.81 ± 1.56	3.89 ± 1.27*
% of time pH >3	29.11 ± 29.92	59.62 ± 27.61*
% of time pH >4	20.41 ± 30.64	48.91 ± 31.12*
% of time pH >5	15.08 ± 32.13	35.32 ± 32.36*
% of time pH >6	12.17 ± 31.51	13.96 ± 17.49

SD = Standard Deviation
* Statistically significantly different from the corresponding Baseline value ($p \leq 0.05$).

- Administration of 15 and 30 mg doses of lansoprazole resulted in similar mean PK parameters (AUC and C_{max}) for the pediatric GERD patients aged 12-17 years relative to healthy adult subjects (Table 1). In addition, AUC and C_{max} increased in a linear manner with dose from 15 mg to 30 mg. However, when compared on PD data (mean 24-hr intragastric pH and % time pH > 3, 4, 5 & 6), the higher lansoprazole dose (30 mg) resulted in similar changes in the PD parameters relative to the lower dose (15 mg) (Table 2).

- High inter-individual variability was observed with the mean PK parameter estimates (Table 1).
- Most of the measured PD parameters (mean 24-hr intragastric pH and % time pH > 3 & 4) on day 5 were statistically significantly increased when compared to baseline.
- The PD parameters for Lansoprazole in 12-17 year old pediatric GERD patients suggest that the 15 mg and 30 mg doses are similar on their acid inhibitory effects in this age group.

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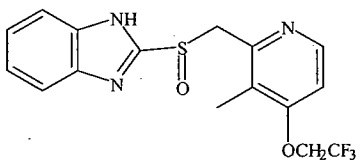
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-428/S-004

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW 1	1. Organization: HFD-180	2. NDA Number: 20-406, 21-281, 21-428
3. Name and Address of Applicant (City & State): TAP Pharmaceuticals 675 North Filed Drive Lake Forest, IL 60045		4. AF Number:
		Supplement(s)
6. Name of Drug: Prevacid, Delayed Release Capsules, Solutab-Delayed Release Orally Disintegrating Tablets, Delayed Release Oral Suspension	7. Nonproprietary Name: Lansoprazole	Number(s): 20406/SE5-057, 21281/SE8-014, 21428/SE8-004 / Date(s): December 19, 2003
8. Supplement Provides for: Efficacy supplement- for pediatric labeling provides for the safety and efficacy data in a new sub-population of pediatric patients 12-17 years of age.		9. Amendments and Other (Reports, etc.) Dates: None
10. Pharmacological Category: Proton Pump Inhibitors	11. How Dispensed: Rx	12. Related IND/NDA/DMF(s):
13. Dosage Form: Capsules	14. Potency: 15 mg &30 mg	
15. Chemical Name and Structure:  2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl] methyl] sulfinyl] benzimidazole		16. Records and Reports:

17. Comments: See Review Notes.
HFD-180/Div File
HFD-181/CSO/mfurness
HFD-180/rjustice
HFD-180/rraghavachari
R/D init by:lzhou

18. Conclusions and Recommendations: *Based on the CMC point of view these supplements may be approvable pending review of the requested dissolution data. (Please see Conclusions and Recommendations in the review notes).*

19. Reviewer

Name:	Signature	Date Completed:
Ramesh Raghavachari		March 25, 2004

5 Page(s) Withheld

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

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry-21-928
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Liang Zhou
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CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-428/S-004

STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS
DIVISION OF BIOMETRICS II

STATISTICAL REVIEW AND EVALUATION
Clinical Studies

NDA:	21281/SE8-014, 21428/SE8-004, 20406/SE5-057
Name of drug:	Prevacid (lansoprazole) for Delayed-Release Oral Suspension
Applicant:	Tap Pharmaceutical Products Inc.
Indication:	Lansoprazole is intended for use in the treatment of GERD in children 12 to 17 years of age.
Project manager:	Ms. Melissa Furness
Clinical reviewer:	Eric Brodsky, MD.
Dates:	Received 12/19/03; user fee 6/23/04.
Statistical reviewer:	Wen-Jen Chen, Ph.D.
Statistics team leader:	Stella Grosser, Ph.D.
Biometrics division director:	Edward Nevius, Ph.D.

Keywords: NDA review, clinical studies, pediatric exclusivity.

TABLE OF CONTENTS

1.0 EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 CONCLUSIONS AND RECOMMENDATIONS

- ✓ Based on the sponsor's and this reviewer's analyses through the sponsor's study data, the efficacy of lansoprazole, assessed from the statistical perspective, is supported for the use in the treatment of GERD in children of ages 12 to 17 years old.
- ✓ If from the clinical perspective, the concern for not recruiting sufficient patients with severe esophagitis and GERD symptoms is not critical for the use of the drug in the pediatric population, then the efficacy of lansoprazole, assessed from the statistical perspective based upon the sponsor's study data, is supported for the use in the treatment of GERD in children of ages 12 to 17 years old.

1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

In this NDA pediatric supplement (SNDA) submission, two studies, Study M00-158 and Study M97-640, were submitted to support the use of lansoprazole in the treatment of GERD in children with ages 12 to 17.

Study M00-158 was an open-label study in adolescents with GERD, ages 12 to 17 years at 20 investigative sites. The study comprised two periods: a 7 to 14 day pre-treatment and an 8 to 12 week treatment periods. According to disease status (non-erosive GERD or erosive esophgitis), of the 87 enrolled children, 64 with non-erosive GERD were assigned to receive lansoprazole 15mg QD dose for 8 weeks and 23 with erosive esophagitis were assigned to receive lansoprazole 30mg QD dose for 8 to 12 weeks to assess efficacy and safety of lansoprazole. The primary efficacy endpoint was the change in frequency and severity (grading scale: none, mild, moderate, severe, and very severe) of GERD symptoms based on subject diary data from the pretreatment period to the Week 8 treatment period.

Study M97-640 was a randomized, double blind study conducted in the United States with ten sites enrolled 63 children. Of theses, 32 were randomized to receive lansoprazole 15mg QD dose and 31 subjects were randomized to receive lansoprazole 30mg QD dose for 5 days. Efficacy variables included symptom relief based on investigator interview and the percentage of days/nights with heartburn or other predominant symptom, severity of the heartburn or other predominant symptom, and Gelusil use recorded on subject diaries.

In addition, the objective of Study M00-158 was designed to assess the safety and efficacy of lansoprazole in adolescents, ages 12 to 17 years, with GERD while that of Study M97-640 was to assess the safety, pharmacokinetics, and pharmacodynamics of lansoprazole in pediatrics patients. Consequently, to evaluate the clinical efficacy of lansoprazole in adolescents subjects (ages 12 to 17 years) with GERD, in this review, Study M00-158 is considered as a pivotal study while Study M97-640 is a supportive study.

1.3 STATISTICAL ISSUES AND FINDINGS

1.3.1 Pivotal Study M00-158

The applicant found that for all subjects (87), non-erosive GERD subjects (64), and erosive esophagitis subjects (23), statistically significant ($p < 0.001$) reductions from the pretreatment period to the Final Visit Period were observed in the percentage of days the subjects had GERD symptoms, and the average daily severity of GERD symptoms. This reviewer's analyses did not contradict these results. However, there were the following issues:

- ✓ It is noted that less than 30% (26%; 23/87) of enrolled subjects had erosive esophagitis at baseline and only 3.4% (3/87) of subjects had esophagitis grade greater than 2. Therefore, due to lack of sufficient more severe esophagitis subjects enrolled, the efficacy of lansoprazole is not clear for the use in the treatment of more severe esophagitis disease in children of ages 12 to 17 years old.
- ✓ Similarly, most of the enrolled patients (90%; 78/87) were not with the severe GERD symptoms. Due to lack of sufficient subjects enrolled with severe GERD symptoms, the study did not provide sufficient evidence to demonstrate the efficacy of lansoprazole to treat children with more severe GERRD symptoms.

1.3.2 Supportive Study M97-640

Due to the following facts, the sponsor's efficacy analysis on the GERD symptoms assessed by investigators and patient diary data did not demonstrate significant evidence to support the efficacy of lansoprazole in the use of treatment of GERD in children of ages 12 to 17:

- ✓ Instead of assessing the drug efficacy, the objectives of this 5-day study were to evaluate the safety, pharmacokinetics, and pharmacodynamics of once daily (QD) administration of lansoprazole 15 mg or 30 mg in pediatric subjects, ages 12 to 17 with symptomatic GERD.
- ✓ Of 20 types of GERD symptoms assessed by the investigators, at 5% significance level, only 5 and 2 of them respectively for lansoprazole 15 mg and 30 mg showed significantly improved from baseline to Final Visit. In addition, the percentages of enrolled subjects with severe symptoms at baseline were small (less than 17%).
- ✓ Although the enrolled subjects underwent endoscopy exam during Screening Visit, due to short study time period (5-day study), the results of endoscopy analyses at end of the study may not provide meaningful information.

2.0 INTRODUCTION

2.1 OVERVIEW

In Volume 1 of this NDA submission, the sponsor made the following observations with regard to lansoprazole:

Lansoprazole is a compound of the substituted benzimidazole class which inhibits gastric acid secretion. Some lansoprazole-approved indications for adults in the United States include the short-term treatment of symptomatic, non-erosive gastroesophageal reflux disease (GERD), the short-term treatment of erosive esophagitis, and the long-term maintenance treatment of erosive esophagitis.

Lansoprazole, when administered orally to adults, is well absorbed with a reported absolute bioavailability of approximately 80% and a Tmax of less than 2 hours. The terminal elimination half-life is approximately 1.2 hours with no accumulation during multiple, once daily dosing. Lansoprazole is metabolized extensively in the liver, by CYP3A4 to the sulfone metabolite and by CYP2C19 to the hydroxylated sulfinyl metabolite. In addition, TAP has conducted 2 studies (Study M97-640 and M97-808) using lansoprazole in a pediatric population. Both studies showed that the pharmacokinetics of lansoprazole in the adolescents was similar to that previously observed in healthy adult subjects.

In this NDA pediatric supplement (SNDA) submission, two studies, Study M00-158 and Study M97-640, were submitted to support the use of lansoprazole in the treatment of GERD in children with ages 12 to 17.

Study M00-158 was an open-label study in adolescents with GERD, ages 12 to 17 years at 20 investigative sites. The study comprised two periods: a 7 to 14 day pre-treatment and an 8 to 12 week treatment periods. According to disease status (non-erosive GERD or erosive esophgitis), of the 87 enrolled children, 64 with non-erosive GERD were assigned to receive lansoprazole 15mg QD dose for 8 weeks and 23 with erosive esophagitis were assigned to receive lansoprazole 30mg QD dose for 8 to 12 weeks to assess efficacy and safety of lansoprazole. The primary efficacy endpoint was the change in frequency and severity (grading scale: none, mild, moderate, severe, and very severe) of GERD symptoms based on subject diary data from the pretreatment period to the Week 8 treatment period.

Study M97-640 was a randomized, double blind study conducted in the United States with ten sites enrolled 63 children. Of theses, 32 were randomized to receive lansoprazole 15mg QD dose and 31 subjects were randomized to receive lansoprazole 30mg QD dose for 5 days. Efficacy variables included symptom relief based on investigator interview and the percentage of days/nights with heartburn or other predominant symptom, severity of the heartburn or other predominant symptom, and Gelusil use recorded on subject diaries.

In addition, the objective of Study M00-158 was designed to assess the safety and efficacy of lansoprazole in adolescents, ages 12 to 17 years, with GERD while that of Study M97-640 was to assess the safety, pharmacokinetics, and pharmacodynamics of lansoprazole in pediatrics patients. Consequently, to evaluate the clinical efficacy of lansoprazole in adolescent subjects (ages 12 to 17 years) with GERD, in this review, Study M00-158 is considered as a pivotal study while Study M97-640 is a supportive study.

2.2 DATA SOURCES

To assess the clinical efficacy of lansoprazole in adolescent patients (ages 12 to 17) with GERD, this reviewer reviewed NDA Volumes 1 to 19, dated December 19, 2003. Data used by this

reviewer's statistical analysis was submitted by the sponsor on February 24, 2004, located at "\\Cdsesub1\n20406\S_057\2004-24-04\crt\datasets\".

3.0 STATISTICAL EVALUATION

3.1 EVALUATION OF EFFICACY

3.1.1 Study M00-158

Study Design and Endpoints

This open-label study was designed to assess the safety and efficacy of once daily administration of lansoprazole 15 mg and 30 mg in adolescents, ages 12 to 17 years, with GERD including non-erosive GERD and erosive esophagitis.

Eighty subjects were planed to be enrolled in the study. Of the 80 subjects, a minimum of 20 subjects respectively with non-erosive GERD (assigned to Treatment Group I defined below) and erosive esophagitis (Treatment Group II) were to be enrolled. The remaining subjects were to be enrolled in the appropriate treatment group based on endoscopic findings. The study comprised two periods: a 7 to 14 day pre-treatment and an 8 to 12 week treatment periods. During the pretreatment period, a pretreatment diary and antacid were dispensed; subjects/parents/caregivers, as necessary, were to record the severity of their GERD symptoms and the frequency of antacid use in the diary. Symptoms also were assessed by investigator interview. In addition, all subjects had endoscopies during the pretreatment period. Subjects with erosive esophagitis (esophagitis Grade ≥2 per TAP Grading Scale) at the Pretreatment Visit had follow-up endoscopies at the Week 8 Visit. Subjects with unhealed erosive esophagitis at the Week 8 Visit were treated for an additional 4 weeks with endoscopies repeated at Week 12 Visit.

Subjects who had completed all pretreatment procedures and met all eligibility requirements were assigned to one of the following two treatment groups based upon the disease status (non-erosive GERD or erosive esophagitis):

- Treatment group I - subjects with non-erosive GERD at the pretreatment visit (esophagitis Grade ≤ 1 per TAP grading scale) were to be treated with lansoprazole 15 mg, administered orally, once daily for 8 weeks.
- Treatment group II - subjects with erosive esophagitis at the pretreatment visit (esophagitis Grade ≥2 per TAP grading scale) were to be treated with lansoprazole 30 mg, administered orally, once daily for 8 weeks. In addition, subjects with unhealed erosive esophagitis at the Week 8 Visit were to be treated for another 4 weeks.

Antacid was provided during the treatment period for relief of discomfort as needed. Throughout the treatment period, subjects maintained a daily diary, in which they recorded severity of GERD symptom(s), the frequency and amount of antacid usage, and study drug dosing. In addition, at Weeks 4, 8, and 12 (if applicable), the subject answered a questionnaire regarding overall GERD

symptom relief during the preceding week as compared with before treatment. At the Week 4, 8, and 12 Visits, the following procedures were completed: a physical examination, adverse event assessment, concomitant medication assessment, laboratory evaluations, and overall GERD symptom assessment based on investigator interview.

All efficacy analyses were carried out using intent-to-treat population comprising subjects who received at least one dose of study drug and had efficacy measurements within the defined evaluated time period. Data from all subjects who entered the treatment period and received at least one dose of study drug were included in the safety analyses.

The sponsor indicated that due to few subjects expected to have treatment beyond Week 8, efficacy analyses at Week 12 (for subjects whose treatment was extended) per protocol for diary and investigator interview symptom assessment were not carried out.

The primary efficacy endpoint was the change in frequency and severity (grading scale: none, mild, moderate, severe, and very severe) of GERD symptoms based on subject diary data from the pretreatment period to the Week 8 treatment period. The percentage (frequency) of days with GERD symptoms and the average GERD symptom severity score based on 0 for none, 1 for mild, 2 for moderate, 3 for severe, and 4 for very severe was calculated by treatment group during the pretreatment period and during the first 8 weeks of treatment using diary data recorded on or prior to Day 1 and Days 2-57, respectively.

The secondary efficacy endpoints were 1) the percentage of subjects with pretreatment endoscopically-proven erosive esophagitis who had complete healing; 2) the change in antacid use from the pretreatment period to the Week 4, Week 8, and Final Visit Periods based on subject diary data; 3) the change in frequency and severity of GERD symptoms from the pretreatment period to during the first 4-week treatment period and over the entire treatment period based on subject diary; 4) and the change from the pretreatment period to the Week 4, Week 8, and Final Visits in overall GERD symptom severity (grading scale: none, mild, moderate, and severe) based on investigator interview.

For the sample size determination, 80 adolescents, aged 12 to 17 years, were to be enrolled in this study (approximately 6 subjects per investigative site). The sponsor indicated that given this sample size, if the incidence rate for an adverse event was 10%, the probability of observing an adverse event in four or more subjects is 0.96.

Statistical Methodologies

The change from the pretreatment period to each evaluated time interval during the treatment period in the frequency and severity of GERD symptoms and the change in antacid use based on subject diary data were analyzed using the sign test. The change from the pretreatment period to each evaluated time point in overall GERD symptom severity based on investigator interview was also analyzed using the sign test.

In addition, the percentage of subjects with pretreatment endoscopically-proven erosive esophagitis who had complete healing was tabulated.

Patient Disposition

Table 3.1.1.1 presents the number of subjects planned and analyzed by treatment group.

Table 3.1.1.1 (Sponsor's) Number of subjects planed and analyzed by treatment group

	All Lansoprazole-Treated Subjects	Lansoprazole 15 mg QD	Lansoprazole 30 mg QD
Number of subjects planned	80	Minimum 20	Minimum 20
Number of subjects enrolled	87	64	23
Number of subjects received study drug (analyzed)	87	64	23

Table 3.1.1.1 indicates that eighty-seven adolescent subjects were enrolled in the study and treated with lansoprazole. Subjects were assigned to receive either lansoprazole 15 mg or 30 mg based on the results of their pretreatment endoscopies. Sixty-four subjects with non-erosive GERD (esophagitis Grade $\leq$1 per TAP grading scale) were assigned to receive lansoprazole 15 mg and 23 subjects with erosive esophagitis (esophagitis Grade $\geq$ 2 per TAP grading scale) were assigned to receive lansoprazole 30 mg.

In addition, five subjects in the lansoprazole 15 mg treatment group were prematurely discontinued from the study: 3 for symptomatic therapeutic failure, 1 due to an adverse event, and 1 for poor compliance. No subjects were prematurely discontinued from the lansoprazole 30 mg treatment group.

Demographics and Baseline Characteristics

All subjects enrolled were considered by the investigators to have symptomatic GERD (including erosive and nonerosive esophagitis subjects). Table 3.1.1.2 (extracted from Table 11.2a at page 63 of the sponsor's electric submission for Clinical/Statistical Study Report) presents the demographic information for all lansoprazole-treated subjects, and separately, for lansoprazole 15 mg and 30 mg dose groups.

Table 3.1.1.2 (Sponsor's) Baseline Subject Demographics

Demographic Characteristic	All Subjects	Non-erosive GERD Lansoprazole 15 mg QD	Erosive Esophagitis Lansoprazole 30 mg QD
Gender			
N	87	64	23
Female	60.9% (53)	64.1% (41)	52.2% (12)
Male	39.1% (34)	35.9% (23)	47.8% (11)
Race			
N	87	64	23
Caucasian	80.5% (70)	79.7% (51)	82.6% (19)
Black	16.1% (14)	15.6% (10)	17.4% (4)
Other[a]	3.4% (3)	4.7% (3)	0
***H. pylori* Status[b]**			
N	86	63	23
Positive	3.5% (3)	1.6% (1)	8.7% (2)
Negative	96.5% (83)	98.4% (62)	91.3% (21)
Age (years)			
N	87	64	23
Mean (SD)	14.1 (1.6)	14.1 (1.7)	14.3 (1.3)
Range	11-17[c]	11-17[c]	13-17
Weight - Females (pounds)			
N	53	41	12
Mean (SD)	135.4 (31.3)	135.6 (32.3)	134.6 (28.9)
Range	74-222	74-222	100-198
Weight - Males (pounds)			
N	34	23	11
Mean (SD)	139.7 (49.4)	132.0 (46.8)	155.7 (52.9)
Range	65-290	65-225	86-290
Height - Females (inches)			
N	53	41	12
Mean (SD)	63.2 (2.5)	63.2 (2.7)	63.3 (2.0)
Range	57-69	57-69	60-66
Height - Males (inches)			
N	33	22	11
Mean (SD)	65.3 (4.8)	64.3 (5.1)	67.3 (3.6)
Range	54-73	54-73	62-72

Table 3.1.1.2 indicated that the except for gender and H.pylori status, the baseline demographics were comparable between the two treatment groups, lansoprazole 15 mg QD and lansoprazole 30 mg QD.

As for the baseline characteristics, of the 87 subjects, 30 had a history of GERD less than one year, 13 had a one- to two-year history of GERD, 28 had a history of GERD greater than two years and less than five years, and 16 had a history of GERD greater than five years.

The most frequently reported predominant GERD symptoms were heartburn, abdominal / stomach pain, epigastric pain, chest pain, regurgitation, sour taste, nausea, and vomiting. Some subjects reported more than one predominant symptom. In addition, fifty-three (61%) of the 87 subjects had received previous gastrointestinal therapy within 12 months prior to the study start and 18 of these had been treated previously with a PPI.

Sponsor's Efficacy Analysis Results and Conclusions

For symptom relief assessed using the subject diary, the Week 4 Period includes the time from Day 1 through the first 4-week treatment period; the Week 8 Period includes the time from Day 1 through the first 8-week treatment period; and the Final Visit Period includes the time from Day 1 through the entire treatment period (8 or 12 weeks). A summary of the analysis results on diary data is presented in Table 3.1.1.3 (extracted from the sponsor's Table 11.4a at page 68 of Volume 7).

Table 3.1.1.3 (Sponsor's) Diary results from the pretreatment period to Week 4, Week 8 and Final Visit [a]

	Pretreatment Period Median	Week 4 Period Median	Week 8 Period Median	Final Visit Period Median
All Subjects (N=87)				
GERD Symptioms				
% of Days with GERD Symptoms	88.9	42.9*	33.3*	33.3*
Average Daily Severity [b] of GERD Symtoms	1.6	0.6*	0.5*	0.5*
Antacid Use				
% of Days Used	54.5	7.1*	5.5*	5.5*
Average number of Teaspoons/Day	1.4	0.1*	0.2*	0.2*
Non-erosive GERD subjects (N=64) Lansoprazole 15 mg QD				
GERD Symptioms				
% of Days with GERD Symptoms	90.7	50.9*	43.1*	43.1*
Average Daily Severity [b] of GERD Symtoms	1.6	0.7*	0.6*	0.6*
Antacid Use				
% of Days Used	55.1	9.1*	7.3*	7.1*
Average number of Teaspoons/Day	1.3	0.3*	0.3*	0.3*
Erosive Esophagitis Subjects (N=23) Lansoprazole 30 mg QD				
GERD Symptioms				
% of Days with GERD Symptoms	84.6	18.5*	16.0*	15.7*
Average Daily Severity [b] of GERD Symtoms	1.9	0.3*	0.2*	0.2*
Antacid Use				
% of Days Used	50.0	0.0*	1.8*	1.7*
Average number of Teaspoons/Day	1.6	0.0*	0.1*	0.1*

a: Each subject's daily diary results were averaged over the evaluated time period and the median value for treatment group is reported in this table; b: Severity score as 0=none, 1=mild, 2=moderate, 3=severe, 4=very severe;

***: Statistically significant different from pretreatment at significance level of 0.001 using Sign rank tests.**

Table 3.1.1.3 indicates that for all subjects (87), non-erosive GERD subjects (64), and erosive esophagitis subjects (23), statistically significant ($p < 0.001$) reductions from the pretreatment period to the Week 4, Week 8, and Final Visit Periods were reported in the percentage of days the subjects had GERD symptoms, the average daily severity of GERD symptoms, the percentage of days antacid was used, and the average number of teaspoons of antacid taken per day

As for the relief of the overall GERD symptoms judged by the subjects at the Final Visit, Table 3.1.1.4 (extracted from the sponsor's Table 11.4b at page 71 of Volume 7) presents the results.

Table 3.1.1.4 (Sponsor's) Diary Results for Relief of Overall GERD Symptoms judged by the subjects at the Final Visit

Overall GERD Symptoms	All Subjects (N = 82)[a]	Non-erosive GERD Lansoprazole 15 mg QD (N=59)	Erosive Esophagitis Lansoprazole 30 mg QD (N=23)
	n (%)	n (%)	N (%)
Better	60 (73.2%) *	42 (71.2%) *	18 (78.3%) *
No change	19 (23.2%)	14 (23.7%)	5 (21.7%)
Worse	3 (3.7%)	3 (5.1%)	0

a: No data available for 5 subjects;
*** : Significant higher percentage on "better" declared at significance level of 0.001 using Sign tests.**

Table 3.1.1.4 shows that a statistically significantly ($p < 0.001$) higher percentage of subjects in all treatment categories (all subjects, lansoprazole 15 mg, and lansoprazole 30 mg) judged their overall GERD symptoms as "better" than the percentage judged as having "no change" or being "worse."

In addition, for the healing of erosive esophagitis, twenty-three subjects who had erosive esophagitis at the baseline endoscopy had follow-up endoscopies at the Final Visit (Week 8 or Week 12). One subject (No. 424) had his endoscopy for the Week 8 Visit and was not eligible for this analysis. However, his endoscopy did show healing (Grade 0) of esophagitis. Analysis of healing rates for the 22 eligible erosive esophagitis subjects is presented in Table 3.1.1.5.

Table 3.1.1.5 (Sponsor's) Analysis of Healing Rates for Erosive Esophagitis Subjects

Visit	Erosive Esophagitis Subjects	
	% Healed[a]	n/N
Week 8 Visit	95.5%	21/22
Week 12 Visit	0	0/1
Final Visit	95.5%	21/22

a: Defined as a return of the esophageal mucosa to Grade 0 or Grade 1.

Table 3.1.1.5 showed that of the twenty-two subjects, twenty-one were healed at the Week 8 Visit. One subject (No. 471) was unhealed at the Week 8 Visit and received an additional 4 weeks of treatment with lansoprazole 30 mg QD. His esophagitis (Grade 2) remained unchanged from Baseline at both the Week 8 and the Week 12 Visits.

Finally, for the overall GERD symptoms assessed by investigator interview, the sponsor indicated that the majority subjects experienced overall GERD symptoms resolved or improved from Baseline to the Final Visit. The difference between Baseline and Final Visit was statistically significant for the two treatment groups and for all subjects combined ($p < 0.001$). Actually, among all subjects, 63 (74%) of 85 who had Baseline symptoms were resolved or improved by the Final Visit based on investigator assessment of overall GERD symptoms. Of the 63 resolved or improved subjects, 41 (65%; 41/63) were non-erosive GERD subjects treated with lansoprazole 15 mg QD and 22 (100%; 22/22) were erosive esophagitis subjects treated with lansoprazole 30 mg QD. The sponsor further emphasized that results for all subjects were similar at the Week 4 and Week 8 assessments.

Reviewer's Analysis and Comments

In order to validate the sponsor's efficacy claim, this reviewer first, comments on the status of Baseline GERD disease for the enrolled subjects and then, performs the following two analyses 1) Exact test on overall GERD symptoms and 2) Subgroup analysis. Data used in this reviewer's analysis were submitted by the sponsor on Feb., 24, 2004. Subgroup analyses are reported in section 4 of review.

Reviewer's comments on Baseline GERD disease conditions

The Baseline esophagitis grades and Baseline GERD symptoms assessed by the investigator's interview are presented in Table 3.1.1.6 (extracted from sponsor's Table 11.2b in Volume 7) and Table 3.1.1.7 (extracted from sponsor's Table 11.2f in Volume 7), respectively, for all enrolled subjects.

Table 3.1.1.6 Esophagitis Grade at Baseline Endoscopy

		All Subjects (N = 87)
	Baseline Esophagitis Grade	**n (%)**
Non-erosive GERD		
	Grade 0	18 (20.7%)
	Grade 1	46 (52.9%)
Erosive Esophagitis		
	Grade 2	20 (23.0%)
	Grade 3	3 (3.4%)
	Grade 4	0

Table 3.1.1.7 (sponsor's) Baseline Overall GERD Symptoms Based on Investigator Assessment

	Severity of Overall GERD Symptoms				
	N	**None**	**Mild**	**Moderate**	**Severe**
All Subjects	87	1	16	61	9
Non-erosive GERD Subjects (Lansoprazole 15 mg QD)	64	0	15	45	4
Erosive Esophagitis Subjects (Lansoprazole 30 mg QD)	23	1	1	16	5

For esophagitis disease, Table 3.1.1.6 indicates that only 26% (23/87) of enrolled subjects had erosive esophagitis at baseline and only 3.4% (3/87) of subjects had esophagitis grade greater than 2. Therefore, due to lack of sufficient more severe esophagitis subjects enrolled, the efficacy of lansoprazole is not clear for the use in the treatment of more severe esophagitis disease in children of ages 12 to 17 years old.

Similarly, for overall GERD symptoms, Table 3.1.1.7 indicates that low percentages of enrolled subjects for the two treatment groups had severe baseline overall GERD symptom assessed by the investigator's interview (6% for lansoprazole 15 mg and 22% for lansoprazole 30 mg), showing most of the enrolled patients not with the severe GERD symptoms. As a result, due to lack of sufficient subjects enrolled with severe GERD symptoms, the study did not provide sufficient evidence to demonstrate the efficacy of lansoprazole to treat children with more severe GERRD symptoms.

Reviewer's analysis

i.) Exact test on overall GERD symptoms

For the analysis, this reviewer applied exact test to the improvements (better responses) on the overall GERD symptoms from baseline to the Final Visit using patient diary data from ITT population. The exact test is used for testing the null hypothesis (H_0) that the probability of improvements is not greater than .5. Table 3.1.1.8 presents the results by treatment group.

Table 3.1.1.8 (Reviewer's) Diary results of exact test for improvements on GERD symptoms at the Final Visit

TREATMENT GROUP	BETTER RESPONSE % (n/N)	P-VALUE FOR TESTING H_0 [a]
Lansoprazole 15 mg QD (N=59)	71% (42/59)	0.0013*
Lansoprazole 30 mg QD (N=23)	78% (18/23)	0.009*

a: null hypothesis (H_0) that probability of improvements is not greater than .5.
*: Significant at the .05 significance level.

Table 3.1.1.8 indicates that for both treatment groups, the patient had a probability significantly higher than 50% for the improvement on the relief of overall GERD symptoms at Final Visit when compared with the pre-treatment period.

3.1.2 Study M97-640

Study Design and Endpoints

This was a randomized, double-blind study designed to evaluate the pharmacokinetics and pharmaeodynamics of once daily administration of lansoprazole 15mg or 30mg in adolescents, ages 12 to 17 with symptomatic GERD.

This study was conducted in the United States with ten sites enrolled 63 children with symptomatic, endoscopically and/or historically proven GERD. Of these, 32 were randomized

to receive lansoprazole 15mg QD dose and 31 subjects were randomized to receive lansoprazole 30mg QD dose for 5 days. Subjects were to be assessed the drug efficacy and safety throughout the treatment period.

Efficacy variables included symptom relief based on investigator interview and the percentage of days/nights with heartburn or other predominant symptom, severity of the heartburn or other predominant symptom, and Gelusil use recorded on subject diaries.

As for the sample size, the sponsor indicated that a total of 60 subjects were to be enrolled into the study, with 30 subjects assigned to each of the two treatment groups. If the incidence rate for an adverse event was 15% for a treatment, the probability that the event would be observed in three or more subjects in a group was 0.8.

Patient Disposition

Table 3.1.2.1 presents the number of subjects planed and analyzed by treatment group.

Table 3.1.2.1 (Sponsor's) Number of subjects planed and analyzed by treatment group

	Lansoprazole 15 mg QD	Lansoprazole 30 mg QD
Number of subjects planned	30	30
Number of subjects enrolled	32	31
Number of subjects received study drug	32	31

Table 3.1.2.1 indicates that a total of 63 adolescent subjects were enrolled in the study. Of these, 32 were randomized to receive lansoprazole 15 mg QD and 31 were randomized to receive lansoprazole 30 mg QD. One subject [redacted], in the lansoprazole 15 mg QD group was prematurely discontinued from the study after four days of therapy due to adverse events of peripheral edema, maculopapular rash, and urticaria. Therefore, a total of 62 subjects (31 lansoprazole 15 mg QD and 31 lansoprazole 30 mg QD) completed dosing in the study and analyzed.

Baseline Demographics

There were no statistically significant differences between the treatment groups with respect to gender, race, weight, or height. In addition, the mean age of the 63 adolescent subjects enrolled in this study was 14.1 years (range: 11 to 17 years) and the mean weight of the male and female subjects was 137.3 and 126.1 pounds, respectively.

Fifty-one percent (51%) of the subjects were male and 49% of the subjects were female. However, the distribution of males and females by treatment group showed that the majority of the subjects in the lansoprazole 15 mg QD group were male (63%) while the majority of the subjects in the lansoprazole 30 mg QD group were female (61%). Most of the subjects were Caucasian (79%), followed by black (10%), and "other" races (11%).

Statistical Methodologies

Symptom relief from Baseline to Day 5 Visit, based on investigator interview, was tabulated. The average severity score and the percentage of days and nights with heartburn or other predominant symptom as recorded in the subject diaries during the pre-treatment and treatment periods were summarized.

Sponsor's Efficacy analysis Results and Conclusions

i. Results for symptom assessments based on investigator's interview

At 5% significance level, no statistically significant differences were observed between the lansoprazole 15 mg QD and lansoprazole 30mg QD groups for relief of heartburn based on investigator interview. However, for each of the two treatment groups, subjects had statistically significant reductions from Baseline to the Day 5 Visit in the severity of heartburn. Additionally, from baseline to the Day 5 Visit, subjects in the lansoprazole 15mg QD group had statistically significant reductions in the severity of regurgitation, nausea, abdominal pain, and flatulence while subjects in the lansoprazole 30mg QD group had a statistically significant reduction in the severity of abdominal distention.

ii. Results for diary data analysis

Subjects in both the lansoprazole 15 mg QD and lansoprazole 30 mg QD groups demonstrated reductions [but no results from statistical inferences were reported] from the pretreatment period to the Day 5 Visit in the percentage of days with heartburn or other predominant symptom, the percentage of nights with heartburn or other predominant symptom, the percentage of days or nights with heartburn or other predominant symptom, the severity of the heartburn or other predominant symptom, the percentage of days Gelusil was used, and the average number of Gelusil tablets used per day during the treatment period. In addition, no statistically significant differences were observed between the two treatment groups for any of these diary variables during the pretreatment period or the treatment period. Table 3.1.2.2 presented a summary of the diary results during the pretreatment and treatment periods by treatment group.

Table 3.1.2.2 (Sponsor's) Diary results during the pretreatment and treatment periods

Variable	Lansoprazole Group (Median)			
	15 mg QD		30 mg QD	
	Pretreatment (N=31)[a]	Treatment (N=32)	Pretreatment (N=31)	Treatment (N=31)
Daytime Heartburn or Other Predominant Symptom				
% of Days with Heartburn or Other Predominant Symptom	85.7	77.5	62.5	25.0
Average Severity/Day[b]	1.25	0.90	1.00	0.50
Nighttime Heartburn or Other Predominant Symptom				
% of Nights with Heartburn or Other Predominant Symptom	16.7	0.0	50.0	25.0
Average Severity/Night[b]	0.25	0.0	0.67	0.25
Heartburn or Other Predominant Symptom (Day or Night)				
% of Days or Nights with Heartburn or Other Predominant Symptom	85.7	77.5	85.7	50.0
Average Maximum Severity[c]	1.29	0.90	1.25	0.75
Gelusil® Use				
% of Days Used	50.0	20.0	50.0	0.0
Average Number of Tablets Taken/Day	1.13	0.40	0.78	0.0

a One subject did not have diary results during the Pretreatment Period.
b Severity scored as: none = 0; mild = 1; moderate = 2; and severe = 3.
c Maximum severity of day or night heartburn or other predominant symptom scored as: none = 0; mild = 1; moderate = 2; and severe = 3.
Cross-reference: Tables 14.2__2.1 and 14.2 __2.2

Statistical Reviewer's analysis

For this study, there is no statistical analysis performed by this reviewer.

3.2 EVALUATION OF SAFETY

3.2.1 Study M00-158

Of the 87 subjects enrolled, fifty-seven (65.5%) experienced one or more treatment-emergent adverse event(s). Headache in 14 (16.1%) subjects and abdominal pain in 12 (13.8%) subjects were the most frequently reported adverse events. As for the treatment related adverse events, the sponsor indicated that twelve (18.8%) of 64 subjects in the non-erosive GERD treatment group (lansoprazole 15 mg QD) and 1 (4.3%) of 23 subjects in the erosive esophagitis treatment group (lansoprazole 30 mg QD) experienced adverse events that were considered possibly or probably treatment-related. No adverse event was considered to be definitely treatment-related.

Most adverse events were mild or moderate in severity. Four subjects reported SAEs, 3 of these experienced 4 events (suicide attempt, gastroenteritis, dehydration, accidental injury) that were described as not related to study drug and 1 of these experienced an event (cholecystitis) that was described as unlikely to be related to study drug. One subject was terminated prematurely from the study due to dizziness and vomiting described as possibly related to study drug.

3.2.2 Study M97-640

The incidence of treatment-emergent adverse events was comparable between the lansoprazole 15 mg QD and the lansoprazole 30 mg QD treatment groups (28% and 39%, respectively). Pharyngitis (6%; 2/32) was the most commonly reported treatment-emergent adverse event among subjects in the lansoprazole 15 mg QD group, whereas headache (13%, 4/3 1) was the

most commonly reported treatment-emergent adverse event among subjects in the lansoprazole 30 mg QD group. The sponsor indicated that most of the adverse events were not considered related to study drug administration and all adverse events were considered to be mild or moderate in severity.

4.0 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 GENDER, RACE, AND AGE

Study M00-158

In order to assess the consistency of the treatment effect of prevacid across subgroups, this reviewer performed the subgroup analysis using signed rank test on the percentage of days with GERD symptoms change from baseline to Week 8 Visit (PDGSCH8) and average daily severity of GERD symptoms change from baseline to Week 8 Visit (ADSGSCH8) based upon ITT patient population. Since this NDA submission is for pediatrics use on children from ages 12 to 17, the subgroups analyzed are only for Gender (Male and Female), Race (Caucasian and Non-Caucasian).

Gender (Females and Males)

Table 3.1.1.9 presents the results of treatment efficacy comparisons for prevacid by gender.

Table 3.1.1.9 (Reviewer's) GERD symptom changes from baseline to Week 8 Visit using ITT population

	CHANGE IN % DAYS WITH GERD		CHANGE IN AVERAGE DAILY SEVERITY	
	median	(p-value)[1]	median	(p-value)
Females				
Lansoprazole 15 mg QD (N=41)	-24.1	(< 0.0001*)	-0.54	(< 0.0001*)
Lansoprazole 30 mg QD (N=12)	-49.8	(0.001*)	-1.12	(0.0005*)
Males				
Lansoprazole 15 mg QD (N=23)	-41.5	(< 0.0001*)	-0.82	(< 0.0001*)
Lansoprazole 30 mg QD (N=11)	-54.4	(0.001*)	-1.0	(0.001*)

[1]: P-Value for testing GERD symptom changes from baseline to Week 8 Visit using Sign rank test;
*: Significant at significance level of .05.

For both females and males, Table 3.1.1.9 indicates that at significance level of 0.05, GERD symptom changes from Baseline to Week 8 Visit assessed by percentage of days with GERD symptoms and average daily severity with GERD symptoms are statistically significantly reduced for both treatment groups.

Race (Caucasian and Non-Caucasian)

Table 3.1.1.10 presents the results of treatment efficacy comparisons for prevacid by race.

Table 3.1.1.10 (Reviewer's) GERD symptom changes from baseline to Week 8 Visit using ITT population

	CHANGE IN % DAYS WITH GERD		CHANGE IN AVERAGE DAILY SEVERITY	
	median	(p-value)[1]	median	(p-value)
Caucasian				
Lansoprazole 15 mg QD (N=51)	-31.5	(< 0.0001*)	-0.78	(< 0.0001*)
Lansoprazole 30 mg QD (N=19)	-55.8	(< 0.0001*)	-1.11	(< 0.0001*)
Non-Caucasian				
Lansoprazole 15 mg QD (N=13)	-39.8	(0.002*)	-0.83	(0.005*)
Lansoprazole 30 mg QD (N=4)	-15.5	(0.25)	-0.72	(0.13)

[1]: P-Value for testing GERD symptom changes from baseline to Week 8 Visit using Sign rank test;
*: Significant at significance level of .05.

Similarly, for Caucasian and Non-Caucasian patients, Table 3.1.1.10 indicates that at significance level of 0.05, GERD symptom changes from baseline to Week 8 Visit assessed by percentage of days with GERD symptoms and average daily severity with GERD symptoms are statistically significantly reduced for both treatment groups with the exception of the Non-Caucasian patients in the lansoprazole 30 mg group. However, there were only four patients in this subgroup and the medians of both outcome variables are numerically less than zero, indicating the results in favor of the study drug lansoprazole 30 mg.

4.2 OTHER SPECIAL/SUBGROUP POPULATIONS - Not applicable

5.0 SUMMARY AND CONCLUSIONS

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

5.1.1 Pivotal Study M00-158

The applicant found that for all subjects (87), non-erosive GERD subjects (64), and erosive esophagitis subjects (23), statistically significant ($p < 0.001$) reductions from the pretreatment period to the Final Visit Period were observed in the percentage of days the subjects had GERD symptoms, and the average daily severity of GERD symptoms. This reviewer's analyses did not contradict these results. However, there were the following issues:

- It is noted that less than 30% (26%; 23/87) of enrolled subjects had erosive esophagitis at baseline and only 3.4% (3/87) of subjects had esophagitis grade greater than 2. Therefore, due to lack of sufficient more severe esophagitis subjects enrolled, the efficacy of lansoprazole is not clear for the use in the treatment of more severe esophagitis disease in children of ages 12 to 17 years old.
- Similarly, most of the enrolled patients (90%; 78/87) were not with the severe GERD symptoms. Due to lack of sufficient subjects enrolled with severe GERD symptoms, the study did not provide sufficient evidence to demonstrate the efficacy of lansoprazole to treat children with more severe GERRD symptoms.

5.1.2 Supportive Study M97-640

Due to the following facts, the sponsor's efficacy analysis on the GERD symptoms assessed by investigators and patient diary data did not demonstrate significant evidence to support the efficacy of lansoprazole in the use of treatment of GERD in children of ages 12 to 17:

- Instead of assessing the drug efficacy, the objectives of this 5-day study were to evaluate the safety, pharmacokinetics, and pharmacodynamics of once daily (QD) administration of lansoprazole 15 mg or 30 mg in pediatric subjects, ages 12 to 17 with symptomatic GERD.
- Of 20 types of GERD symptoms assessed by the investigators, at 5% significance level, only 5 and 2 of them respectively for lansoprazole 15 mg and 30 mg showed significantly improved from baseline to Final Visit. In addition, the percentages of enrolled subjects with severe symptoms at baseline were small (less than 17%).
- Although the enrolled subjects underwent endoscopy exam during Screening Visit, due to short study time period (5-day study), the results of endoscopy analyses at end of the study may not provide meaningful information.

5.2 CONCLUSIONS AND RECOMMENDATIONS

- Based on the sponsor's and this reviewer's analyses through the sponsor's study data, the efficacy of lansoprazole, assessed from the statistical perspective, is supported for the use in the treatment of GERD in children of ages 12 to 17 years old.
- If from the clinical perspective, the concern for not recruiting sufficient patients with severe esophagitis and GERD symptoms is not critical for the use of the drug in the pediatric population, then the efficacy of lansoprazole, assessed from the statistical perspective based upon the sponsor's study data, is supported for the use in the treatment of GERD in children of ages 12 to 17 years old.

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/s/

Wen-Jen Chen
6/3/04 03:48:08 PM
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Stella Grosser
6/4/04 09:58:48 AM
BIOMETRICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-428/S-004

ADMINISTRATIVE DOCUMENTS AND CORRESPONDENCE

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Predecisional Agency Information

Date: June 15, 2004

From: Shannon Benedetto

To: Melissa Furness
Re: Prevacid (lansoprazole) delayed release capsules
NDA 20-406/SE5-057, NDA 21-281/SE8-014, NDA 21-428/SE8-004
Document Date 11/24/03

DDMAC has no comments at this time on the pediatric supplement for Prevacid.

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/s/

Shannon Benedetto
6/15/04 02:29:23 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 20-406/S-057
NDA 21-281/S-014
NDA 21-428/S-004

PRIOR APPROVAL SUPPLEMENT

TAP Pharmaceutical Products Inc.
Attention: Nancianne Knipfer, Ph.D.
Product Manager, Regulatory Affairs
675 North Field Drive
Lake Forest, IL 60045

Dear Dr. Knipfer:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Prevacid (lansoprazole) Delayed-Release Capsules Prevacid (lansoprazole) For Delayed-Release Oral Suspension Prevacid SoluTab (lansoprazole) Delayed-Release Orally Disintegrating Tablet
NDA Number:	NDA 20-406 NDA 21-281 NDA 21-428
Supplement number:	S-057 S-014 S-004

Review Priority Classification: Priority (P)

Date of supplement: December 19, 2003

Date of receipt: December 22, 2003

This supplemental application proposes the following change(s): in the labeling sections **SPECIAL POPULATIONS - PEDIATRICS, PEDIATRIC USE, DOSAGE AND ADMINSTRATION** and **DESCRIPTION** section of the package insert for the treatment of symptomatic GERD, nonerosive esophagitis and erosive esophagitis in patients 12-17 years of age.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February February 22, 2004 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be June 22, 2004.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have submitted pediatric studies for ages 12-17 with this application, completed studies for ages 1-11 (NDA 20-406/S-047), and plan to initiate studies in children less than 1 year of age after the completion of your required rat toxicity study. Once the review of this application is complete we will notify you whether you have partially fulfilled the pediatric study requirements for this application.

All communications concerning these supplements should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: Division Document Room 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, please call me at (301) 827-7450.

Sincerely,

{See appended electronic signature page}

Melissa Hancock Furness
Regulatory Health Project Manager
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Melissa Furness
4/29/04 06:02:43 PM

EXCLUSIVITY SUMMARY for NDA #: NDA 20-406 NDA 21-281 and NDA 21-428
SUPPL #: SE5-057, SE8 -014, and SE8-004, respectively

Trade Name: Prevacid (lansoprazole) Delayed-Release Capsules, Prevacid (lansoprazole) For Delayed-Release Oral Suspension, and Prevacid SoluTab (lansoprazole) Delayed-Release Orally Disintegrating Tablet

Generic Name: (lansoprazole)

Applicant Name: Tap Pharmaceutical Products, Inc.
HFD- 180

Approval Date: 06/17/04

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/___/ NO /_x__/

   b) Is it an effectiveness supplement? YES /__x_/ NO /___/

   If yes, what type(SE1, SE2, etc.)? SE5, SE8, and SE8, respectively

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

   YES /__ x _/ NO /_ __/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   If it is a supplement requiring the review of clinical

data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /__/ NO /__x_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /__x_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /___/ NO /__x_/

If yes, NDA #

Note: NDA 20-406/S-047 (Peds 1-11) was approved for the same indications - these efficacy supplements are for ages 12-17.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /__x_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An

active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_x_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the

investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_x_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /__/ NO /_x_/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /__/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_x_/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # M97-640

Investigation #2, Study # M00-158

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /_x_/
Investigation #2	YES /___/	NO /_x_/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_x_/

Investigation #2 YES /___/ NO /_x_/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # M97-640

Investigation #__, Study # M00-158

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # 30,159 YES /_x/ NO /___/ Explain:

Investigation #2

IND # 30,159 YES /_x_/ NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are

there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_x_/

If yes, explain: _____

_____

_____

Melissa Furness
Signature of Preparer Date

Title: Regulatory Health Project Manager

Dr. Joyce Korvick
Signature of Office or Division Director Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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/s/

Joyce Korvick
1/7/05 01:56:04 PM

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : NDA 20-406 NDA 21-281 and NDA 21-428 Supplement Type (e.g. SE5): SE5, SE8, and SE8, respectively

Supplement Number: 057, 014, and 004, respectively Stamp Date: 12/22/03 Action Date: 06/17/04 HFD-180

Trade and generic names/dosage form: Prevacid (lansoprazole) Delayed-Release Capsules, Prevacid (lansoprazole) For Delayed-Release Oral Suspension, and Prevacid SoluTab (lansoprazole) Delayed-Release Orally Disintegrating Tablet

Applicant: Tap Pharmaceutical Product, Inc. Therapeutic Class: Proton Pump Inhibitor

Indication(s) previously approved (for pediatrics): the treatment of symptomatic GERD, nonerosive esophagitis and erosive esophagitis in patients 1-11 years of age

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 3

Indications: the treatment of symptomatic GERD, ~~~~ and erosive esophagitis in patients 12-17 years of age.

Is there a full waiver for this indication (check one)?

- ☐ Yes: Please proceed to Section A.
- X No: Please check all that apply: ____Partial Waiver __x__Deferred __x__Completed
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver: Please note that a waiver was not granted prior to the Pediatric Rule being challenged in court.

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Other:_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____	kg_____	mo._____	yr._____	Tanner Stage_____
Max_____	kg_____	mo._____	yr._____	Tanner Stage_____

Reason(s) for partial waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study

- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____	**kg**_____	**mo.**_____	**yr.** 17	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.** < 1	**Tanner Stage**_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- X **Adult studies ready for approval**
- X **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Comments Regarding Sections C and D

We note that the firm has submitted pediatric studies for ages 12-17 with NDA 20-406/S-057, completed studies for ages 1-11 (NDA 20-406/S-047), and plans to initiate studies in children less than 1 year of age after the completion of their required rat toxicity study as per their currently issued WR.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA
HFD-950/ Terrie Crescenzi
HFD-960/ Grace Carmouze
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA
HFD-960/ Terrie Crescenzi
(revised 1-18-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

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/s/

Melissa Furness

9/3/04 03:28:48 PM

EXCLUSIVITY SUMMARY for NDA #: NDA 20-406 NDA 21-281 and NDA 21-428

SUPPL #: SE5-057, SE8 -014, and SE8-004, respectively

Trade Name: Prevacid (lansoprazole) Delayed-Release Capsules, Prevacid (lansoprazole) For Delayed-Release Oral Suspension, and Prevacid SoluTab (lansoprazole) Delayed-Release Orally Disintegrating Tablet

Generic Name: (lansoprazole)

Applicant Name: Tap Pharmaceutical Products, Inc.
HFD- 180

Approval Date: 06/17/04

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/___/ NO /_x__/

   b) Is it an effectiveness supplement? YES /__x_/ NO /___/

   If yes, what type(SE1, SE2, etc.)? SE5, SE8, and SE8, respectively

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

   YES /__ x _/ NO /_ __/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /__/ NO /__x_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /__x_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /_x__/ NO /___/

If yes, NDA # NDA 20-406/S-047 (Peds 1-11) was approved for the same indications - these efficacy supplements are for ages 12-17.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /___/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An

active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /__/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement

without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /__/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /__/ NO /__/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /__/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /__/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study #

Investigation #2, Study #

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /__/

Investigation #2 YES /___/ NO /__/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /__/

Investigation #2 YES /___/ NO /__/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study #

Investigation #__, Study #

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # YES /_/ NO /___/ Explain:

Investigation #2

IND # __ YES /__/ NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /__/

If yes, explain: _____

_____

_____

Melissa Furness
Signature of Preparer Date

Title: Regulatory Health Project Manager

Dr. Joyce Korvick
Signature of Office or Division Director Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

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Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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/s/

Joyce Korvick
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